Proposed MAPS-Sponsored Israeli Pilot Study:
MDMA-assisted Psychotherapy in Twelve People with War and Terrorism-related Posttraumatic Stress Disorder (PTSD)

Principle Investigator: Dr. Moshe Kotler, Tel Aviv University, Sackler School of Medicine

Draft 4, March 16, 2005

Introductory Statement and General Investigational Plan

This application is for a pilot study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy in people with posttraumatic stress disorder (PTSD) arising from combat or terrorism. This research builds on findings from Phase I studies conducted in the US and Europe (Cami et al. 2000; Forsling et al. 2001; Farre et al. 2004; Gamma et al. 2000; Grob et al. 1996; Grob et al., Unpublished; Harris et al. 2002; Lamers et al. 2003; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Pacifici et al. 2001; Pacifici et al. 2004; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998), and on one sponsor-conducted randomized, placebo-controlled Phase II study of MDMA-assisted psychotherapy in people with crime-related PTSD (Mithoefer 2004). This study first only enrolled people with crime-related PTSD but now may enroll people with war or terrorism-related PTSD.

This study is part of a program of research to evaluate MDMA as an adjunct to psychotherapy. To date, ongoing and planned studies will focus on MDMA in combination with psychotherapy for people with PTSD and in people suffering from anxiety as a result of advanced stage cancer. If it is found that MDMA-assisted psychotherapy seems safe and efficacious in one or more of these patient populations, then MAPS will seek to conduct Phase III studies of MDMA-assisted psychotherapy in larger populations. This is part of a plan to develop MDMA into a prescription medication.

This study is also intended to provide the research team headed by Dr. Kotler with training in and experience with MDMA-assisted psychotherapy, and to develop and standardize this potential treatment. Once the research team is trained and has experience with MDMA-assisted psychotherapy, then they will be prepared for conducting further studies.

A conference held in 1999 discussed the possibility of conducting research into the safety and efficacy of MDMA-assisted therapy in Israel. At the conference, attendees concluded that research into the potentially therapeutic uses of MDMA is important and that such studies can be safely conducted (Doblin 1999). The proposed study will be the first to take place in Israel. It will be one of several planned and ongoing pilot studies of MDMA-assisted therapy in people with PTSD. One study is already underway in the US, and the sponsor plans to conduct another study using a similar design in Spain. These

studies will all provide data for the development of MDMA-assisted therapy as a novel treatment for PTSD.

MDMA is a ring-substituted phenylisopropylamine derivative. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s. It has the chemical name N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C11H15NO2. Though this compound is structurally related to the psychostimulant methamphetamine and the psychedelic (hallucinogen) mescaline, many researchers believe that its unique pharmacological profile place it in a separate drug class, the entactogens or empathogens. Entactogens reduce fear associated with emotionally upsetting thoughts, feelings or memories and generate or enhance feelings of closeness to others and empathy for the self and others.

Before MDMA became a Schedule I drug in the United States, it was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists (Greer and Tolbert 1986: Saunders 1993; Stolaroff 2004). There are a number of published case reports and uncontrolled studies of its therapeutic effects. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways: Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" (Greer and Tolbert 1998). Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. It has also been asserted that MDMA causes increased empathy for self and others, decreased defensiveness, and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert,1998, Holland, 2001).

The population of chronic PTSD patients was selected in part because of patient and therapist reports as to the effectiveness of MDMA-assisted psychotherapy in treating PTSD, from treatments conducted prior to the criminalization of MDMA in 1985. The qualities that have been associated with MDMA in anecdotal reports (i.e. decreased defensiveness and enhanced therapeutic alliance) seem to have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value. Early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. It is also a disorder for which there is, to date, only two FDA-approved medications in the US, and about which there are still many unanswered questions regarding psychological and pharmacological interventions (Montgomery and Beck 1999). The lifetime prevalence of PTSD in the general population may be as high as 10% (Meltzer-Brody et al. 2000), so the search for additional and more effective treatments is extremely important. This is especially true for people who have not achieved remission after at least one treatment, including both psychotherapy and pharmacotherapy.

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

Initial human trials of MDMA demonstrated that the drug can be administered safely under controlled conditions, and no drug-related serious adverse events have been reported during the course of the Phase II study. Preliminary examination of this data has found no deterioration in condition after MDMA-assisted psychotherapy. When the blind was broken for the first five subjects, it was found that people receiving MDMA demonstrated greater improvement than people receiving placebo.

There has been no evidence of significant or lasting toxicity in phase I studies. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g., Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of current or former repeated users of illicit MDMA and other drugs (i.e. Gouzoulis-Mayfrank et al. 2003; Gouzoulis-Mayfrank et al. 2004; Halpern et al. 2004; Thomasius et al. 2003). In contrast, our all available phase I data (published and yet unpublished) indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is not affected by participation in clinical MDMA trials (Boone et al. in preparation, see also **Table 2.5** in Investigator's Brochure; Ludewig et al. 2003, data presented at the 58th Conference for the Society for Biopsychiatry; Vollenweider et al. 2001). Vollenweider and colleagues (2000) recently presented positron emission tomography data at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose of MDMA similar to our proposed dose of 125 mg was given to MDMA-naïve volunteers. Based on these data and an extensive review of the MDMA literature, we conclude that risks of neurocognitive, serotonergic, or other toxicity are low in the proposed protocol.

Based on these findings, which will be discussed further below in the section on Pharmacology and Toxicology, it is very unlikely that the doses we propose to administer in a controlled clinical setting will cause memory impairment or other neurological or physiological damage. These low risks are more than balanced by the potential benefits to

the volunteers. All participants will have had at least one unsuccessful attempt at treatment with medications and/or psychotherapy, and they may find some relief associated either with MDMA-assisted psychotherapy or with the non-drug psychotherapy to be administered to the control subjects.

The Protocol

Study Objectives

This protocol is for a randomized, double-blind, active placebo controlled study of the safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in people with posttraumatic stress disorder (PTSD). In this study, 12 people with PTSD arising from war or terrorism will receive either an active placebo dose or a fully active dose of MDMA during two six to eight hour psychotherapy sessions scheduled two to four weeks apart. Active placebo will be 25 mg MDMA followed by 12.5 mg, and the fully active dose will be 125 mg followed by 62.5 mg. Extent of PTSD symptoms will be assessed at baseline, and two, six and 12 months after the second MDMA-assisted session. The Clinician Administered PTSD Scale (CAPS) will serve as the primary outcome measure. We hypothesize that PTSD symptoms will be reduced in participants receiving the fully active dose of MDMA, and that MDMA-assisted psychotherapy will be well-tolerated and will not produce serious adverse effects in this population.

Participants assigned to receive the active placebo and participants assigned to receive the fully active dose will receive the same course of psychotherapy. Participants in this study will receive eight to ten hour-long psychotherapy sessions and the two MDMA-assisted psychotherapy sessions described above. Psychotherapy sessions include two introductory sessions prior to the first experimental (low or fully active dose MDMA) session, psychotherapy sessions occurring a day after each experimental session, and two to three psychotherapy sessions conducted on a weekly basis after each experimental session, with the first of these sessions scheduled a week after each experimental session. An independent assessor will administer outcome measures at baseline, and at two, six and 12 months after the second experimental session.

The proposed study has been designed as part of a program of research supported by the Multidisciplinary Association for Psychedelic Studies (MAPS) to develop MDMA into a prescription medication with US Food and Drug Agency (FDA) approval. Other MAPS-supported studies include a study of MDMA-assisted therapy in people with PTSD taking place in Charleston, South Carolina, and a planned study of MDMA-assisted therapy in people with PTSD to be conducted in Madrid, Spain. All studies so far are intended to collect preliminary data on MDMA-assisted therapy. MAPS is also supporting a study to take place at Harvard Medical School's McLean Hospital that will investigate MDMA-assisted psychotherapy in people with advanced stage cancer and anxiety related to their cancer diagnosis.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. MDMA is a white, crystalline powder and will be administered orally in capsule form. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was made a Schedule 1 (illegal) drug in 1985

as a result of extensive non-medical use (Greer and Tolbert 1986: Saunders 1993; Stolaroff 2004). Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD (Adamson 1985; Greer and Tolbert 1998; Metzner and Adamson 2001l; d'Otolora, 2001). Case reports and narrative accounts of MDMA-assisted therapy indicate that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways: Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" (Greer and Tolbert 1998). Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. It has also been asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert, 1998, Holland, 2001). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender, 1990). The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

This study of MDMA-assisted therapy will be the first to take place in Israel, and the first examining MDMA-assisted psychotherapy as a potential treatment for people with war or terrorism-related PTSD. If the results of this study of MDMA-assisted therapy in people with PTSD indicate that MDMA shows promise in producing significant improvement in PTSD symptoms and can be administered with a favorable risk/benefits ratio, then we will design a second pilot study. The second study will enroll a larger sample to increase the statistical power of the study, and study procedures will be informed by the proposed study. The study will also provide an opportunity for training the research team in Israel to perform MDMA-assisted psychotherapy.

If data from pilot studies continue to produce promising results, then MAPS will use the information gathered form these studies to formulate at least one large multi-site Phase III study of MDMA-assisted psychotherapy in a sample of at least 250. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least 5 years and will involve at least 600 subjects.

Background and Significance

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder arising after a personally threatening life-event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. The search for more effective treatments and a wider array of treatments is crucial. A study of 512 Israelis indicated that while 10% were diagnosed with PTSD, up to 75% exhibited behaviors associated with PTSD, such

as avoidance of a trauma-related area, and over 50% avoid public places or feel "despondent" (as reported in Yedioth Abronoth 11/21/02). Another study of 2975 Israelis receiving primary care found that 23% of the individuals reported experiencing a traumatic event. Of these, 39% were diagnosed with PTSD (Taubman-Ben-Ari et al. 2001). The search for more effective treatments is of major public health significance.

The DSM IV criteria for PTSD include: 1) Exposure to a significant traumatic event accompanied by an intense acute emotional response. 2) Persistent reexperiencing of the event or aspects of the experience. 3) Persistent avoidance of stimuli associated with the event, and/or withdrawal from some aspects of life. 4) Persistent symptoms of increased arousal. The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD (DSM-IV). In the National Comorbidity Study, the median time to remission was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of patients still had symptoms several times per week after 10 years (Kessler et al., 1995). These data highlight the importance of research to develop new treatments and to thoroughly investigate any treatments, such as MDMA-assisted psychotherapy, which have shown promise in anecdotal reports.

In humans, MRI studies have now demonstrated decreased hippocampal volume in patients with PTSD. This is in keeping with the decreased neurogenesis and resultant stress-induced hippocampal atrophy in animal models. In addition, PET scans have revealed decreased metabolic rates in the temporal and prefrontal cortex in patients with combat related PTSD (Bremner et al. 1997). In another study, PTSD patients showed increased blood flow in limbic regions and decreased flow in mid-temporal, left inferior frontal and medial prefrontal cortex, compared with controls (Bremner 1999; Rauch 1996; Shin 1997). It is not known how rapidly the neurobiological changes develop after trauma or to what degree they are enhanced or sustained by the ongoing stress of the re-experiencing and hyper-arousal symptoms of PTSD. Changes in blood flow patterns on PET scans have been observed when patients are exposed to reminders of the original trauma (Bremner 1999). This is consistent with what seems intuitively likely, that the ongoing stress of the disorder is in some sense self-perpetuating and contributes to the adverse neurobiological effects as well as the suffering that stems from PTSD. If that is true, then the ongoing neurotoxicity of the chronic disorder itself is an important factor to weigh against any concerns regarding toxicity from drug treatment. Charney points out that, "in animals, the amygdala, hippocampus, locus coeruleus, and prefrontal cortex are involved in the fear reaction (Grillon 1996). In humans, however, idiosyncratic differences contribute to the development of PTSD in some individuals but not in others exposed to the same stressor. Chronic noradrenergic activation can lead to down-regulation of noradrenergic receptors and depletion of norepinephrine, both of which can increase susceptibility to future stress (Grillon 1996). Chronic elevation of glucocorticoids can result in neurotoxic effects in the hippocampus that adversely affect learning and memory (Ling 1981; Sapolsky 1990; Wolkowitz 1990). Re-experiencing the trauma through intrusive symptoms or other reminders can serve as a chronic or intermittent stressor. This effect reinforces the neurobiological disturbance and establishes a process of "kindling" in which the patient is chronically prepared to respond

to specific reminders of the trauma or even to neural stimuli (such as loud noises) with the same intensity experienced during the original traumatic event. (Van der Kolk 1997)

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

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Greer and Tolbert 1998; Metzner and Adamson 2001; Shulgin 1990; Widmer 1998). Treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a brief to moderate course of psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD

To date, several Phase I trials have been conducted by seven research teams in the United States, England, Spain, Switzerland, and the Netherlands, with MDMA administered to over 245 subjects overall without the occurrence of any serious adverse events (Cami et al. 2000; Chang et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Farre et al. 2004; Forsling et al. 2001; Frei et al. 2001; Gamma et al. 2000; Gamma et al. 2004; Grob et al, In Preparation, Data presented to FDA; Grob et al. 1996; Harris et al. 2002; Hernandez-Lopez et al. 2003; Lamers et al. 2004; Lester et al. 2000; Liechti and Vollenweider 2000a; Liechti et al. 2000b; Liechti et al, 2001a: Liechti et al. 2000b; Mas et al. 1999; Navarro et al. 2001; Pacifici et al. 2000; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004; Pichini et al. 2002; Pichini et al. 2002; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004; Samyn et al. 2002; Segura et al. 2001;Tancer and

Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998; Vollenweider et al. 1999). When MDMA is used in doses similar to those proposed for this study, and in a controlled setting, the risk/benefit ratio is favorable. By and large, MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds (Mas et al. 1999; Tancer and Johanson 2003), such as amphetamine (Adderall), that have been used clinically for many years.

Acute effects reported are in agreement with those reported in earlier uncontrolled studies (Downing 1986; Greer and Tolbert 1986) and anecdotal reports (Adamson 1985; Widmer 1997). These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication (Vollenweider et al. 1998).

The potentially therapeutic effects of MDMA were investigated in a dose-response pilot study in Spain (Bouso et al. 2001) in women survivors of sexual assault with treatment-resistant PTSD, and an FDA-approved study has begun in the United States of MDMA-assisted psychotherapy in men and women with treatment-resistant PTSD as a result of sexual or criminal assault, and now accepting people with combat-related PTSD (Mithoefer and Wagner 2001; see also Ruse et al. 2005). Unfortunately, the first study has been halted due to political pressure from the Madrid Anti-Drug Authority. However, prior to its suspension, six women were enrolled in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg. Seven subjects have undergone treatment in a study in the US without any drug-related serious adverse events, and it appears that people who received MDMA had improvements in PTSD symptoms. The safety and efficacy of MDMA-assisted therapy specifically in people with war or terrorism-related PTSD has yet to be studied. The proposed study is intended to investigate whether this novel treatment may assist those with war or terrorism-related PTSD. While there are significant risks associated with the consumption of illicit ecstasy (which may or may not contain MDMA alone or in combination with other drugs) in uncontrolled recreational contexts, the administration of pure MDMA by trained therapists to prescreened subjects within a controlled setting entails far fewer risks and can be conducted with an acceptable level of safety.

There has been no evidence of significant or lasting toxicity in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g., Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of repeated users of illicit MDMA and other drugs (for example Bhattachary and Powell 2001; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Reneman et al. 2001; Thomasius et al. 2003). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is

not affected by participation in clinical trials with MDMA (Boone et al., unpublished data supplied to MAPS; see also Table 2.5 in Investigator's Brochure; Ludewig et al. 2003; Vollenweider et al. 2001). Vollenweider and colleagues (2000) presented positron emission tomography (PET) data at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose close to 125 mg MDMA was given to MDMA-naïve volunteers. The same team of researchers failed to detect any differences in performance on a measure of executive function and memory in 15 drug-naïve volunteers given two doses of 1.5 to 1.7 mg/kg MDMA (Ludewig et al. 2003, data presented at the 58th Annual Conference of the Society for Biological Psychiatry, San Francisco CA).

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

Previous Clinical Experiences with MDMA

Prior to its scheduling in the US, MDMA was used in psychotherapy to treat neuroses, relationship difficulties, and PTSD (Adamson 1985; d'Otalora 2001; Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004). Anecdotal and narrative accounts of MDMA-assisted psychotherapy reported successful treatment of PTSD. People reported reduced PTSD symptoms and improved quality of life. It should be noted that during this period in time, MDMA may have been given to thousands of individuals without any fatalities or serious adverse events (Holland 2001; Rosenbaum and Doblin 1991).

Greer and Tolbert's (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29 individuals with mild to moderate psychological difficulties reported obtaining at least some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986). During MDMA-assisted therapy, nearly all participants described experiencing both positive and undesirable effects. Positive effects included increased closeness to others and positive changes in attitude, and undesirable effects included self-dissatisfaction and mild depression. Written follow-up questionnaires completed two months to two years after the therapy session found that many participants continued to experience positive life changes, including changes in attitudes and beliefs, strengthened interpersonal relationships, and decreased non-medical or habitual substance use. Given the lack of appropriate controls and unblinded study design, one cannot exclude the possibility that some factor other than MDMA produced these improvements, but the study does demonstrate that individuals with mild to moderate psychological disorders can safely undergo MDMA-assisted therapy without deterioration in mental health, and that people undergoing MDMA-assisted psychotherapy experienced some improvements in quality of life afterwards.

As described in the Introductory Statement and Rationale, a sponsor-supported pilot study of MDMA-assisted psychotherapy in people with PTSD is underway in Charleston, South Carolina. The FDA gave permission for this study to take place in November, 2001, and the study finally was granted approval by an IRB in September, 2003. The study has been underway for nearly a year and has enrolled seven subjects to date. This study also employs the CAPS as a primary outcome measure, with PTSD symptoms measured by an independent assessor a week after each experimental (MDMA or placebo) session, and two months after the second experimental session. To date, all participants in this study have tolerated MDMA, and there is some indication that MDMA is associated with greater improvement in PTSD than placebo, though this observation only involves the first five participants in this study.

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

Investigators and Institutional Review Board

Moshe Kotler MD is Chair of the Psychology Department at Tel Aviv University. Previously, he was the chief psychiatrist for the Israeli Defense Forces. He currently works at the Israeli Ministry of Health. Dr. Kotler also plans to be the principle investigator in a study of ibogaine, a plant-derived psychoactive compound isolated from the root bark of a West African shrub that possesses both anti-addictive and psychedelic effects, in people with opiate addictions.

The institutional review board or ethics board is currently not known, but may be the Tel Aviv University ethics board.

Study Design

This protocol is for a randomized, double-blind, active placebo-controlled pilot study of MDMA-assisted psychotherapy in twelve people with war and terrorism-related PTSD. People with PTSD will undergo two sessions of MDMA-assisted therapy scheduled to occur two to four weeks apart. PTSD symptoms will be assessed by an independent rater once prior to MDMA-assisted psychotherapy, and again two, six and twelve months later, with the CAPS serving as a primary outcome measure. This Israeli study is being designed in conjunction with a proposed MAPS-sponsored study of MDMA-assisted psychotherapy in people with PTSD to take place in Madrid, Spain, under the direction of Jose Carlos Bouso, Ph.D. candidate.

This Israeli pilot study is designed to meet three goals. It is intended to explore the safety of MDMA-assisted psychotherapy in this patient population, and to provide the research team with the opportunity to gain experience in this treatment modality before the

possible initiation of larger-scale studies. This study will also gather preliminary data testing the hypothesis that people receiving the larger, fully active dose of MDMA in combination with non-drug psychotherapy will demonstrate greater symptomatic improvement than people given an active placebo dose of MDMA in combination with non-drug psychotherapy.

Eight participants will be randomly assigned to receive the fully active dose (125 mg MDMA during the start of each experimental session, followed two and a half hours later by 62.5 mg), and four will be assigned to receive the active placebo dose (25 mg MDMA followed two and a half hours later by 12.5 mg). The supplemental dosing schedule is expected to prolong the duration of the peak effects without increase the intensity of drug effects.

All participants will receive two six to eight-hour sessions of MDMA-assisted therapy scheduled two to four weeks apart. In addition, all participants will receive two introductory non-drug psychotherapy sessions prior to the first experimental session, and two to three non-drug psychotherapy sessions after each experimental session, including one session always scheduled for the morning after the MDMA-assisted psychotherapy session. PTSD symptoms will be assessed at baseline, and again 2, 6 and 12 months after the second of two sessions of MDMA-assisted psychotherapy, with CAPS scores serving as the primary outcome measure, and with Impact of Events scale (IES), Posttraumatic Diagnostic Scale (PDS) and Symptom Checklist 90-Revised (SCL90R) serving as additional outcome measures.

Participants assigned to the active placebo condition will be given the opportunity to take part in an open-label continuation of the study, referred to here as “Stage 2.” Data gathered two months after the second experimental session will be treated as the baseline for Stage 2, and outcome measures will be administered 2, 6, and 12 months after baseline for all people who consent to take part in Stage 2.

Specific hypotheses

This study of MDMA-assisted therapy in people with war or terrorism-related PTSD will test two hypotheses.

1. There will be trends for people receiving the fully-active dose of MDMA to demonstrate greater symptomatic improvement after receiving MDMA-assisted therapy than people receiving the low dose of MDMA, including greater reduction in symptom severity and intensity, and overall improvement in PTSD symptoms, as measured via the CAPS, IES, PDS, and SCL90R, with CAPS score serving as the primary outcome measure.

2. People receiving the fully active dose of MDMA will not experience any serious adverse events and that the supplemental dose of MDMA will be tolerated both in the low and fully active dose conditions.

We also predict that subjects assigned to receive active placebo during Stage 1 will show greater improvement when assessed after undergoing two experimental sessions with the fully active dose of MDMA during Stage 2. However, formal testing may be precluded by the small number of people taking part in Stage 2.

This is a pilot study and is underpowered for detecting the efficacy of MDMA-assisted psychotherapy. However, it is expected that any trends toward symptomatic improvement will be detected.

Participants

Participants may be men or women aged 18 or older with a confirmed diagnosis of PTSD as a result of a war or terrorism-related trauma who have undergone at least one treatment for PTSD without achieving remission. Prior treatment can include psychotherapeutic or pharmacological treatments, and people who have undergone one or more prior treatment are eligible for study participation. Participants must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Participants will be recruited through referrals from other psychiatrists, psychotherapists or physicians. The first twelve participants who meet all inclusion criteria without meeting any exclusion criteria will be admitted to the study.

Inclusion Criteria:

Participants who meet the following criteria will be considered for inclusion in this study:

1. Participants must either meet DSM IV criteria for current PTSD (within the past 6 months) in response combat or incidents of terrorism. An individual would not be excluded if she or he experienced more than one traumatic event, but would be excluded if a traumatic event unrelated to combat or terrorism was a significant contributor to the PTSD symptoms. Participants must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.

2. They must have had at least one unsuccessful attempt at treatment for PTSD. Treatments include psychotherapy and pharmacotherapy. Pharmacotherapies may include selective serotonin uptake inhibitors (SSRIs). Psychotherapeutic treatments may include, but are not limited to, cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy (Foa et al. 2003; Jaycox et al. 2002; Krupnik 2002; Resick and Schenk 1992). Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of people with other mood and anxiety disorders is essential because recent literature (Brady et al., 1994; Faustman & White, 1989), indicate the marked frequency of the co-existence of other psychiatric disorders among patients with PTSD.

4. Participants must be at least 18 years old.

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

6. Participants must be willing to refrain from taking any psychiatric medications from the outset of the study until the final follow-up evaluation, which will occur two months after the second experimental session, with the exception of gabapentin prescribed for pain control. If they are being treated with psychoactive drugs at the time they are recruited into the study, agreement to suspend treatment must be obtained in writing from their outside treating physician. The drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first experimental (MDMA or placebo) session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life).

7. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. If they desire that the investigators communicate directly with the therapist, participants must sign a release for the investigators to communicate directly with their therapist. They may not change therapists, increase the length and frequency of treatments, or commence any new type of therapy until after the final administration of outcome measures occurring two months after the second experimental session.

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

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

10. Participants must be willing to remain overnight at the clinic after each experimental session until the non-drug session occurring the next morning**.** A medical resident or registered nurse will be present to assist with any personal needs and to monitor the participant during the overnight stay. The resident or nurse will be instructed to

contact Dr. Kotler at the request of the participant or if there are signs that the participant is under physical or psychological distress.

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

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

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

14. Participants must be literate. They must be able to read documents in Hebrew.

Exclusion Criteria:

Prospective participants with the following conditions will be excluded:

1. People who indicate that a non-combat or non-terrorism related traumatic event is a significant contributor to their PTSD symptoms, as assessed by the CAPS.

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

3. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1.

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

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

6. People with uncontrolled hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.

7. People weighing less than 50 kg or more than 105 kg.

8. People reporting prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months.

9. People who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.

10. People requiring ongoing concomitant therapy with a psychotropic drug.
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11. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.

12. Any person who is not able to give adequate informed consent will be excluded.

Initial Screening and Diagnostic Evaluation

After a brief interview with the principal investigator conducted over the telephone, prospective participants will meet with the investigator to discuss the study and to give their written informed consent to take part in the study if they wish to do so.

If they consent to participant, an initial psychiatric and medical evaluation will be performed on each applicant prior to enrollment. **T**he psychiatric evaluation will be performed by the principal investigator. The CAPS will be used to provide a DSM-IV PTSD diagnosis arising from a war or terrorism-related trauma. If the subject meets DSM-IV PTSD criteria, the rest of the SCID (First et al. 1994) will be administered for the purpose of ruling out patients for exclusionary Axis I diagnoses (i.e., exclusion criteria of substance dependence, psychotic disorder, eating disorder, or bipolar disorder). The participant must have a CAPS score of 50 or higher to be enrolled in the study.

Any prospective participant who appears at imminent risk for trauma and victimization as assessed by information gathered during the screening will be counseled in specific risk-reduction strategies, and referred for immediate protection or care as needed. These individuals will not be eligible for study participation. People who do not meet eligibility criteria at this point or who do not wish to participate will be referred for alternative treatment.

If the participant has a CAPS score of 50 or higher and continues to meet eligibility for study participation, then he or she will undergo a medical evaluation no later than two weeks after the psychiatric evaluation. The medical evaluation will include a medical history, a standard physical examination, electrocardiogram (ECG), metabolic profile, and assessment of blood levels of thyroid hormones, serum electrolytes, presence of HIV, and urinary drug and pregnancy tests (when appropriate).

If the prospective participant continues to meet all eligibility criteria, then the principal investigator will contact the participant and the two of them will schedule the baseline assessment and the first introductory psychotherapy sessions. If it is feasible at this point, the first experimental session may be scheduled as well.

Methods

Drugs and Dosage

Upon enrollment in the study, the participant will be randomly assigned to the Low Dose or the Fully Active Dose condition. Condition assignment will be performed with a table of random numbers generated and maintained by the clinic pharmacy. All study investigators will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, the blind may be broken for an individual participant.

Participants in the Low Dose condition are assigned to receive an initial dose of 25 mg MDMA followed 2.5 hours later by a supplemental dose of 12.5 mg MDMA. Participants assigned to the Fully Active dose condition will receive an initial dose of 125 mg followed 2.5 hours later by a supplemental dose of 62.5 mg MDMA. Eight of 12 subjects, or 66.6%, will be assigned to the Fully Active dose condition, and 4 of 12, or 33.3%, will be assigned to the Low Dose condition.

The two doses of MDMA chosen for the Low Dose condition have been selected on the basis of their ability to produce minimal but detectable subjective effects (Grob et al. unpublished; Harris et al. 2002) and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose may produce slight alterations in consciousness, such as increased relaxation or tension (Harris et al. 2002). The initial 125 mg dose of MDMA selected for the Fully Active Dose condition was chosen on the basis of case reports of MDMA-assisted psychotherapy conducted in the US prior to scheduling (Greer and Tolbert 1986). This dose is expected to reduce fear in response to emotionally upsetting thoughts, feelings or memories and to increase access to emotionally intense material, and is thus expected to be therapeutically active. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA (Cami et al. 2000; Grob et al. 1996; Grob et al. Unpublished; Harris et al. 2002; Lester et al. 2000; Mas et al. 1999; Tancer et al. 2001; Tancer et al. 2003; Vollenweider et al. 1998). The cumulative dose of 187.5 mg has been exceeded by single doses in some previous research studies without any adverse events (Grob et al., unpublished). With participants carefully monitored for any indicators of adverse events, the initial dose of 125 mg and the cumulative dose of 187.5 mg MDMA will prove to be tolerable and pose no more than minimal risk.

Table 1. Dose Regimen

	Initial Dose	**Supplemental Dose**	**Cumulative Dose**
Low Dose	25 mg	12.5 mg	37.5 mg
Fully Active Dose	125 mg	62.5 mg	187.5 mg

Supplemental doses for both the Low and the Fully Active dose conditions were chosen to be half the size of initial doses, and the dosage and schedule of dosing was chosen on

the basis of case reports describing the use of MDMA in psychotherapy (Greer and Tolbert 1998; Stolaroff 2004). Supplemental dosing performed 2.5 hours after the initial dose is expected to extend the course of drug effects without increasing the intensity of these effects. Both the Low and Fully Active dose conditions use supplemental doses that are half of the initial dose, to make dosing schedule equivalent across the conditions.

Participants will receive an initial dose of MDMA approximately an hour to an hour and a half after they arrive at the clinic for each experimental session. If the investigators believe the participant is able to tolerate a supplemental dose and the participant agrees to take it, then a supplemental dose will be offered 2.5 hours later. The investigators will not administer the supplemental dose if the participant is exhibiting signs or symptoms that would place him or her at greater risk of experiencing a serious adverse event.

Each dose will consist of the specified amount of racemic MDMA mixed with an inactive substance, such as lactose, to prevent the investigators from distinguishing doses through weight or appearance of the capsules. Initial doses will be distinguished from supplemental doses through labeling them "Dose 1" and "Dose 2" or "first" and "second" dose to ensure that the correct dose is administered at the scheduled time. Each dose of MDMA will be administered along with 250 to 300 mL electrolyte-containing fluid. MDMA will be administered during each of the two experimental sessions, with the second session scheduled to fall two to four weeks after the first experimental session.

Assessments and Measures

Psychiatric diagnoses will be made through the Structured Clinical Interview for Diagnoses (SCID), and PTSD symptoms will be measured during screening to determine whether an individual may participate in the study.

PTSD symptoms will be assessed four times in this study. Baseline data will be gathered at the start of the study. Subsequent to this baseline measurement, participants will be assessed again two months after the second experimental session. All participants assigned to the Fully Active Dose condition, and all participants assigned to the Low Dose condition who choose not to take part in the open-label study continuation will be assessed again six and 12 months after the second experimental session. Participants who choose to take part in the open label study continuation, ("Stage 2") will be assessed six and twelve months after the second experimental session in Stage 2. All outcome measures will be administered by an independent assessor. The independent assessor will remain blind to subject condition and will not be present during psychotherapy sessions. The CAPS will serve as the primary outcome measure, and the IES, the PDS, and the SCL90R will serve as additional measures of PTSD symptoms and psychological well-being. The CAPS, the IES and the PDS are specifically designed to assess PTSD, and SCL90R is a self-report measure of psychological and psychiatric symptoms. Hebrew versions of all measures will be used in this study.

Degree of psychological distress will be assessed during the course of each experimental (Low or Fully Active Dose MDMA) session with a simple, one-item visual analog scale,

the Subjective Units of Distress. The participant's beliefs concerning his or her condition assignment will be assessed during the non-drug psychotherapy session occurring a day after each experimental session. Neither of these measures will be treated as outcome measures. The first is intended to monitor the participant's emotional state throughout the experimental session, and the second measure will be used to assess the degree to which the blind remains intact.

Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ), administered along with outcome measures two months after the second experimental session. The RRPQ is intended to assess the participant's experience as a research subject, perceived reasons for consenting to be a research participant, and perceived freedom to take part in the study. The RRPQ will not serve as an outcome measure.

A brief description of each measure follows below, including its purpose in the study.

1. Clinician-Administered PTSD Scale (CAPS: Blake et al., 1990). The CAPS is a structured clinical interview designed to assess the seventeen symptoms of PTSD along with eight associated features. The CAPS provides a means to evaluate (a) the frequency and intensity dimensions of each symptom (b) the impact of symptoms on the patient's social and occupational functioning (c) the overall severity of the symptom complex (d) global improvement since baseline and the validity of the ratings obtained. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability (Blake et al, 1990: Nagy et al., 1993). This measure will serve both as a screening measure and as a primary outcome measure.

2. Impact of Event Scale (IES; Horowitz et al, 1979). The Impact of Event Scale is a 15-item self-report scale designed to measure the extent to which a given stressful life event produces subjective distress. Each item, which represents either a symptom of intrusion or avoidance, is rated on a 4-point scale (0, 1, 3, and 5) for the extent to which the item was true for the participant during the past seven days. Scores range from (0) for "not at all" to (5) for "often". The Intrusion subscale, Avoidance scale, and Total IES scores will be used in the analyses. Internal consistency and reliability of the IES has been found to be adequate. IES scores were found to be meaningful in discriminating between psychotherapy patients and non-patients (Zilberg et al. 1982). This measure will serve as an outcome measure.

3. Posttraumatic Diagnostic Scale (PDS; Foa et al. 1993; Foa et al. 1997). The PDS is a 49-item self-report measure assessing presence of PTSD symptoms as described in DSM-IV, including type of traumatic event, length since the event occurred, degree of distress, and presence of intrusive thoughts, avoidance, and hypervigilance. The PDS also assesses duration of symptoms, and degree of impairment. A Cronbach alpha for the symptom severity scale is reported to be 0.92, and 0.91 for the whole scale, and test-retest reliability of 0.74 after two-

week and one month intervals was 0.74. This measure will serve as an additional outcome measure.

4. Reactions to Research Participation-Questionnaire-Short Form (Revised) (Newman and Kaloupek, 2001). This is a 24-item assessment of participants' experience of study participation, reasons for participation, and perceived costs and benefits of participation. The measure contains items addressing participation due to perceived coercion or undue influence by the investigators. A Hebrew translation will be developed for the study.

5. SCID-IV (First et al. 1994). The SCID is a semi-structured interview, typically performed by a psychiatrist that permits accurate diagnosis of lifetime and current psychiatric disorders, using DSM-IV criteria. It will be used as a screening measure only.

6. Participant Beliefs on Condition Assignment: All participants will be asked to indicate whether they believe they have received MDMA or placebo during the experimental sessions. This measure will serve as a means of measuring the success of study blinding for participants and investigators.

7. Subjective Units of Distress. This is a standardized subjective rating scale by which a participant can quickly rate comfort level throughout the session (l-7 scale). The parameters of the scale are explained at study initiations. This measure will serve as a means of safety monitoring during experimental sessions.

8. Symptom Checklist 90: This is a standardized instrument used to measure subjective, feeling states. It gives subscales on several dimensions. This measure will serve as an additional measure of PTSD symptoms.

Methods and Schedule of Events

The study consists of eight conventional (non-drug) psychotherapy sessions, two sessions of MDMA-assisted psychotherapy, and four separate administrations of outcome measures (see Table 2, below). Most non-drug psychotherapy sessions will be scheduled on a weekly basis, and the two experimental sessions will be scheduled two to four weeks apart. The open-label continuation of the study ("Stage 2") will be nearly identical in structure to the active-placebo controlled study except that only one introductory session is scheduled prior to the first experimental session. MDMA-assisted therapy will be performed by Dr. Kotler and a female co-therapist. Both cotherapists will also be present during one of the introductory therapy sessions and during each of the two psychotherapy sessions scheduled to occur 24 hours after each MDMA-assisted psychotherapy session.

After psychiatric and medical screening, a total of 14 visits will occur in the following schedule.

1) The baseline evaluation of PTSD symptoms, expected to last for an hour and a half, will be scheduled to occur between two and four weeks after initial screening. The CAPS will be administered by an independent assessor, and the participant will complete the IES, PDS, and SCL90R.
2) Two sixty-minute introductory psychotherapy sessions will be scheduled approximately a week after baseline evaluation, with both therapist-investigators present at one of the two introductory therapy sessions.
3) The first of two experimental (Low or Fully Active Dose MDMA) sessions, lasting up to eight hours, will be scheduled to occur a week after the second introductory session. Both therapist-investigators are present. Prior to the start of the session, participants will undergo urinary drug screen, and all female participants will undergo a urinary pregnancy screen. Blood pressure, pulse, body temperature and subjective distress will be assessed periodically throughout the session. The participant remains overnight at the clinic after the experimental session is complete.
4) One non-drug sixty to ninety-minute long psychotherapy session, will be scheduled on the morning after the experimental session, with both therapist-investigators present during the psychotherapy. The participant and both investigators will complete the measure of beliefs concerning condition assignment. The participant will return home or to his or her place of residence after this psychotherapy session.
5) One to two sixty-minute non-drug psychotherapy sessions scheduled on a weekly basis will occur between the first and second experimental session with one of the therapist-investigators.
6) The second experimental session will be scheduled to occur two to four weeks after the first experimental session if the participant tolerated the dose of MDMA and if the investigators conclude that the participant can safely undergo the second experimental session. It will also last up to eight hours and include an overnight stay at the clinic. Procedures are identical to those for the first experimental session, including drug and pregnancy screens prior to drug administration, and blood pressure, pulse, body temperature, and subjective distress measured periodically throughout the session.
7) A non-drug psychotherapy session with both therapist-investigators and lasting sixty to ninety minutes will be scheduled for 24 hours after the second experimental session. Participant and investigator beliefs about condition assignment will be assessed.
8) One to two sixty-minute long non-drug therapy sessions will be scheduled to occur on a weekly basis and will follow the same procedures described for non-drug psychotherapy sessions occurring after the first experimental session. The participant will meet with one of the investigators.
9) The second 1.5 hour long evaluation of PTSD symptoms is scheduled to occur eight weeks (two months) after the second experimental session and six weeks after the last non-drug psychotherapy session. The CAPS, IES, PDS and SCL90R will be administered by an independent assessor. Participants will meet with the investigators and will learn their condition assignment. Participants assigned to the Low Dose condition will be given the opportunity to take part in Stage 2 at

this point. They will give written informed consent to take part in Stage 2, with data from this assessment treated as the baseline for Stage 2.

10) The third 1.5 hour long evaluation of PTSD symptoms will be scheduled to occur six months after the second experimental session for all participants in the Fully Active Dose condition and any Low Dose participants who declined to participant in Stage 2. An independent rater administers the CAPS and participants complete the IES, PDS and SCL90R. Participants taking part in "Stage 2" will complete outcome measures six months after the second experimental session in "Stage 2." (see below)
11) The fourth and final 1.5 hour long evaluation of PTSD symptoms will be scheduled to occur one year (12 months) after the second experimental session for all participants in the High Dose condition and any Low Dose participants who declined to take part in Stage 2. The same procedures described above will occur, including administration of CAPS, IES, PDS and SCL90R. The RRPQ will be administered. The participant completes the study. Participants taking part in "Stage 2" will complete outcome measures and the RRPQ 12 months after the second Stage 2 experimental session (see below).

The open-label continuation of the study (Stage 2) is scheduled to begin upon obtaining written informed consent, with outcome measures assessed two months after the second experimental session considered baseline measures for Stage 2. Every participant taking part in Stage 2 will receive two sessions of MDMA-assisted therapy scheduled two to four weeks apart, with all Stage 2 participants will receive an initial dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA. Stage 2 follows the same schedule of events described above, except that participants will undergo only one introductory psychotherapy session. Outcome measures will be administered two, six and twelve months after the second Stage 2 experimental session.

Nature of Psychotherapy and MDMA-Assisted Therapy Sessions:

Introductory Psychotherapy Sessions

The two 60 minute introductory sessions with the therapist-investigators will be used to facilitate the therapeutic alliance, identify the subject's significant issues and concerns, prepare for the experimental sessions, and set goals for the course of the study. As described above and noted on Table 2, both investigators will be present for one of the introductory psychotherapy sessions.

Table 2. Schedule of Events for Stage 1

Time	Pre study	Baseline	Intro Ther 1	Intro Ther 2	**MDMA 1**	24 h post 1	Post 1	Post 2	**MDMA 2**	24 h post 2	Post 3	Post 4	2 mo post MDMA	6 mo post-MDMA	12 mo post MDMA
weeks from start	-4 to -2	0	1	2	3	3 + 1 d	4	5	6	6 + 1 d	7	8	14	30	54
Medical Exam	x												x	x	x
Informed consent	x														
SCID	x														
Metabolic profile, Thyroid Panel	x														
Liver Enzymes	x														
ECG	x														
Urine Drug Screen	x														
Urine Pregancy Screen	x														
CAPS		x											x	x	x
IES		x											x	x	x
PDS		x			x				x				x	x	x
SCL90R		x											x	x	x
RRPQ															x
Nondrug Therapy			x	x		x	x	x		x	x	x	x**		
MDMA Therapy					x				x						
Vital Signs	x				x				x						
SUDS					x				x						
Both therapists present			x*	x*	x	x			x	x					

*Both therapists present at either one of the two introductory sessions.
**A half-hour meeting with the investigators; Participants learn condition assignment.

Experimental Sessions

The experimental treatment sessions themselves will be supervised and facilitated by the male investigator (Dr. Kotler) and a female co-therapist investigator. Both therapists will be present throughout the sessions. The sessions will be conducted following principles and procedures similar to those developed by Stanislav Grof, MD for LSD psychotherapy (Grof, 1980, pp. 123-147) and for Holotropic Breathwork (Grof, 2000: pp. 178-183) and

adapted for MDMA-assisted psychotherapy by Metzner and by Greer and Tolbert (Metzner 1988; Greer & Tolbert 1998). Both therapists will be trained to follow the procedures described in treatment manual for MDMA-assisted psychotherapy in people with PTSD (Ruse et al. 2005). Additionally, the investigators may be trained and certified in Holotropic Breathwork to familiarize them with the experience of and dealing with alterations in consciousness.

The protocols will be exactly the same for each experimental session. All treatment sessions will begin at 10:00 AM and will take place at a suitable research facility available to Dr. Kotler. There will be sufficient equipment for assessing blood pressure, pulse and body temperature, and for dealing with potential adverse events, such as hypertension. The ambient temperature will be kept comfortably cool to decrease the likelihood of hyperthermia. Participants will have had nothing by mouth except alcohol-free liquids since 12 AM on the evening before each experimental session. They will be asked to arrive at 9:00 AM for collection of a urine specimen for drug screening and, for females, a pregnancy test. These results must be negative for the subject to continue in the study. At the beginning of the session, the therapists will discuss with the participant his or her intentions for the session, including intentions regarding working with psychological issues related to their PTSD. Participants will complete the SUD just prior to initial dose administration (25 mg for Low Dose participants and 125 mg for Fully Active Dose participants). After the session begins, participants will lie or recline in a comfortable position with eyes closed or wearing eyeshades if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material (Bonny and Savary 1990; Grof 2000: pp.186-191; Grof 1980; Unkefer 1990). After the first hour, if the participant has not spoken spontaneously, the therapist-investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapist-investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging. The therapist-investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of their inner experience. Electrolyte containing fluids will be available ad lib throughout the session within the limits described under "Monitoring for Toxicity." Food will be available during the latter part of the session. Participants will remain overnight in the clinic or appropriate research facility where the study will be taking place.

Blood pressure and pulse will be measured at the outset of each experimental session, once every 15 minutes for 4 hours, and then every 30 minutes for 2 more hours if the established thresholds for normal blood pressure and pulse have not been exceeded. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. The principle investigator may also call for more frequent measurements of pulse, blood pressure or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of

hypertension, cardiovascular problems or hyperthermia. The SUD will be repeated at 60-90 minute intervals. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

Table 3. Schedule of Procedures and Measures for Experimental Sessions

TIME	**Procedure or Action**
9:00 AM	Urine drug screen and pregnancy test. Participant acclimated to environment
9:45 AM	Baseline BP, Pulse, Temp, Subjective Units of Distress Rating (SUDS)
9:55 AM	2nd Baseline BP, Pulse, SUDS
10:00 AM	Drug Administration, begin audiotaping
10:15 AM	BP, Pulse
10:30 AM	BP, Pulse.
10:45 AM	BP, Pulse
11:00 AM	BP, Pulse, Temp, SUDS
11:15 AM	BP, Pulse
11:30 AM	BP, Pulse
11:45 AM	BP, Pulse
12:00 Noon	BP, Pulse, Temp
12:15 PM	BP, Pulse
12:30 PM	BP, Pulse, SUDS
12:45 PM	BP, Pulse
1:00 PM	BP, Pulse, Temp
1:15 PM	BP, Pulse
1:30 PM	BP, Pulse,
1:45 PM	BP, Pulse
2:00 PM	BP, Pulse, Temp, SUDS
Every half-hour, and as needed	BP, Pulse,
Every 60-90 minutes	SUDS, Temp

Approximately two and a half hours (2.5) hours later, the therapist-investigators will offer the participant the supplemental dose of MDMA. They will only do so if, in their judgment, the participant does not show any signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event. If the participant agrees to take the supplemental dose, then it will be administered with 250 to 300 mL electrolyte-containing beverage. Participants in the Low Dose condition will receive 12.5

mg MDMA, and participants in the Fully Active Dose condition will receive 62.5 mg MDMA.

All experimental sessions will be audiotaped in their entirety**.** Sessions will last from six to eight hours, depending on when the participant feels that he or she has arrived at a point of completeness with the process and on dependent the therapists' determination of the mental and physical state of the participant. Participants will receive a copy of the experimental session recording as soon as one is available.

After approximately eight hours, if all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will end. During the last 30 - 60 minutes of the session, a medical resident or RN will join the participant and investigators in order to become familiar with the participant's state of mind, and any wishes the participant might have in the way of food or activity during the evening. If the participant so desires, an additional designated support person (a spouse, partner, relative or friend) may join in this meeting. After the researchers leave (when they have judged the participant to be emotionally and medically stable), the participant will spend the rest of the evening and night in the clinic or research facility where the MDMA-assisted therapy session will take place. There will be a medical resident or nurse will be on duty during this time. Participants will be encouraged to use much of the time for rest and for a period of reflection and integration in a quiet atmosphere. The participant may request that their designated support person, described above remain with them during the night, but this must first be approved by Dr. Kotler after he has met this support person and has discussed the possible advantages and pitfalls with the study subject.

During the night following the experimental session, the principle investigator will be available to return to the clinic or research facility if requested to do so by the participant or the medical resident or nurse. He will evaluate whether the participant is in need of any further medical intervention and will assist the participant in coping with increased psychological distress if necessary. Throughout the study, Dr. Kotler will remain available to participants via 24-hour pager.

Non-Drug Psychotherapy Conducted 24 Hours Post-Experimental Session

When the researchers return to meet with the participant for the scheduled sixty to ninety-minute therapy session occurring on the following morning, the medical resident or nurse will go off duty. After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual willing or able to take them home, or if the designated person is unable to assist the participant due to unforeseen events, the investigators will assist the participant in finding an alternative means of returning home.

The therapist-investigators and the participant will discuss the experimental session and nay material that arose during the session and will seek to integrate this material. The therapist-investigators will assist the participant in addressing any residual psychological distress he or she is experiencing. The participant and both investigators will complete

measures of their beliefs concerning the participant's condition assignment. The non-drug psychotherapy session can also serve as an opportunity for the therapist-investigators to gather information about the effects of MDMA on the participant in an unstructured manner.

Starting on the day of the non-drug psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone on a daily basis for one week. The investigators will use clinical judgment to assess the psychological well-being of the participant during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study.

Follow-up therapeutic sessions:

During the 60-minute follow-up sessions, participants will be encouraged to describe their experiences during the experimental sessions and to freely express any thoughts, feelings, questions or concerns they have, as was done during the non-drug psychotherapy session 24 hours after each experimental session. The primary purpose of these sessions will be to support the participant in further processing, understanding and integrating the experience.

Outcome Measure Administration

Outcome measures will be administered on four occasions after baseline administration. They will be administered to all participants in both conditions at the start of the study and again two months after the second experimental session. All participants in the Fully Active Dose condition and any participants in the Low Dose condition who are not participating in Stage 2 will complete outcome measures six and twelve months after the second experimental session, and participants in the Low Dose condition taking part in Stage 2 complete outcome measures two, six and twelve months after the second MDMA-assisted session in Stage 2. On each occasion, an independent assessor will administer CAPS, IES, PDS and SCL90R, and scores at each administration will be compared with baseline scores. The assessment of PTSD symptoms and the MDMA-assisted therapy aspects of this project will be kept as separate and distinct as possible. The independent assessor administering and scoring the outcome measures will not be involved in monitoring participants during the medication portion of the protocol. He or she will, therefore, be naïve to complaints of medication side effects. Outcome measures may be administered at the same hospital or research facilities where the MDMA-assisted therapy sessions are performed, or in the offices of the independent assessor. Participants' views on their participation in this study will be assessed on the final administration of outcome measures with the RRPQ.

Open Label Continuation for Active Placebo Subjects ("Stage 2")

After each participant completes all outcome measures on the administration scheduled two months after second experimental session, the participant will have a 30-minute meeting with the principal investigator. During this meeting, the blind will be broken for the individual participant while retaining the blind for the independent assessor. If a participant had received the Low (25 mg followed 2.5 hours later by 12.5 mg) dose of MDMA during the course of the study, she or he would be offered an opportunity to enroll in the open label continuation of the study, referred to as Stage 2. He or she would give written informed consent to take part in this second stage of the study, with consent given separately from the initial consent. If the participant consents to take part in Stage 2 of the study, he or she would receive the Fully Active dose of MDMA (125 mg followed 2.5 hours later by 62.5 mg) during two experimental sessions scheduled two to four weeks apart. Outcome measures administered two months after the second experimental session will serve as baseline measures for Stage 2. The participant would undergo one preparatory non-drug psychotherapy session 1 to 2 weeks prior to the first experimental session, and he or she would receive non-drug psychotherapy follow-up sessions according to the same schedule described for the active placebo controlled study. Procedures for non-drug psychotherapy sessions, experimental sessions, weekly telephone contact and outcome measure administration will be the same as those employed in the first stage of the study. Outcome measure scores gathered during Stage 2 will be compared with the participants' Stage 2 outcome measure scores, but it may be the case that there will not be enough data for formal analysis.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from these doses of MDMA used in this kind of setting is very low. To date, MDMA has been administered to over 245 people in controlled and uncontrolled trials in clinical settings. Phase I studies conducted in the United States and Europe have failed to demonstrate toxicity (Boone et al. unpublished; Cami et al. 2000; Chang et al. 2000; de la Torre 2000a; de la Torre 2000b; Gamma et al. 2000; Frei et al. 2001; Grob et al. unpublished; Grob et al. 1996; Hernandez-Lopez et al. 2003; Lester et al. 2000; Lamers et al. 2004; Liechti and Vollenweider 2000a; Liechti and Vollenweider 2000b; Liechti et al. 2001a: Liechti et al. 2001b; Mas et al. 1999; Navarro et al. 2001; Pacifici et al. 2000; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004; Pichini et al. 2003; Pichini et al. 2002; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004; Segura et al. 2001; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998; Vollenweider et al. 1999). Single doses of up to 2.5 mg/kg were employed in one of the studies conducted in the US (Grob et al. unpublished), with eight participants receiving single doses equal to or exceeding 125 mg MDMA, and with two participants single doses over 187.5 mg during one session (data cited on p. 52 of IND #63,384). In another Phase I study in the US (Tancer and Johanson 2001), over twenty participants were administered doses larger than 125 mg. The same team of researchers administered 2 mg/kg to participants in a subsequent study (Tancer and Johanson 2003), including 9

single doses above 125 mg (Tancer 2003, personal communication to L Jerome, January 17, 2003).

Likewise, psychiatrists in the US and Europe reported using MDMA in a large number of patients before the drug was placed into Schedule I. When describing their experiences (Adamson 1985; Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998), these therapists did not report any severe adverse effects occurring during or after MDMA-assisted psychotherapy sessions

In spite of this reassuring data, we intend to closely monitor closely for the unlikely possibility of an untoward reaction. The sessions will be conducted in a general medical setting where a crash cart and other emergency equipment will be immediately available, medical staff and experienced nurses will be on hand and there will be ready access to specialty medical back up and intensive care beds if necessary. Blood pressure and pulse will be measured at the outset and then once every 15 minutes for 4 hours, and every 30 minutes for 2 more hours. Temperature will be measured at the outset and hourly for 6 hours. The principal investigator may also call for more frequent measurements of pulse, blood pressure, or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of hypertension, cardiovascular problems or hyperthermia. After approximately eight hours, if all medical parameters are acceptable and the patient is alert, ambulatory and emotionally stable, the session will be ended. Participants will have a means of contacting the principal investigator if any problem occurs.

In the unlikely occurrence of an adverse event requiring immediate medical intervention, all participants will be transported to the nearest medical facility.

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Hypertension and related cardiovascular complications:

> Blood pressure and pulse will be measured at the outset of each treatment session, then once every 15 minutes for the first 4 hours, and then every 30 minutes for the next 2 hours. 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 ICU would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. A crash cart will be immediately available and will contain nitroprusside in addition to the usual resuscitation drugs and equipment. This will allow treatment to be instituted without transferring the patient if that should become necessary. The investigator may, at any time, make a clinical judgment to transfer the patient to the ICU for closer monitoring and additional treatment. f

needed, additional care will also be provided by the board-certified emergency room physician and licensed emergency room nurse who will be on standby in the next room.

Any participant who experiences sustained blood pressure of > 220 systolic or > 120 diastolic or heart rate > 75% predicted maximum during the first experimental session will not be given a second experimental session.

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, he or she will undergo a stat ECG, receive oxygen and an IV and will be monitored as described above. If necessary, he or she will be transported to ICU or a location in the hospital where appropriate care can be given. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. 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. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI (J Am Coll Cardiol 34:890, 1999).

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 oxygen and an IV and will be monitored as described above. He or she will be transported to the nearest hospital for a head CT scan and further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3 hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines (Neurology 47:835, 1996).

Psychological Toxicity

During the preparatory sessions, patients 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. Using the

methods described in the treatment manual, every effort will be made to help participants move through difficult symptoms and to 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 zolpidem as a "rescue medication".

The potential for destabilizing psychological distress will be minimized by excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders), by preparing people before the experimental session, by creating an atmosphere of trust during the experimental session, by close monitoring, by daily contact with subjects for the period of a week after the experimental session, and by providing non-drug integrative psychotherapy sessions. Participants will remain at the clinic or research facility for the night after each experimental session. A medical resident or registered nurse will remain on duty and will be able to attend to the participant if there is a need to deal with continued psychological distress.

If, by the end of the 6 to 8 hour experimental 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 (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. A psychiatric nurse, therapeutic assistant or therapist (whose availability we will have arranged ahead of time), will stay with the participant until the time of his or her appointment with 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. Kotler 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 second experimental session and drop the participant from the study. This decision will be made after discussion with the ethics committee and any other appropriate regulatory agency.

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

In the event of a participant's experiencing severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an experimental session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." If a participant should become psychotic or suicidal, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility of their choice. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

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

Hyperthermia:

Body temperature will be taken every 60 to 90 minutes throughout each experimental session. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN, creatinine, glucose, CPK, PT, PTT, platelets and liver enzymes, and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity the participant will be transferred to the nearest ICU.

If, during the first experimental session, a participant's temperature rises more than 1 ° C. and does not rapidly come down after the above adjustments have been made in blankets, clothing, ambient temperature and ventilation, then that participant will not be given a second experimental session.

Dehydration:

In order to avoid dehydration, participants will be encouraged to drink 750 - 1500 ml. of Gatorade or a similar electrolyte-containing fluid during the session depending on their size, level of activity and body temperature.

Hyponatremia

Participants will be given electrolyte solutions such as Gatorade instead of water in order to decrease the likelihood of dilutional hyponatremia. They 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. If there are any signs or symptoms of hyponatremia such as confusion, vomiting, myoclonus or ataxia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, If serum sodium is less than 125mEq/L, serum and urine osmolality and sodium will be measured, and the subject will be transported to the ICU.

If a participant had low serum sodium during the experimental session and exhibited signs of clinically significant hyponatremia, then the principal investigator will not enroll the participant in a second experimental session unless, in the clinical judgment of the investigators, further fluid restriction during the second experimental session would be a sufficient means of preventing hyponatremia.

Liver toxicity:

Liver enzymes will be measured as part of the initial screening visit. Volunteers with preexisting abnormalities will be excluded from the study. If a participant exhibits signs of liver toxicity after the first experimental session, then he or she will not receive a second experimental session.

Neuropsychological toxicity:

Psychological and neurological status will be clinically monitored by the therapists during the MDMA sessions and during therapy sessions at frequent intervals thereafter. If, on clinical examination after the first experimental session, a participant is found to have cognitive deficits that persist for more than two weeks, this participant will not be given a second experimental session.

Chemistry, Manufacturing and Control Information

Drug Product

The drug product is (3,4)-methylenedioxymethamphetamine HCl. As described in the Introductory Statement, MDMA is also referred to as N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C11H15NO2. The drug is a white, crystalline powder. The drug will be administered orally in capsules. Complete details on the chemistry, manufacturing and control of the MDMA HCl to be used are described in US FDA Drug Master file # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was reconfirmed using HPLC in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor in relation to the study of MDMA-assisted psychotherapy in people with posttraumatic stress disorder, the analysis found it to be more than 99.7% pure. There was no evidence of deterioration at that time, 17 years following original synthesis in 1985. Only one lot of MDMA was manufactured.

As described in "Drugs and Dosage" above, MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose 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 Low Dose condition, and the highest dose contained in one capsule will be 125 mg, which is the initial dose offered to participants in the Fully Active Dose condition. Capsules will be prepared in such a way as to prevent investigators and participants from distinguishing contents of a Low Dose capsule from capsules containing Fully Active doses.

Lactose or a similarly inactive substance will be used as the inactive compound used in admixture with MDMA to ensure that all doses will be of the same weight.

MDMA will be handled in accordance with all federal, hospital and university regulations, and forms pertaining to the use of scheduled substances will be maintained by the investigators. If stored in the pharmacy, only the compounding pharmacist will have direct access to the drug product, and the pharmacist will provide the therapist-investigators with the drug product upon request. If stored within the clinic or research facility where the experimental sessions will occur, MDMA will be stored in an alarmed, locked safe and only the therapist-investigators will have access to the drug product.

Environmental Analysis Requirements

MAPS claims categorical exclusion from the requirement to submit an environmental assessment (21 CFR 25.15[a]). MAPS claims categorical exclusion (under 21 CFR 25.31[e]) for the study under this IND. To its knowledge, no extraordinary circumstances exist.

Pharmacology And Toxicology

Primary Pharmacodynamics

Mechanisms of Action

MDMA interacts with plasma monoamine transporters and storage vesicles to increase extracellular levels of 5-HT, dopamine, and norepinephrine (Cozzi et al. 1999; Fitzgerald and Reid 1990; Gudelsky and Nash 1996; 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-HT_{2A} receptors and α-2 adrenoceptors also contributes to MDMA's effects. For example, dopamine release is also indirectly increased by MDMA stimulation of 5-HT_{2A} receptors on GABAergic striatonigral neurons (Gudelsky and Nash 1996; Koch and Galloway 1997; Palfreyman et al. 1993; Schmidt et al. 1992; Yamamoto et al. 1995).

Although the specific mechanisms of MDMA's therapeutic effects are not fully understood, several observations and hypotheses can be made. Increased extracellular levels of dopamine and norepinephrine are known to be important to the reinforcing effects of psychostimulants (Ritz and Kuhar 1993; Rothman et al. 2001; Wise and Bozarth 1985). These neurotransmitters likely play a similar role with MDMA, producing feelings of excitement, euphoria, and well-being. When the D_2 receptor antagonist haloperidol was combined with MDMA, human volunteers reported less positive mood and greater anxiety (Liechti and Vollenweider 2000a), findings in keeping with these hypotheses. Central dopamine and norepinephrine are also thought to regulate readiness for action and arousal, with dopamine possibly mediating behavioral readiness, and locus coeruleus norepinephrine mediating conscious registration of external stimuli (Clark et al. 1987; Robbins and Everitt 2000). Increasing these neurotransmitters may therefore place the individual in a state of alertness that is ideal for recalling or even re-experiencing state-dependent memories of stressful events. This potentially aversive state may be modified by MDMA effects on both the serotonergic system and postsynaptic α-2 adrenoceptors.

MDMA effects on the serotonergic system are likely important for its therapeutic effects. MDMA induces 5-HT release and is a 5-HT2 agonist. Serotonergic dysfunction is associated with anxiety, aggression, and depression. Increasing 5-HT release is thought to have opposite effects. For example, stimulation of 5-HT_{1A} and 5-HT_{1B} receptors decreases anxiety and aggression in rodent behavioral studies (Brunner and Hen 1997; Graeff et al. 1996) and likely contributes to reduced defensiveness and increased self-confidence reported after MDMA. 5-HT_{1A} receptors in the hippocampus have also been specifically hypothesized to enable disengaging from previously learned associations if they lead to adverse outcomes (Guimaraes et al. 1993). MDMA also has moderate 5-HT_{2A} activity (Nash et al. 1994), which leads to modest alterations in perception of meaning (Liechti et al. 2000b), possibly facilitating new ways of thinking. Case reports suggest increasing extracellular 5-HT levels may facilitate recovery of remote memories (Robertson 1997), a phenomenon that has been reported by psychotherapists

administering MDMA to patients (Downing 1985). Studies in humans suggest that serotonergic activity plays an important role in generating the subjective effects of MDMA, since co-administration of a serotonin uptake inhibitor reduces most subjective effects (Liechti et al. 2000a; Tancer and Johanson 2004). Thus, MDMA effects on the serotonergic system may decrease anxiety and aggression and create a state of mind that is conducive to psychotherapy.

Direct MDMA stimulation of postsynaptic α-2 adrenoceptors may modify this state by altering the balance of α-1 and α-2 stimulation, allowing the individual to remain emotionally calm despite noradrenergic activation. MDMA is an α-2 agonist (Lavelle et al. 1999). Like other α-2 agonists, such as guanfacine and clonidine (Arnsten 1998), MDMA produces feelings of calmness and relaxation (Cami et al. 2000). It is worth noting that open label trials suggest that clonidine may be helpful for treating symptoms of PTSD (Harmon and Riggs 1996; Kinzie and Leung 1989), indicating that α-adrenergic action may possess anxiolytic effects in humans.

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 1998; 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. 2000; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998). These effects make it likely that MDMA would be useful in psychotherapeutic treatment of many different complaints.

The subject population of chronic PTSD patients was selected because of patient testimonials concerning the effectiveness of MDMA-assisted therapy and because the effects of MDMA have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value, and early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. Downing (1985) testified that MDMA was very helpful in treating a woman who experienced incapacitating panic attacks after sexual assault. Anecdotal reports have been published of improvement in PTSD among people who took MDMA in therapeutic or quasi-therapeutic settings (Adamson 1985). These reports are consistent with the observations of other therapists that MDMA-assisted psychotherapy is particularly useful in patients with a history of child abuse or sexual assault (Greer 1985). Preliminary results were encouraging in a pilot study of MDMA treatment for 20 soldiers with combat-related PTSD, but political instability in Nicaragua prevented further research (Doblin 1995). In 2000, a currently ongoing MDMA/PTSD therapy study was approved in Spain (AEM #99-309).

PTSD causes a great deal of suffering, impairing work productivity, relationships, and overall health. PTSD is also a disorder for which there is, to date, only one FDA-approved medication with efficacy only reported in one gender (women). There are still many unanswered questions regarding this pharmacological intervention. (Montgomery and Beck 1999). The lifetime prevalence of PTSD in the general population may be as high as 10% (Meltzer-Brody et al. 2000), so the search for additional and more effective treatments is extremely important. The terrible burden that PTSD places on patients, lack of effective treatments, and high prevalence of PTSD lend the proposed research considerable importance.

Secondary Pharmacodynamics

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure (Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2001, Tancer and Johanson 2003 and see pp 44-48 of IND #63,384). Physiological effects of MDMA reach their maximum within 1 and 2 hrs after oral MDMA administration and have largely subsided within 6 hrs of drug administration (Gamma et al. 2000; Lester et al. 2000; Mas et al. 1999; Tancer and Johanson 2003; Vollenweider et al. 1998, 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 the Investigators' Brochure. Data from more recent reports (e.g. Farre et al. 2004; Hernandez-Lopez et al. 2002; Lamers et al. 2003; Tancer and Johanson 2003) are similar to data collected in previous reports. Pre-treatment a serotonin uptake inhibitor attenuated or prevented elevations in blood pressure and heart rate (Liechti and Vollenweider 2000), and the $5HT_{2A}$ receptor antagonist ketanserin reduced elevated diastolic pressure (Liechti et al. 2000a), while the D_2 antagonist haloperidol failed to attenuate any of the cardiovascular effects of MDMA (Liechti et al. 2000b). 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; Lester et al. 2000; Liechti et al. 2000b; Tancer and Johanson 2003), with the increase undetected in a number of studies (Farre et al. 2004; de la Torre et al. 2000; Liechti et al. 2000a).

On the basis of data from human studies of physiological effects, an initial dose of 25 mg is expected to have a minimal impact on blood pressure, heart rate, or body temperature, and effects are also expected to be minimal after a total dose of 37.5 mg MDMA, though findings from at least one study suggest that this dose might produce detectable increases in tension and relaxation (Harris et al. 2002). Both the initial dose of 83.3 mg and 125 mg, which will serve as the total dose during the first session and the initial dose on the second session, are similar or identical to the dose used in the study of MDMA-assisted therapy in people with PTSD (IND #63,384). These doses are expected to produce significant increases in blood pressure and heart rate, but are not expected to produce sustained increases in heart rate or blood pressure above 170/100 mm Hg. There is no data from controlled studies on the effects of 187.5 mg MDMA, the total dose for the second experimental session. It is expected that elevation in blood pressure and heart rate

may be greater than the elevation seen after 125 mg, but with the increase in blood pressure and heart rate not greatly exceeding the elevation reported after 2.5 mg/kg MDMA. The physiological effects of a second dose of MDMA that is half the original dose and given two and a half hours after the first dose are not yet known. Administering a second dose of 100 mg MDMA a day after an initial 100 mg dose increased systolic blood pressure, diastolic blood pressure and heart rate to levels greater than seen after the initial dose, but not significantly greater.

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocortictropic hormone concentrations (Farre et al. 2004; Grob et al. 1996; Grob et al. Unpublished; Harris et al. 2002; Mas et al. 1999; Pacifici et al. 2004; Tancer and Johanson 2003), 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. 2001), and a dose of 100 mg MDMA given 24 hours after an initial dose stimulated a greater release of cortisol, but not prolactin (Farre et al. 2004). In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA (Harris et al. 2002), with DHEA levels peaking 2 to 3 h post-drug. Harris and colleagues failed to detect any changes in luteinizing hormone (LH), estradiol, progesterone or follicle stimulating hormone (FSH) in women participants. 40 mg MDMA acutely increased circulating levels of antidiuretic hormone (arginine vasopressin) in eight male volunteers (Forsling et al. 2001; Henry et al. 1998). Antidiuretic hormone reached maximum levels between 1 to 2 hours after MDMA administration. Increased retention of fluid is unlikely to be of any consequences in a clinical setting. Nonetheless, precautions will be taken to avoid dilutional hyponatremia, including providing electrolyte-containing beverages and restrictions on fluid consumption.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifici et al. 1999;; Pacifici et al. 2000; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutin A-induced lymphocyte proliferation. MDMA decreased levels of the immune system stimulating and proinflammatory cytokine interleukin 2 (IL-2) and increased levels of the immunosuppressive and anti-inflammatory cytokine interleukin 10 (IL-10) (Pacifici et al. 2004; Pacifici et al. 2001). Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase the amount of Th2 cytokines measured in blood. 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. 2001; 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. These acute changes are unlikely to

be of consequence in healthy individuals and are of a similar magnitude to changes produced by other pharmacological agents. 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. 2001). The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity, and activity at alpha adrenergic receptors (Connor et al. 2004). Serotonin release probably plays a role in these changes, since paroxetine pretreatment attenuates and in some cases completely eliminated the immunological effects of MDMA (Pacifici et al. 2004) while only partially reducing elevated cortisol levels after MDMA. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 1998; Connor et al. 2000a; Connor et al. 2000b; Connor et al. 2004). This immunomodulation is an acute effect of MDMA and is not likely to persist for more than 48 hours after MDMA administration.

Safety Pharmacology

Neurological Effects

In clinical studies, doses of MDMA similar to that currently proposed (125 mg) have led to acute neurological changes such as impaired gait, tremor, or nystagmus in a minority of volunteers. The incidence of these effects in clinical MDMA studies is summarized in Tables 2.2 to 2.4 in the Investigators' Brochure. Studies published subsequent to the Investigator's Brochure found similar effects, as reviewed in the first and second updates to the Investigator's Brochure. These effects resolve within several hours. Lasting neurological effects have not been noted.

MDMA appears to produce modest acute changes in neurocognitive performance during peak drug effects. The acute effects of MDMA, generally at doses of either 125 mg or 1.7 mg/kg, have been assessed using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000; Hernandez-Lopez et al. 2002), a continuous performance attention task (Gamma et al. 2000), the Stroop task (Vollenweider et al. 1998), and a prepulse inhibition measure of sensorimotor gating (Liechti et al. 2001b; Vollenweider et al. 1999b). Of these tasks, only the digit symbol substitution task and the prepulse inhibition task have detected MDMA-induced performance alterations. A study employing the slightly lower dose of 75 mg assessed skills potentially used in driving motor vehicles (Lamers et al. 2003), including visual tracking, divided attention, Object Estimation Under Divided Attention (OMEDA), the Tower of London, and verbal fluency (word generation). Seventy-five mg MDMA did not affect performance on most of the tasks listed above except for the estimation of time needed for a temporarily hidden object to move from one place to another.

Participation in clinical MDMA studies has not been associated with chronic alterations in neurocognitive performance. Data collected by Grob and associates (described in "Previous Human Experience" below) and by Vollenweider and colleagues (Ludewig et al. 2003; Vollenweider et al, 2000, see also pp. 189-190 for IND #63,384) indicate that performance on tests of neurocognitive function is not altered after receiving one or two

doses of MDMA in a clinical setting. In contrast, studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance, specifically in the areas of memory and executive function (planning and decision making). While a majority of studies have detected these differences (see the Investigator's Brochure and subsequent updates (Baggott et al. 2001; Baggott and Jerome 2003; Jerome 2004 for a detailed discussion), not all studies have detected lower cognitive performance in ecstasy users. A number of studies employing more appropriately matched controls (Halpern et al. 2004; Thomasius et al. 2003) have tended to find fewer differences in cognitive function, with Halpern and colleagues failing to find impaired verbal memory even in ecstasy users reporting use on 50 or more occasions, indicating that differences detected in earlier studies were at least partially due to use of other drugs, or factors associated with polysubstance use. Subtle but detectable impairments in cognitive function may also appear in people reporting heavy use of ecstasy (Back-Madruga et al. 2004; Bolla et al. 1998; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004). In a retrospective study finding impairment in very high dose recreational users of ecstasy, there was no effect seen among those who had taken up to an estimated 440 mg of "ecstasy" per month for a year or longer and had used it a minimum of 25 times (unpublished table from published study, Bolla et al. 1998). A recent study employing samples of ecstasy users and non-ecstasy users well-matched for moderate use of other substances detected impaired information processing and executive function in people who reported taking ecstasy on 50 or more occasions, but not in people who reported taking ecstasy on fewer than 50 occasions (Halpern et al. 2004). Another study detected impaired memory in ecstasy users who had consumed at least 80 ecstasy tablets over a lifetime, but failed to detect memory impairment in ecstasy users who had taken fewer than 80 tablets (Gouzoulis-Mayfrank et al. 2003).

An examination of the literature relating to ecstasy use and signs and symptoms of anxiety, depression, and other psychiatric symptoms found inconclusive support for increased psychopathology or psychological difficulties in ecstasy users. A number of recent investigations failed to support claims that ecstasy use is uniquely associated with increases in psychological problems. Increased rates of psychiatric symptoms or psychological difficulties in ecstasy users appear to be more strongly associated with polysubstance use or with pre-existing conditions associated with drug use (see for example Dafters et al. 2004; Daumann et al. 2004; Daumann et al. 2001; Lieb et al. 2002; Thomasius et al. 2003). Given the tenuous link between repeated ecstasy use and psychiatric symptoms, it is not expected that two doses of MDMA will have any effects upon subsequent psychological well-being.

Clinical studies have investigated the effects of MDMA on cerebral blood flow. MDMA acutely alters regional cerebral blood flow (rCBF) and may decrease rCBF for several weeks after drug exposure. Gamma et al. (2000a) used [H2 15O]-Positron Emission Tomography (PET) to measure rCBF at 75 min after 1.7 mg/kg MDMA in 16 volunteers. They detected increases in prefrontal, inferior temporal, and cerebellar cortex rCBF. Decreased rCBF was detected in limbic, paralimbic, central frontal, and temporal areas. These acute effects of MDMA on rCBF may be followed by decreases in rCBF (Chang et al. 2000), as found in a study where SPECT was performed upon eight volunteers 10 to

21 days after receiving the second of two doses of MDMA administered in a clinical setting. These decreases appeared to be time-limited. Two additional volunteers assessed at 41 and 80 days after last MDMA exposure did not show decreases. Similarly, Gamma et al. did not detect differences in cerebral blood flow between ecstasy users and nonusers during a vigilance task (Gamma et al. 2001). Finally, in the study of acute changes in rCBF (Gamma et al. 2000), the eight volunteers who received 1.7 mg/kg MDMA in their first session did not have altered cerebral blood flow in their second session, which was conducted at least two weeks later (Vollenweider 2001, letter of support, pp. 189-190, Mithoefer and Wagner 2001; IND #63,384).

Cardiovascular Effects

The acute cardiovascular effects of MDMA were investigated by Lester et al. (2000). 8 volunteers were administered placebo, 0.5 mg/kg, and 1.5 mg/kg (approximately 105 mg) MDMA in a three session placebo-controlled, double blind study. Two-dimensional Doppler echocardiograms were performed one hour after MDMA administration. MDMA was well tolerated and produced hemodynamic effects similar in magnitude to the α-agonist dobutamine, 40 mcg/kg per minute intravenously. As discussed above, the dose-dependent effects of up to 2.5 mg/kg (approximately 175 mg) MDMA on heart rate and blood pressure have been characterized by five different research groups, including three in the United States.

In vitro studies of human heart cells demonstrate that MDMA activates 5-$HT2_B$ receptors, which stimulate heart valve cell growth (Setola et al. 2003). 5-$HT2_B$ receptor agonism is associated with increased incidence of heart valve disease associated with the serotonin releaser fenfluramine (Rothman and Baumann 2002). However, only fenfluramine and its metabolite dexfenfluramine produced statistically significant increases in heart valve cell growth. It is also important to note that valvular heart disease is associated with daily use of fenfluramine, whereas MDMA will not be administered on a daily basis in this study.

Abuse Liability

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as “rave” dance parties. It should be noted that instead of experiencing euphoria, individuals undergoing MDMA-assisted psychotherapy are likely to experience deeply emotional thoughts, feelings, and memories, including thoughts associated with grief, rage, and fear. As a result, it seems unlikely that people undergoing this emotionally challenging psychotherapy will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings.

Healthy drug-naïve volunteers exposed to MDMA in previous Phase 1 clinical studies with MDMA have been not been motivated to seek out and use MDMA in non-medical settings. Liechti et al. (2001) reviewed the effects of MDMA in 54 male and 20 female volunteers who had participated in clinical studies and stated “none of the participants

expressed any interest in taking MDMA as a recreational drug" after participation in an MDMA study.

In the currently proposed study, diversion is not an issue because MDMA will only be administered under supervision of a research psychiatrist and no take-home doses will be permitted. As discussed elsewhere, MDMA will be stored and handled in compliance with Federal and local regulations for Schedule I compounds. The issue of abuse liability is discussed in more detail in this application under "Additional Information."

Pharmacokinetics/Toxicokinetics

Summary of Pharmacokinetic Parameters

Table 4. MDMA Pharmacokinetics

MDMA Dose	**N**	**Cmax** *μg/l*	**Tmax** *H*	**AUC $_{0-24}$** *μg*h/l*	**AUC/dose** *μg*h/(l*mg)*	**Reference**
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8 .6	Mas et al. 1999
75	12	178 (no SD)	3	Not reported	NA	Lamers et al. 2003
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	24.31 ± 7.7	de la Torre et al. 2000b
100	9	180 ± 33	2 ± 0.26	1452 ± 771	14.52 ± 7.7	Farre et al. 2004
100	7	208.7 ± 17.1	16 ± 0.4	Not reported	NA	Pizarro et al. 2004
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	de la Torre et al. 2000a

MDMA Dose	**N**	**k_a** */h*	**k_e** */h*	**$T_{1/2}$** *H*	**MDA $T_{1/2a}$** *H*	**Reference**
50	2	Na	na	2.7 and 5.1	Na	de la Torre et al. 2000b
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.7 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	De la Torre et al. 2000b
100	7	na	0.07 ± 0.03	11.8 ± 4.4	na	Pizarro et al. 2004
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	De la Torre et al. 2000a

The pharmacokinetics of MDMA, summarized above in Table 4, have been primarily characterized by a group of Spanish researchers, 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).

As can be seen in Table 4, 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_{max} was 232.± 39 μ/L, $AUC_{(24-48)}$ was 2564 ± 762 μg/*h/L, $T_{max(24-48)}$ was 25.5 ± 0.33 h, and AUC/dose was 25.64 ± 7.6 μg/*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), and probably results from non-linear pharmacokinetics. Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly higher maximal values than expected after the supplemental dose only or the combined dose, or whether it will instead lengthen T_{max}.

Absorption/Distribution/Metabolism/Excretion

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 which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called alpha-methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la

Torre et al. 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).

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 (de la Torre et al. 2000; Kraemer and Maurer 2002; Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylenation, including CY1A2 and CYP3A4.

Although it was hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, this is no longer a concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Heydari et al. 2004; 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. This is likely the result of inhibition of CYP2D6-mediated DHMA formation. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant. In fact, there currently seems to be no evidence that the poor metabolizer genotype is by itself a major risk factor for acute MDMA toxicity. Kreth et al. (2000) reported that the poor metabolizer trait did not lead to significant alteration in maximal drug plasma concentrations in an individual participating in a clinical study of the MDMA analogue, MDE. At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (Pacifici et al. 2002, see also Pacifici et al. 2004) 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. Issues involved in MDMA metabolism is addressed in a review by de la Torre and colleagues (De la Torre et al. 2004). Evidence from in vitro and in vivo studies and the cases described above provide further evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor for immunocompetent individuals participating in clinical research with MDMA.

Enzymes involved in the formation of MDA from MDMA in human liver microsomes have been investigated by two groups (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their experiments. Kreth et al., in a publication focusing on MDE metabolism, reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome

CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

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

Table 5. Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

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

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Segura et al. 2001; Pizarro et al. 2004; Pizarro et al. 2003). Urinary excretion of the MDMA metabolite HHMA reported after the administration of 100 mg MDMA to four men are

91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Toxicology

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

Serious MDMA toxicity is rare in uncontrolled settings, considering the millions of users taking "ecstasy" of unknown identity, potency, and purity (Baggott 2002; Gore 1999; Henry and Rella 2001). Under these conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) in an area with a high ambient temperature. Reports of toxicity in illicit ecstasy users are summarized in the Investigator's Brochure (Baggott et al. 2001), and a brief review of more recent reports are covered in the latest update of the Investigator's Brochure (Jerome 2004). In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hepatotoxicity, and hyponatremia. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events, as discussed in "Monitoring for Toxicity," above. As described in "Previous Human Experience" below, exposure to MDMA in a controlled clinical setting has not been associated with toxicity. As well, improvement in quality of life occurring after MDMA-assisted psychotherapy should be weighed out against any concerns of MDMA toxicity.

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. Neurotoxicity will be discussed in two sections; the first concerning serotonergic axon damage and the second concerning neuronal cell death. Finally, the issue of reproductive and developmental toxicity will be briefly mentioned.

<u>Hyperthermia</u>

As discussed above, MDMA administered in a controlled setting produces only a slight increase in body temperature. However, hyperthermia is one of the most commonly reported serious adverse events in ecstasy users. Peripheral vasoconstriction (Pedersen and Blessing 2002), non-shivering heat production and possible effects on heat-production related uncoupling proteins (Mills et al. 2003; Sprague et al. 2003), and activity at serotonin or norepinephrine receptors (Fantegrossi et al. 2003; Fantegrossi et al. 2004) all may play a role in generating hyperthermia. 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). Studies in rats and mice suggest that crowded housing (Fantegrossi et al. 2003) and high ambient temperature (see for example Brown and Kiyatkin 2004; Green et al. 2004; Malberg et al. 1998) promotes a hyperthermic reaction to MDMA. It is expected that hyperthermia will be very unlikely in the proposed study setting, since the participant will be in a room maintained at a comfortable temperature and he or she will not experience crowding. The investigators will periodically measure body temperature with an automatic temperature sensor and telemetry device worn on the skin, and the investigators will also measure ambient temperature during the course of the study.

Hepatotoxicity

Because hepatotoxicity has been noted in ecstasy users, five *in vitro* and two *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that MDMA can impair liver cell viability, but that this is very unlikely to occur in the proposed clinical study. The 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.

In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one, hour incubation with 0.1 mM MDMA). A second *in vitro* study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the collagen characteristics of a fibrotic liver. Expression of α1(I) procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA for 8 h did not increase mRNA expression. A third *in vitro* study using mouse hepatocytes showed that MDMA increases lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability, yet it did not affect lipid peroxidation over 60 to 180 min under normothermic (37º C) conditions. When temperature was raised to 41º C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41º C but not at 37º C. The fourth study incubated rat liver cells with 0.5 to 5 mM MDMA for 8 or 24 hours and assayed for apoptosis with cell staining, Western blot for apoptosis-related factors, and bax assays (Montiel-Duarte et al. 2002). Higher concentrations increased signs of apoptosis, but at doses that are about eleven times those usually seen in humans. The fifth study examined the effects of 3 hours of incubation with 0.8 to 1.6 mM MDMA metabolites MDA and alpha-MeDA on liver cells (Carvalho et al. 2003) and found that alpha-MeDA but not MDA increased signs of liver peroxidation at the higher concentrations.

In vivo studies in mice indicate that ambient temperature and oxidative stress may be involved in liver toxicity. Carvalho and colleagues assayed liver sections from mice given a single i.p. injection of 5, 10 or 20 mg/kg MDMA in either a 20 ºC or a 30 ºC environment for antioxidant enzyme levels, signs of lipid peroxidation, and cell histology (Carvalho et al. 2002). The researchers found that increases in MDMA dose and ambient temperature during MDMA administration affected degree of apparent oxidative stress and detectable liver abnormalities. In the second study, repeated injections of 10 mg/kg, but not 5 mg/kg, of the MDMA enantiomer S-(+)-MDMA (4 s.c. every 2 h), produced some hepatic necrosis (Johnson et al. 2002), with more pronounced effects in mice fed a vitamin E deficient diet than in mice receiving sufficient amounts of vitamin E.

Hepatotoxicity has not yet been reported to occur in any of the clinical studies where MDMA was administered to research subjects, and the drug exposures that can damage liver cells would not occur in the currently proposed clinical study. The lowest concentration that impaired cell functioning in these studies (0.1mM or ~19.3 mg/l MDMA) affected indices of cell viability after 24, but not 6, hours in the study by Beitia et al (2000). This same concentration had no significant pro-fibrogenic effect after 24 hr in the study by Varela-Rey et al (1999). This lowest toxic concentration is approximately 82 times higher than the expected peak MDMA plasma level (236.4 ± 57.97 µg/l MDMA) after 125 mg, the proposed dose in this study. Liver exposure to drugs is often higher than plasma levels. In an autopsy of a deceased ecstasy user, liver MDMA concentration was 7.2 times higher than femoral blood MDMA concentration (Rohrig and Prouty 1992). Thus, the peak liver exposure to MDMA in a clinical setting should be approximately one-eleventh the concentration shown to impair cell viability in these studies. This peak concentration would only be briefly sustained. Therefore it is unlikely that MDMA exposures in clinical studies will approach those demonstrated in these studies to impair rat liver cell viability or induce procollagen mRNA. Higher ambient temperatures appear to amplify the degree and likelihood of hepatotoxicity, and since study participants will receive MDMA in a comfortable room and the investigators will monitor ambient temperature during the course of the study, it seems especially unlikely that MDMA will induce hepatotoxicity. Nonetheless, people with significant liver disease will be excluded from the study, and participants will be monitored for hepatotoxicity with liver panels performed before MDMA administration and at the time of medical examination follow-up ("Day 36" – see Table 1 above).

Neurotoxicity

Extensive studies in animals indicate that high or repeated dose MDMA exposure can oxidatively damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem. 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 is discussed in more

detail in the Investigator's Brochure and subsequent updates of the Investigator's Brochure (Baggott et al. 2001; Baggott and Jerome 2003; Jerome 2004).

A study published in 2004 comparing MDMA administration (3 7.5 mg/kg doses given i.p.) with the serotonin neurotoxin 5,7-DHT in rats found that DHT, but not MDMA, reduced serotonin transporter and brain serotonin while increasing levels of glial fibrillary acidic protein (GFAP), a marker of neuronal injury (Wang et al. 2004). MDMA lowered brain serotonin without altering levels of serotonin transporter or GFAP, suggesting a dissociation between brain serotonin levels and other presumed markers of neurotoxicity, and an investigation of neurons from the substantia nigra of mice given four 5 mg/kg doses every 2 hours found signs of oxidative stress, such as increased signs of DNA fragmentation and ubiquitin-positive whorls, but no signs of cell death (Fornai et al. 2003). However, in contrast, raphe neurons taken three weeks after rats received twice-daily s.c. doses of MDMA on four consecutive days were much less able to transport radioactively labeled praline, used as a measure of axonal neurotoxicity (Callahan et al. 2001). Examining and considering these and other research findings continues to demonstrate the contentious nature of findings relating to MDMA neurotoxicity.

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 in previous clinical MDMA studies. A series of letters in the journal *Neuropsychopharmacology* discussed the risks of neurotoxicity in MDMA studies (Gijsman et al. 1999; Lieberman and Aghajanian 1999; McCann and Ricaurte 2001; Vollenweider et al. 1999a; Vollenweider et al. 2001), leading two of the journal editors to conclude that there is no evidence that the MDMA exposures in the studies of Vollenweider and colleagues (similar to those currently proposed) were neurotoxic (Aghajanian and Lieberman 2001). Finally, studies in rhesus monkeys suggest that use of interspecies scaling to arrive at dosing in previous studies produced inappropriately high doses of MDMA.

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [^{11}C]McN5652 before and after a single clinical MDMA exposure (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 additional volunteers (n = 8). This ligand and measurement technique had been previously reported by another group to be sensitive to apparent serotonin transporter changes in illicit ecstasy users with at least 70 drug exposures (McCann et al. 1998). 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. A more recent study in humans that employed this ligand also found reduced levels of serotonin transporter in current ecstasy users, but did not report as large a reduction in serotonin transporter as did the original study (Buchert et al. 2003; Buchert et al. 2004). Given the small sample size

in the study by Vollenweider et al., it is possible that a modest change in SERT density could have gone undetected. However, very little variance in ligand binding was found in baseline measures of ligand binding.

Imaging studies in repeated ecstasy users have consistently found lower serotonin transporter levels, but these findings are also qualified by degree of exposure and period of abstinence. One study using the same ligand used by McCann and colleagues (Buchert et al. 2003; Buchert et al. 2004) and one study using a different ligand (Reneman et al. 2001) both found that serotonin transporter levels returned to normal in people who abstained from ecstasy for a year to a year and a half. Both studies also found greater reductions in serotonin transporter, greater numbers of affected areas, in women. Reneman and colleagues (2001) also compared people reporting at least 50 exposures with people who reported fewer than 50 exposures, and they found that moderate ecstasy users (those reporting use on fewer than 50 occasions) did not have significant reductions in serotonin transporter sites. These findings suggest that effects on serotonin transporter may be at least partly dependent on degree of use and time since last exposure.

Because of findings in humans and non-human animals, the possibility of neurotoxicity will be discussed with all volunteers, even though strong evidence from studies in humans and non-human animals suggests that the risk of neurotoxicity posed by participating in this study is low.

Interspecies pharmacokinetic comparisons support the safety of 125 mg MDMA in humans. Vollenweider et al. (2001) compare published pharmacokinetic data for humans and rats and conclude that human exposure to MDMA after 125 mg is significantly less than the lowest known consistently neurotoxic MDMA dose in Sprague-Dawley rats, 20 mg/kg, sc, (Battaglia et al. 1988; Commins et al. 1987). At these doses, human MDMA plasma AUC are approximately 30% of the rat AUC. Similarly, human Cmax are approximately 10% of rat Cmax.

We note that this comparison is limited by several considerations. First, it is not known whether rats and humans have different vulnerability to the same MDMA exposure. Second, it is not known whether metabolites of MDMA contribute to neurotoxicity. If they do, then the margin of safety for 125 mg MDMA should be even wider because formation of metabolites is more extensive in rodents than in humans. Third, rats and humans may differ in the brain concentration of drug produced by a given blood concentration. In rats, MDMA concentrations in the brain are 7 to 10 times higher than in plasma (Chu et al. 1996). In a human fatality, postmortem MDMA concentrations were about 6 times higher in the brain than in the plasma (Rohrig and Prouty 1992), although postmortem drug redistribution may have occurred. If these data are reliable, rats may have similar peak brain levels to humans when plasma levels are the same. Fourth, neurotoxicity in rodents appears to be increased by hyperthermia in many studies. Finally, the threshold for neurotoxicity is not well established in rats. The threshold for neurotoxicity in Sprague-Dawley rats appears to be above 10 mg/kg (Battaglia et al. 1988) and below 20 mg/kg (Commins et al. 1987). Therefore, a conservative comparison indicates that human MDMA exposure (measured as plasma AUC) after 125 mg is likely

between 30% and 60% of the exposure required for neurotoxicity in rats. Because of non-linear pharmacokinetics and possible differences in rat versus human MDMA disposition, at least one researcher has concluded that using interspecies scaling is not recommended for calculating equivalent doses in neurotoxicity studies (De la Torre and Farre 2004). We think that the margin of safety is probably wider due to the presence of hyperthermia and increased formation of toxic metabolites in animal studies but not in clinical MDMA trials.

In conclusion, the lack of apparent toxicity in previous clinical MDMA studies, evidence of unaltered serotonin transporter density after similar doses, and toxicokinetic comparisons suggest that the doses of MDMA used in this study are unlikely to produce measurable neurotoxicity or significant adverse functional consequences.

MDMA-Induced Neuronal Apoptosis (Programmed Cell Death)

Two *in vitro* studies have suggested that MDMA may trigger programmed neuronal cell death (apoptosis) under certain conditions. This phenomenon has not been verified *in vivo*. No cell death occurs in regions containing the cell bodies of serotonergic neurons after MDMA exposure (Fischer et al. 1995; Hatzidimitriou et al. 1999; O'Hearn et al. 1988). However, one study detected evidence of non-serotonergic cell body damage in the rat somatosensory cortex after 80 mg/kg MDMA (Commins et al. 1987). It is theoretically possible that this damage was due to apoptosis. MDMA-induced apoptosis appears to require high concentrations and exposure times. It is unlikely that 125 mg MDMA in the currently proposed clinical study will trigger programmed cell death in neurons. In the currently proposed study, the peak brain concentration of MDMA is estimated to be approximately 6% of a concentration that produced no toxicity after 96 hr of exposure *in vitro*.

Forty-eight hours of incubation with MDMA dose-dependently decreased survival of cultured human placental serotonergic cells (Simantov and Tauber 1997). This decreased cell viability was accompanied by DNA fragmentation and cell cycle arrest (in the G2M phase). Forty-eight hour exposure to 0.4 mM MDMA decreased cell survival by 1.4 ± 4%, while 1.2 mM MDMA decreased cell survival by 61 ± 9%. In another study, the effects of MDMA on cultured rat neocortical neurons were studied at concentrations of 125 to 1000 μM MDMA and exposure times of 1, 24, and 96 hours (Stumm et al. 1999). Cell survival was decreased by 34.2 ± 11.4% at 96 hours after an average exposure of 500 μM MDMA, but not after 125 μM MDMA. Stumm et al. also noted DNA fragmentation and altered expression of the bcl-xLS gene, which supports the interpretation that programmed cell death had occurred. The degree of cytotoxicity noted for MDMA in this study was comparable to the toxicity produced by other structurally related amphetamines.

A study that used fluoro-jade staining to examine brain sections from rats killed 3 days after receiving 10, 20 or 40 mg/kg MDMA found increased staining in most brain areas in rats given 40 mg/kg MDMA, and in some brain areas in some rats given 20 mg/kg MDMA (Schmued et al. 2003). Increased signs of neuronal degeneration were strongly

associated with hyperthermia, suggesting a role of dose and body temperature in producing these effects. However, as discussed earlier, another study examining substantia nigra in mice given a total dose of 20 mg/kg (four doses of 5 mg/kg) found signs of oxidative stress, but failed to find signs of frank cell death (Fornai et al. 2003).

It is unlikely that MDMA exposures in the currently proposed clinical study will approach those demonstrated to trigger programmed cell death in neurons. If MDMA levels in the brain are about 6 times higher than in plasma (Rohrig and Prouty 1992), then 125 mg MDMA should produce peak plasma levels of 236.4 ± 57.97 μg/l MDMA (de la Torre et al. 2000b) and peak brain levels of 1.4 ± 0.3 mg/L. This estimated peak level is significantly less than the lowest drug concentration used in either apoptosis study. While 0.4 mM MDMA or 77.3 mg/L had modest effects in the first study, 125 μM or 24.2 mg/L had no significant effect in the second study. Peak plasma levels after a supplemental dose of 62.5 mg follows 125 mg are liable to be somewhat higher, but they are not likely to approach levels in brain that produced cell death. Given these concentration differences and the long exposure times used in these studies, it does not seem likely that human oral doses of MDMA would be sufficient to induce programmed cell death in neurons. Additionally, body temperature is only slightly elevated in humans given MDMA in clinical settings, further reducing any possible effects due to hyperthermia.

Reproductive and Developmental Toxicity

As discussed in the Investigator's Brochure, one of two studies of polydrug-using ecstasy users found a possibly increased incidence of developmental abnormalities when pregnant women used illicit drugs including ecstasy (McElhatton et al. 1999). There is some contention as to whether the developmental abnormalities reported in the study conducted by McElhatton and colleagues are, in fact, the result of "ecstasy" consumption. Neonatal rats given repeated doses of MDMA show signs of lower brain serotonin and showed impairments in learning and memory, with the neonatal period in rats considered equivalent to the third trimester of pregnancy in humans. In one study, rats given the very high, repeated dose regimen of 20 mg/kg MDMA twice daily from Day 11 to Day 20 performed less well on a task assessing spatial learning and memory (Williams et al. 2003), and had lower brain serotonin and greater increases in the dopamine metabolite homovanillic acid (HVA) in frontal cortex, hippocampus and striatum (Koprich et al. 2003A). Maternal administration has produced contradictory results. Rats born to dams given twice-daily injections of 15 mg/kg for 7 consecutive days were less active in a novel environment (Koprich et al. 2000B), yet lower brain serotonin was not detected in rats born to dams given twice-daily injections of 20 mg/kg MDMA for four days (Kelly et al. 2002). Pregnant women will be excluded from participation in the proposed study and urine pregnancy tests will be performed before each drug administration.

Previous Human Experience

Clinical MDMA research using healthy volunteers has been conducted by at least seven research groups, including three in the United States. Double-blind placebo-controlled MDMA studies have been published in peer-reviewed journals. To date, the most extensive studies have been carried out by Franz Vollenweider of the University of Zurich and his colleagues. They have administered up to two doses of 1.5 to 1.7 mg/kg MDMA to 74 subjects. These researchers have published studies of brain imaging, EEG, cardiovascular, neuroendocrine and subjective effects of MDMA (Frei et al. 2001; Gamma et al. 2000; Liechti et al. 2000a; Liechti et al. 2000b; Liechti et al. 2001a; Liechti et al. 2001b; Liechti and Vollenweider 20001a; Liechti and Vollenweider 2001b; Vollenweider et al. 1998; Vollenweider et al. 1999). The Zurich researchers have also published a review of the data that notes gender differences in MDMA effects (Liechti et al. 20001a), and they have presented data at conferences investigating the effects of up to two doses of 1.5 to 1.7 mg/kg MDMA on levels of serotonin transporter or cognitive function (Ludewig et al. 2003; Vollenweider et al. 2000). A team of researchers in Spain have measured the subjective, cardiovascular, and immunological effects of 50, 75, 100, 125 and 150 mg MDMA, alone and, in some studies, in combination with ethanol (Cami et al. 2000; Hernandez-Lopez et al. 2002; Mas et al. 1999; Pacifici et al. 1999; Pacifici et al. 2001; Pacifici et al. 2002; Pacifici et al. 2004). This same team of researchers has investigated the effects of repeated doses of 100 mg MDMA, with the second dose given four or 24 hours after the initial dose (Farre et al. 2004; Pacifici et al. 2002), and they have published countless pharmacokinetic and drug detection studies (e.g. de la Torre et al. 2000; Navarro et al. 2001; Pichini et al. 2002; Pichini et al. 2003; Pizarro et al. 2002; Pizarro et al. 2003; Segura et al. 2002). While it appears that the researchers reported data form the same sample in several studies, they have administered MDMA to 42 to 54 subjects. A team of researchers at Wayne State University in Detroit has assessed cardiovascular, subjective, and neuroendocrine effects of about 1.1, 1.6, and 2.1 mg/kg MDMA, as compared with the psychostimulant d-amphetamine and the serotonin releaser and serotonin receptor agonist mCPP in 22 men and women with prior use of ecstasy (Tancer and Johanson 2001). This team has also performed a similar study of 1 and 2 mg/kg MDMA in 12 men and women that also measured rewarding effects (Tancer and Johanson 2003). The Wayne State researchers have presented data from studies of ambient temperature and 2 mg/kg MDMA in four subjects, and co-administration of fluoxetine with 1.5 mg/kg MDMA in eight subjects (Tancer et al. 2003; Tancer and Johanson 2004). Researchers at UCLA-Harbor Medical Center assessed cardiovascular, neuroendocrine and some subjective effects of ascending doses of MDMA that varied from 0.25 to 2.5 mg/kg MDMA in 18 men and women who had reported some ecstasy use (see IND #63,384, pp. 44-48 and pp. 52-70 for more details; Grob et al. 1996). They also assessed the effects of two ascending doses of MDMA on cerebral blood flow in a subset of ten individuals in the same sample (Chang et al. 2000). A team of researchers in the Netherlands has studied the cardiovascular and subjective effects of 75 mg MDMA in 12 men and women reporting ecstasy use (Lamers et al. 2003; Samyn et al. 2002), focusing on acute effects of MDMA on skills related to driving. Researchers at the University of California-San Francisco have studied the cardiovascular, subjective and neuroendocrine effects of MDMA in eight men and women with past experience with

ecstasy (Harris et al. 2002; Lester et al. 2000). Lastly, researchers in England studied the neuroendocrine effects and pharmacokinetics of 47.6 mg MDMA (equivalent to 40 mg freebase) in eight drug-naïve men, specifically examining changes in arginine vasopressin release (Fallon et al. 2000; Forsling et al. 2001; Henry et al. 1999). Up to 2.5 mg/kg MDMA was well tolerated in these clinical trials, and no serious adverse events were reported in any of the published or unpublished reports. More information on the acute effects of MDMA can be found in the Investigator's Brochure (Baggott et al. 2001) and the two successive revisions to the IB (Jerome and Baggott 2003; Jerome 2004).

Clinically significant hypertension has occurred in a approximately 5% of individuals enrolled in controlled studies of MDMA (Grob et al., Unpublished, see also pp. 45 in IND #63,384; Vollenweider et al. 1998), and significant hypertension has occurred in at least one participant in the study of MDMA-assisted therapy in people with PTSD (Mithoefer, 2004a, personal communication to R Doblin and L Jerome, Nov 4, 2004). However, hypertension subsided without clinical intervention in all cases. Plans for monitoring and treating hypertension are described in detail below in "Monitoring for Toxicity."

A study of the effects of two separate sessions of MDMA-assisted therapy in people with posttraumatic stress disorder (PTSD) is underway (Mithoefer 2004c). This study is described in IND #63,384 and uses two doses of 125 mg MDMA or placebo given three to five weeks apart. So far, five participants have completed the study without occurrence of any serious adverse events (Mithoefer, 2004b, personal communications to R Doblin Nov 12, 2004), and two more participants are currently enrolled in the study. The blind has been broken for the first five subjects enrolled in this study, and it appears that three of five participants received MDMA. A team of researchers in Spain have administered 50 mg, 75 mg MDMA, or placebo to women with PTSD arising from a sexual assault. This study also reported no serious adverse events. However, this study has since been halted due to political concerns expressed by the local anti-drug authority (Bouso, 2003, communication to R Doblin and L Jerome, January 15, 2003). Since the study was halted without being discontinued, the blind was not broken and it is not known whether participants received the experimental intervention or placebo. MDMA has been tolerated by participants in both the ongoing and the halted study, assuming that one or more participant received MDMA.

There also exists an extensive history of using MDMA as an adjunct to psychotherapy prior to scheduling (Adamson 1985; Greer and Tolbert 1986; Greer and Tolbert 1998; Grinspoon and Bakalar 1986; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998). Narrative accounts and case reports of MDMA given in these circumstances indicated that MDMA was tolerated and that no serious adverse events occurred. Two uncontrolled studies of MDMA (Downing 1986; Greer and Tolbert 1986), including one performed in a psychotherapeutic context (Greer and Tolbert 1986) also found that participants tolerated MDMA and reported no serious adverse events. Lastly, during a period lasting from 1988 to 1993, psychotherapists in Switzerland were permitted to administer MDMA to patients (Gasser 1994; Widmer 1998). These therapists reported

that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration.

In summary, researchers have measured the cardiovascular, physiological, neuroendocrine, neurofunctional (PET and EEG), psychiatric, and subjective effects of MDMA at doses ranging from 0.25 to 2.5 mg/kg, and researchers are currently studying the effects of 125 mg MDMA given as an adjunct to psychotherapy in people with PTSD. MDMA has been generally well tolerated in these studies, and we are aware of no serious adverse events. Participants with and without previous experience with MDMA reported that the effects of MDMA were mostly pleasant and otherwise tolerable (Cami et al. 2000; Farre et al. 2004; Grob et al. 1996; Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti et al. 2001; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider, 1998). Occasionally, dysphoric responses to MDMA have occurred, but have always resolved within several hours, and transient changes in thought processes are reported (Harris et al. 1998; Vollenweider et al. 1998). Clinically significant hypertension has occurred in several volunteers; these cases are discussed above. To date, there is no indication that administration of MDMA in controlled settings has any adverse effects on cognitive function (Grob et al. Unpublished; Ludewig et al. 2003; Vollenweider et al. 2000). Grob et al. did not detect any change in neurocognitive function in their volunteers. Similarly, Vollenweider and colleagues (Ludewig et al. 2003; Vollenweider 2001; IND #63,384 pp. 189-190; Vollenweider et al. 2000) report that retrospective analysis of their studies did not detect any lasting effect of MDMA on psychological and neuropsychological measures, cerebral blood flow ($H_2{}^{15}O$-PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP). Most importantly, preliminary analysis using positron emission tomography (PET) and the radioligand McN-5256 revealed no significant changes in estimated serotonin transporter density four weeks after a single dose of MDMA (1.5–1.7 mg/kg) in MDMA-naive volunteers (Vollenweider et al. 2001). This data and the history of past use of MDMA in psychotherapy prior to scheduling indicate that MDMA can be safely administered to humans.

Drug Dependence and Abuse Potential

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as "rave" dance parties. Whether or not MDMA's abuse potential will negatively affect PTSD patients exposed to MDMA in a therapeutic context is an open question for which there is no direct data. However, as described above in "Abuse Liability", instead of experiencing euphoria, people with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions and memories related to the original traumatic incident. During MDMA-assisted therapy, they are expressly directed to confront and process emotionally intense, and often upsetting, material. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging psychotherapy will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings.

Recreational use of MDMA first appeared possibly as early as the 1960s (see Shulgin 1991) and is known to have occurred during the late 1970s and early 1980s. Instances of abuse and dependence in users have been reported (Jansen 1995; Topp et al. 1999). While studies using non-representative samples, including samples of drug users, have reported diagnosing up to 30% of users with abuse or dependence (Topp et al. 2002; Cottler et al. 2001), a survey of a representative sample of young Munich residents found that 6% of people reporting ecstasy use had signs of abuse or dependence on the drug. This suggests that some people who take ecstasy may develop substance abuse or dependence. It is important to note that several studies have found that in general, people begin using ecstasy only after they have begun using cannabis or other illicit substances (Pedersen and Skrondal 1999; see also age of onset in Daumann et al. 2004, for example). Measuring reward value by finding the point at which people would switch from receiving drug to either giving up or receiving money, Tancer and Johanson (2003) found that 2 mg/kg MDMA and 20 mg d-amphetamine had higher reward value than placebo, and that 1 mg/kg MDMA and 10 mg d-amphetamine did not have significantly higher reward value than placebo. Participants in this study were selected for past use of ecstasy and minimal use of other substances, so it seems likely that participants in this study would assign high reward value to MDMA.

Studies in rodents (e.g. Cornish et al. 2003; Robledo et al. 2004; Schenk et al. 2002; Wakonigg et al. 2004) and non-human primates (Beardsley et al. 1987; Fantegrossi et al. 2002; Fantegrossi et al. 2004; Lamb and Griffith 1987) suggest that animals will self-administer MDMA. Conditioned place preference, referring to the tendency to spend more time in a chamber associated with an injection of the drug, was reported to occur in rats given MDMA (Bilsky et al. 1990; Cole and Sumnall 2003; Meyer et al. 2002). A study that examined the rapidity with which a drug-naive rat descended a runway to obtain an injection of MDMA also found that animals descended the runway more rapidly when MDMA was available (Wakonigg et al. 2004). All of these findings suggest that MDMA possesses some reward value for rats, usually considered a sign of human abuse potential.

A number of studies have found that non-human primates self-administer MDMA, though to date, all studies have employed animals previously experienced with the self-administration of other substances, such as cocaine or methamphetamine. Rhesus monkeys self-administered an average of 2 to 4 mg/kg MDMA in one study (Fantegrossi et al. 2004) during twice-daily hour-long sessions occurring approximately three times a week. Less self-administration was seen at the end of an eighteen-month period, suggesting that when repeatedly self-administered, MDMA loses some reward incentive. However, overall findings in non-human primates support the presence of at least some abuse liability. Baboons that had previously self-administered cocaine also self-administered MDMA (Beardsley et al. 1987).

Drug-naïve participants taking part in clinical trials of 1.5 to 1.7 mg/kg MDMA reported that they had no interest in self-administering the drug outside the confines of a controlled laboratory setting (Liechti et al. 2001). MDMA was administered in a non-psychotherapeutic setting to people with no significant psychiatric illnesses.

There is known to be significant comorbidity for substance abuse among patients with PTSD, though specific data on the relationship between MDMA use and PTSD have not been reported. Currently, there is no definite evidence concerning the casual relations between the two disorders, and it is unclear whether posttraumatic stress disorder precipitates substance abuse or whether people with pre-existing substance abuse are at greater risk for PTSD. Currently, the most commonly accepted hypothesis for the relationship between PTSD and substance abuse is that of self-medication (Meisler, 1996). Since individuals undergoing the proposed treatment will be encouraged to confront the traumatic events during MDMA-assisted therapy rather than defending against them or avoiding them, it seems likely that these individuals will subsequently be less inclined to choose to self-medicate through the self-administration of MDMA. If our hypothesis is correct that MDMA assisted psychotherapy will alleviate symptoms of PTSD, it is possible that participants will be at reduced risk for substance abuse in general following MDMA-assisted psychotherapy because they will have a reduced motivation to self medicate. There will be no opportunity for diversion in this study because all doses of MDMA will be administered within the clinic, and there will be no take-home doses.

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