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1. Introductory Statement – MDMA and Psychotherapy

The proposed study has been designed as part of a program of research sponsored by the USA-based non-profit research and educational organization, the Multidisciplinary Association for Psychedelic Studies (MAPS), with the long-term goal of developing MDMA into a prescription medication with US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) approval. MAPS is currently sponsoring an ongoing study of MDMA-assisted therapy in patients with PTSD taking place in Charleston, South Carolina, in which 11 out of 20 subjects have already completed the protocol. MAPS is also in the protocol design and approval phase for two studies of MDMA-assisted therapy in patients with PTSD, to be conducted in Madrid, Spain, under the direction of Jose Carlos Bouso, Ph.D. candidate, and in Tel Aviv, Israel, under the direction of Dr. Moshe Kotler, Department of Psychiatry, Tel Aviv University. MAPS is also sponsoring an FDA-approved study to take place at Harvard Medical School's McLean Hospital that will investigate MDMA-assisted psychotherapy in people with anxiety related to advanced stage cancer.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s. 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 (Betäubungsmittel) 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 2001; d'Otolora, 2004). 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. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert, 1998, Holland, 2001). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlander, 1990). The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others.

MDMA was made illegal in the US and Switzerland shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia, hyponatremia or liver damage have occurred in association with ecstasy use, 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 (Cole 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 ongoing Phase II study in the US. Preliminary examination of this data has found no deterioration in condition after MDMA-assisted psychotherapy. When the blind was broken for the first 15 subjects, it was found that people receiving MDMA demonstrated greater improvement than people receiving placebo (Mithoefer 2007), and preliminary analyses did not indicate any effects of MDMA on memory. After reviewing data from the last 15 subjects, the Data Safety Monitoring Board (DSMB) recommended that the study continue without any modifications.

This study of MDMA-assisted therapy will be the first Phase II study to take place in Switzerland examining MDMA-assisted psychotherapy as a potential treatment for people with treatment resistant PTSD. If data from MAPS' pilot studies continue to produce promising results, then MAPS will use the information gathered from these studies to formulate two large (N = approximately 280) multi-site Phase III studies of MDMA-assisted psychotherapy, one to be conducted throughout the United States and one to be conducted throughout Europe and Israel. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least five years and will involve at least 600 subjects.

2. The Protocol

2.1. Summary of the Proposed Study

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 patients with treatment-resistant posttraumatic stress disorder (PTSD). In this study, 12 patients will receive either an active placebo dose or a fully active dose of MDMA during three experimental psychotherapy sessions, each six to eight hours long, scheduled three to five weeks apart. Participants assigned to receive the active placebo and participants assigned to receive the fully active dose will receive the same course of psychotherapy, which consists of two introductory sessions prior to the first experimental (active placebo or fully active dose MDMA) session, follow-up psychotherapy sessions occurring a day after each experimental session, and two to four integrative psychotherapy sessions conducted on a weekly basis after each experimental session, with the first of these sessions scheduled a week after each experimental session. Active placebo will be 25 mg MDMA followed two and a half hours later by 12.5 mg, and the fully active dose will be 125 mg followed two and a half hours later by 62.5 mg. Extent of PTSD symptoms will be assessed by an independent rater at baseline, 3 weeks after the second and third experimental session and two, six and 12 months after the third 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, that MDMA-assisted psychotherapy will be well-tolerated and will not produce serious adverse effects in this population, that three experimental sessions will lead to better results than two sessions, and that results are stable at the follow up assessments at 2, 6 and 12 months after the last experimental session.

Participants assigned to the active placebo condition will be given the opportunity to take part in an open-label continuation of the study with fully active doses of MDMA, referred to here as "Stage 2". This opportunity will be offered immediately after the end of treatment outcome measures are completed 3 weeks after the third experimental session, with the blind to be broken by a research assistant not connected with the study in any other way. Data gathered 3 weeks after the third experimental session will be treated as the baseline for Stage 2, and outcome measures will be administered 3 weeks after the second and third experimental session and 2, 6, and 12 months after the

third MDMA session for all people who consent to take part in Stage 2, which will be structured in an identical manner to Stage 1.

Based on the reviewed research, 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 must 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.

2.2. Posttraumatic Stress Disorder (PTSD)

2.2.1. *PTSD: Background and Significance of Expected Results*

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

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

Epidemiologic data for PTSD in Europe and especially Switzerland is scarce to date, indicating lower prevalence rates than in the USA, Canada or Australia: A large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a prevalence of PTSD, including subthreshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased to 10.3%. (Perkonigg et al 2000). A representative community-based cohort of Swiss people from the canton of Zurich, Switzerland was interviewed in 1993 at the age of 34-35 years and again in 1999. The prevalence for subthreshold PTSD was 1.90 % in 1993 and 1.30% in 1999. No single case of full PTSD was found in the sample, and even for subthreshold PTSD the prevalence was very low. (Hepp et al 2005).

Switzerland is exposed to a continuous influx of refugees, 25% of them having been exposed to torture in their countries of origin (Wicker 1991). It has one of the largest population of migrants (21% in 2003) of all European countries and migrants from Ex-Yugoslavia are the second largest subpopulation today. One study found prevalence rates of 25% for PTSD in Kosovarian Albanians one year after the war (Cardozo 2003). Another study in Kosovarian Albanians who returned home two years after the end of the conflict from their country of asylum (Switzerland) showed prevalence rates of 23.5% (Eytan A et al 2004). Apart from this, it is apparent that since 9/11 global violence is increasing. Although Switzerland has been spared up to now from war or major terrorist attacks such 9/11, it has experienced a number of disasters, such as the shooting in the Parliament of the Canton Zug or the Luxor terrorist attack. Violence in everyday life such as sexual and physical assault is also an increasing reality in Switzerland. Especially rape leads to high PTSD prevalence rates of 57% (Resnick 1993).

Another major source of PTSD and related psychiatric conditions are the everyday accidents of which over one million per year happen in Switzerland: A study in 106 accident victims who were treated in a Swiss university hospital showed that at the 1-yr follow-up, two patients (1.9%) had PTSD, and 13 (12.3%) had subsyndromal PTSD. Overall, 27 patients (25.5%) showed some form of psychiatric morbidity, full or subsyndromal PTSD and/or anxiety and/or depression. (Schnyder U, 2001).

In the National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of the patients still had symptoms several times per week after 10 years (Kessler et al., 1995). Generally, the number of people who do not improve after treatment can be high, between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group still were diagnosed with PTSD with high enough CAPS scores (Resick et al. 2002) and another study by Foa et al. (1999) reported similar figures.

PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. Cultural and language barriers make psychotherapeutic treatment of traumatized migrants even more difficult. 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 novel and more effective treatments is therefore of major public health and economic significance.

2.2.2 *PTSD and MDMA-assisted Psychotherapy*

To date the treatment of PTSD has primarily been a psychotherapeutic treatment, the effect size for psychotherapy being higher than for psychopharmacological treatment. Cognitive behavioural therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and EMDR also proved to be effective in treating some aspects of PTSD symptoms (Flatten G et al. 2004).

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 non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD.

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Sertraline and paroxetine, currently the only drugs with an FDA and Swissmedic 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).

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; de la Torre et al. 2005; 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; Johanson et al. 2005; Lamers et al. 2003; 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; Peters et al. 2005; Pichini et al. 2002; Pichini et al. 2003; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004; Ramaekers and Kuypers 2006A; Samyn et al. 2002; Segura et al. 2001; Segura et al. 2005; Tancer and Johanson 2001; Tancer and Johanson 2003; Vollenweider et al. 1998; Vollenweider et al. 1999; Vollenweider et al. 2004). 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 1998). These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication (Vollenweider et al. 1998).

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 is underway in the United States of MDMA-assisted psychotherapy in patients with treatment-resistant PTSD as a result of sexual or criminal assault that is now accepting patients 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. Ten 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 has yet to be studied. The proposed study is intended to investigate whether this novel treatment may assist those with 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 selected 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 will 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). Furthermore, studies in ecstasy users have failed to find impaired cognitive function in moderate ecstasy users (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004).

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

2.2.3. Previous Clinical Experience with MDMA

Prior to its scheduling in the US and Switzerland, MDMA was used in psychotherapy to treat neuroses, relationship difficulties, and PTSD (Adamson 1985; d’Otalora 2004; Gasser 1994; Greer and Tolbert 1986; Greer and Tolbert 1998; Stolaroff 2004; Widmer 1998). Anecdotal and narrative accounts of MDMA-assisted psychotherapy reported successful treatment of PTSD. People reported reduced PTSD symptoms and improved quality of life. It should be noted that during this period in time, MDMA may have been given to thousands of individuals without any fatalities or serious adverse events (Holland 2001; Rosenbaum and Doblin 1991). Greer and Tolbert’s (1986) uncontrolled, non-blinded study of MDMA in a therapeutic context found that most of the 29 individuals with mild to moderate psychological difficulties reported obtaining at least some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986).

As described in the Introductory Statement, a sponsor-supported pilot study of MDMA-assisted psychotherapy in 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 was finally granted approval by an IRB in September, 2003. The study has been underway for nearly a year and nine subjects have completed the study 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 preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo, though this observation only involves the first 15 participants in this study (Mithoefer 2007).

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.

2.4. Principal Investigator

Dr. Peter Oehen is a psychiatrist and psychotherapist in private practice in Biberist, Switzerland. He has undergone training in psycholytic therapy during the 1988-93 period of permission to do psycholytic therapy in Switzerland (MDMA- and LSD-assisted psychotherapy (Widmer 1998)). He also assisted MDMA and LSD-assisted psychotherapy sessions as co-therapist during this time. Dr. Oehen is also a member of the board of the Swiss Medical Association für Psycholytic Therapy (SAePT).

Dr. Oehen’s CV is attached as an appendix.

2.5. Study Design

This study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to either 3 MDMA-assisted sessions with a full dose of 125mg MDMA followed by a supplemental dose of 62.5mg MDMA administered 2.5 h later, or to an active placebo dose of 25mg MDMA followed by 12.5mg MDMA 2.5h later. Participants will undergo three sessions of MDMA-assisted psychotherapy scheduled to occur three to five weeks apart, 1 non-drug-psychotherapy session 24 h after each MDMA-session and 2-4 weekly, integrative psychotherapy sessions after each MDMA session. PTSD symptoms will be assessed by an independent assessor once prior to MDMA-assisted psychotherapy, 3 weeks after the second MDMA-assisted session, 3 weeks after the third experimental session, marking the end of non-drug psychotherapy, and two, six and twelve months later, with the CAPS serving as a primary outcome measure. 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 3 weeks after the third experimental session will be treated as the baseline for Stage 2, and outcome measures will be administered 3 weeks after the second and third experimental session, 2, 6, and 12 months after baseline for all patients who consent to take part in Stage 2. Participants receiving the full dose in either Stage 1 or Stage 2 and not responding with significant improvement will be offered the opportunity to take part in an open-label continuation of the study, referred to as “Stage 3”, consisting of 2 additional MDMA sessions. During these sessions, they may receive 125 mg followed 2.5 hours later by 62.5 mg MDMA, or a 20% larger dose of 150 mg MDMA, followed by a supplemental dose of 75 mg administered 2.5 hours later. Outcome measurements gathered at 2 months after the third experimental session will serve as baseline measures for Stage 3. Procedures for non-drug psychotherapy sessions, experimental sessions and outcome measure administration will be the same as those employed in the first stage of the study.

2.6. Questions and Hypotheses

The following main questions are to be explored in the proposed study:

1. Can MDMA, in the doses to be used in this study, be safely administered in the population of treatment-resistant PTSD patients without any serious adverse events?
2. Will patients receiving the larger, fully active dose of MDMA, in combination with non-drug assisted psychotherapy, demonstrate greater symptomatic improvement than patients given an active placebo dose of MDMA in combination with non-drug psychotherapy?
3. Will patients receiving three MDMA sessions in combination with non-drug psychotherapy demonstrate an additional improvement compared to patients receiving only two sessions?
4. Can treatment effects of MDMA-assisted psychotherapy be maintained beyond end of treatment?

Based on the reviewed research, the following hypotheses were formulated:

Re 1. PTSD patients receiving the fully active dose of MDMA will not experience any serious adverse events. The supplemental dose of MDMA will be tolerated both in the low and fully active dose conditions.

Re 2. 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 and PDS, with CAPS score serving as the primary outcome measure.

Re 3. 3 experimental MDMA-assisted sessions will lead to better results compared to only 2 experimental MDMA-assisted sessions, as measured via the CAPS and PDS, with CAPS score serving as the primary outcome measure.

Re 4. The treatment gains will remain stable at the 2, 6 and 12 months assessments.

2.7. Participants

The first twelve participants who meet all inclusion criteria without meeting any exclusion criteria will be admitted to the study. Participants enrolled in the study who withdraw during treatment or who the researchers decide for any reason should not continue in the study (“drop-outs”) will be replaced. Participants will be recruited for the study by call for referral from specialized institutions such as trauma advice and counseling centers (outpatient clinics for psychotraumatology), as well as psychiatrists and psychotherapists in private practice (see enclosed).

2.7.1. *Inclusion Criteria*

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

1. Participants must meet DSM IV criteria for current PTSD (within the past 6 months) in response to a traumatic experience. An individual would not be excluded if she or he experienced more than one traumatic event. 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 Schnicke 1992). Treatment will be deemed 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) indicates 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 psychotropic medication from the outset of the study until follow-up evaluation at T3 (2 months after MDMA session 3), with the exception of gabapentin prescribed for pain control. The scheduled outcome measures at 6 and 12 months after the third experimental session will still be conducted regardless of whether additional psychotropic medication was used. 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 administration of outcome measures at T3 (2 months after MDMA session 3). The scheduled outcome measures at 6 and 12 months after the third experimental session will still be conducted regardless of whether additional treatments were obtained.
8. Participants must agree that, for one week preceding each experimental session:
They will refrain from taking any herbal supplement (except with prior approval of the research team). 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).

Without 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 24.00 hours (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 Dr. Oehen's office after each experimental session until the non-drug session occurring the next morning.
11. Participants will be asked to locate an individual willing to drive them home after the non-drug therapy session occurring the morning after the experimental sessions. If a participant is unable to locate someone to transport him or herself home, the investigators will assist the participant in obtaining transport from the office 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. Participants who do not adhere to the usual progression of scheduled visits, as may occur when a session is delayed, the participant must maintain weekly telephone contact with the investigators, and must agree to speak with the investigators if there is a significant increase in symptoms for which they were previously medicated, if there is any unanticipated need to contact their treating therapist, or if there are any changes in medication.
14. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
15. Participants must have sufficient proficiency in the German language to participate in MDMA-assisted psychotherapy. Participants must be able to read documents in German.
16. Subjects from the researchers' patient pool must have an interview with another psychiatrist not involved in the design or administration of the study before engaging in the informed consent process. The researchers will be careful when discussing the study with these individuals to ensure that the pre-existing patient-physician relationship does not unduly influence their decision concerning study participation.

2.7.2. *Exclusion Criteria*

Prospective participants with the following conditions will be excluded:

1. Participants who appear at imminent risk for trauma and victimization as assessed by information gathered during the screening will not be eligible for study participation.
2. Women who are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control.
3. Participants with a history of or current primary psychotic disorder or bipolar affective disorder type 1.
4. Participants with dissociative identity disorder, or an eating disorder with active purging or borderline personality disorder.
5. Participants 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. Participants with uncontrolled hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
7. Participants weighing less than 50 kg or more than 105 kg.
8. Patients reporting prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months.

9. Participants who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
10. Participants requiring ongoing concomitant therapy with a psychotropic drug.
11. Participants meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
12. Any participant who is not able to give adequate informed consent. Participants in need of special protection such as minors; participants without the legal ability to act; participants who lack sufficient understanding or capacity to make or communicate responsible decisions concerning themselves by reason of mental illness, mental deficiency, physical illness or disability, advanced age or other cause (incapacitated persons).

2.7.3. 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 participate, an initial psychiatric and medical evaluation will be performed on each applicant prior to enrollment. The psychiatric evaluation will be performed by the principal investigator. The CAPS will be used to provide a DSM-IV PTSD diagnosis. If the subject meets DSM-IV PTSD criteria, the rest of the SCID (First et al. 1994) will be administered by the independent rater for the purpose of ruling out candidates with 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.

Prospective participants will also undergo a testbattery of neurophysiological and psychological measures at the Psychiatric University Hospital in Zürich, also being used in the ongoing study “Psychophysiology of PTSD: a comprehensive parameter study” conducted by Dr. F.X. Vollenweider of the Psychiatric University Hospital in Zürich. This study has been approved by the ethics committee of the University Hospital of Psychiatry and the Canton Zurich. These measures include a number of physiological measures that are known to be altered in PTSD patients but have never been measured together. The first aim is to establish one or two intermediate phenotype markers that are currently not yet well defined. Specifically, prevailing evidence suggests that PTSD patients suffer from deficits in early information processing such as deficits in gating or filtering of internal and external sensory stimuli. Two experimental paradigms designed to assess central inhibition or gating are prepulse inhibition (PPI) of the acoustic startle response and suppression of the P50 event-related potential. The neurophysiologic correlates of PPI and P50 suppression, as well as the interdependency of these gating measures shall be explored using electroencephalographic (EEG) measures in combination with ERP (evoked response potential) technique. The EEG-ERP data will be analyzed by the novel Low-Resolution Electromagnetic Tomography Algorithm (LORETA) analysis of sources of spectral EEG activity. This technique permits detection and evaluation of aberrant stimulus processing in the ms (milliseconds) range and to localize the corresponding neuronal correlates onto brain maps in the 3D space. Further, covariance analysis will be used to explore the relationship between EEG-ERP measures and clinical symptoms of PTSD. Given the high time resolution of EEG-ERP technique, this method is considerably superior to fMRI (functional Magnetic Resonance Imagery) or PET (Positron Emission Tomography). The measures described above will be accompanied by additional psychological and psychiatric assessments and questionnaires (SCL-90, IES-R, DES, BDI, STAI-R, PSS). All measures mentioned above will be administered by a rater from Dr. Vollenweider’s team on the same days as the baseline assessment (T0) and 3 weeks after the third MDMA session (T2) and will take no more than three hours. Participants who take part in “Stage 3” will undergo the same assessment three weeks after their third open-label MDMA session.

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 (research findings indicate a transient lowered immune-response a few days after ingestion MDMA (Connor et al 2000a; Connor et al 2000b; Connor et al 2004; Pacifici et al. 2000; Pacifici et al. 2002; Pacifici et al. 2004)), and there is one report of a fatality associated with an interaction between ecstasy and protease inhibitors (Henry and Hill 1998), and urinary drug and pregnancy tests (when appropriate). Participants aged older than 40 years with a positive family history of coronary heart disease and/or presenting risk factors will have a stress ECG to rule out coronary heart disease.

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.

2.8. Methods

2.8.1. 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 by the Institute for Statistics, University of Bern. 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), as well as on data obtained from Dr. Mithoefer's MAPS-sponsored MDMA/PTSD pilot study currently underway in the United States. 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; Styk 2007; Tancer et al. 2001; Tancer et al. 2003; Vollenweider et al. 1998).

With participants carefully monitored for any indicators of adverse events, the initial doses of either 125 mg or 150 mg, and the cumulative dose of 187.5 mg or 225 mg respectively will prove to be tolerable and pose no more than minimal risk. The side effect profile is expected to increase with the higher dose but it is considered unlikely that there will be any Serious Adverse Events (SAEs) or any persisting side effects.

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
20% Larger Active Dose	150 mg	75 mg	225 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, Styk 2007). Supplemental dosing performed 2.5 hours after the initial dose is expected to extend the course of drug effects without increasing their intensity. 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 1 to 1.5 hours after they arrive at Dr. Oehen's office 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 three experimental sessions, with the second and third session scheduled to fall two to four weeks after the previous experimental session.

2.8.2. Assessments and Measures

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

PTSD symptoms will be assessed six times in this study:

- T0: *Baseline assessment*
- T1: *Post MDMA 2 assessment*: 3 weeks after the second experimental session (MDMA 2)
- T2: *End of treatment assessment*: 3 weeks after the third experimental session (MDMA 3)
- T3: *1st follow-up assessment*: 2 months after the third experimental session (MDMA 3)

T4: *2nd follow-up assessment*: 6 months after the third experimental session (MDMA 3) for 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.

T5: *3rd follow-up assessment*: 12 months after the third experimental session (MDMA 3) for 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.

Participants who choose to take part in the open label study continuation “Stage 2” will be assessed identically to stage 1 three weeks after the second and third (end of treatment) experimental sessions and two, six and twelve months after the third experimental session in Stage 2. The T2 assessment will serve as baseline for stage 2.

Participants who choose to take part in the open label study continuation “Stage 3” will be assessed identically to stage 1 three weeks after the second (end of treatment) experimental session and two, six and twelve months after the experimental session in Stage 2. The T3 assessment will serve as baseline for stage 3.

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 PDS will serve as additional measure of PTSD symptoms. The CAPS and the PDS are specifically designed to assess PTSD. German 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 (SUDS). 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 third 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). The CAPS was translated to German and tested with accident victims. The internal consistency of the German translation proved to be comparable to that of the original English version (Cronbach’s alpha = .88) (Schnyder U, Moergeli, H 2002). The CAPS will serve both as a screening measure and as a primary outcome measure.

2. 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. A translation into German was made by Ehlers 1996. This test has not yet been validated for German populations. This measure will serve as an additional outcome measure.
3. Reactions to Research Participation-Questionnaire-Short Form (Revised) RPQR (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 includes items addressing participation due to perceived coercion or undue influence by the investigators. A German translation will be developed for the study.
4. SCID-II (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.
5. Participant Beliefs on Condition Assignment: All participants will be asked to indicate whether they believe they have received active placebo or fully active doses of MDMA during the experimental sessions. This measure will serve as a means of measuring the success of study blinding for participants and investigators.
6. Subjective Units of Distress: This is a standardized subjective rating scale by which a participant can quickly rate comfort level throughout the session (1-7 scale). The parameters of the scale are explained at study initiations. This measure will serve as a means of safety monitoring during experimental sessions.

All sessions – introductory, MDMA-assisted sessions and integrative sessions - will be video recorded in their entirety. These recordings will be used for further analysis of patient behaviour, defence mechanisms, therapist interventions, manual adherence, etc. Patients will be asked to sign a separate video-IC. Patients can participate in the study in spite of refusing video recordings. The recordings will be stored in a locked file cabinet and treated as confidentially as all other study documents.

2.8.3. Data Analysis

The CAPS and PDS scores will be analyzed by nonparametric methods for analysis of variance (cf. Brunner and Langer (2002), Brunner, Domhof and Langer (2002)). The nonparametric framework is chosen for two reasons, that of the sample size being too small to assess the assumptions that underlie a parametric model, and because the primary outcome measure, CAPS score, is only measured on an ordinal scale. We will also compute descriptive statistics for Stage 1 and Stage 2 CAPS and PDS scores for all participants enrolled in Stage 2. It is unlikely that there will be enough participants in Stage 2 for formal analysis, but scores can be compared across the two stages to see whether Stage 2 scores are reduced compared with Stage 1 scores. Finally, we will compute CAPS and PDS scores for any participant undergoing “Stage 3”.

The first step of the analysis will consist of descriptively summarizing the data by graphing the time course of CAPS for each patient and by computing summary measures for CAPS. The second step will consist of testing the above-mentioned hypothesis. In order to compare the time courses of the control group and the treatment group, we will apply a so-called F1_LD_F1 (cf. Brunner and Langer (2002), Brunner et al. (2002)) with experimental intervention condition (MDMA versus active placebo) serving as a between-group factor and time of measurement serving as a within-subjects factor. We are mainly interested in testing an interaction between experimental intervention condition and time. We expect all participants will have lower CAPS scores two months after the third experimental session than at baseline, but that people given the fully active dose will have lower CAPS scores than people given active placebo. The hypothesis concerning only the treatment group will be analyzed by

comparing differences between subject's baseline CAPS and treatment scores at various time points. This can be done with Wilcoxon's Signed-Rank-Test for paired data. We expect that people will have lower CAPS scores after the third experimental session than after the second experimental session.

Statistical significance will be set at 0.05. Because the sample size is very small, the study has sufficient power only to detect large effects. Therefore, there will be no adjustment for multiple testing; p-values and confidence intervals will be reported instead. We will assess participant CAPS and PDS scores at baseline and two months after each participant has undergone a final session, defined as the last experimental or open-label MDMA-assisted psychotherapy session, using the same nonparametric tests employed in comparisons of active placebo and experimental dose MDMA described above.

2.8.4. Methods and Schedule of Events

Table 2: Schedule of events:

Time																	
	h=hour																
	d=day																
	w=week																
	m=month																
weeks from start	-4 to -2	0	1	2	3	3 + 1 d	4	5	6	6 + 1 d	7	8	9	9	9 + 1 d	10	11
Medical Exam	x															x	
Informed consent	x																
SCID	x																
Metabol. profile, Thyroid Panel	x															x	
Liver Enzymes	x															x	
ECG	x																
Urine Drug Screen ³	x					x				x				x		x	x
Urine Pregancy Screen	x					x				x				x			
EEG/ Startle	x															x	
SCID	x														x	x	x
CAPS		x										x			x	x	x
PDS		x				x				x			x		x	x	x
RRPQ																	x
Nondrug Therapy			x	x		x	x	x		x	x	x		x	x	x	x ²
MDMA Therapy					x				x				x				
Vital Signs	x				x				x				x				
SUDS					x				x			x		x			
Both			x ¹	x ¹	x	x			x	x			x	x			

therapists present																
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x¹: Both therapists present at either one of the two introductory sessions.

x²: A half-hour closing meeting with the investigators; Participants learn condition assignment.

³: Urine drug testing will be done once additionally at random during the treatment phase

The study consists of eleven non-drug psychotherapy sessions, three sessions of MDMA-assisted psychotherapy, and five separate administrations of outcome measures (see Table 2). Most non-drug psychotherapy sessions will be scheduled on a weekly basis, and the three experimental sessions will be scheduled three to five 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. Peter Oehen and Verena Widmer Oehen, a female co-therapist. Both therapists will also be present during one of the introductory therapy sessions and during each of the three 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 according to Table 2.

2.8.5. *Nature of MDMA-assisted Psychotherapy*

MDMA-assisted psychotherapy consists of the following phases and therapeutic elements described in detail in the treatment manual for MDMA-assisted psychotherapy in patients with PTSD (Ruse et al. 2005, unpublished). The manual bases on 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 and Adamson 2001; Greer & Tolbert 1998):

Phase 1: Establishing therapeutic alliance, gathering of information, patient orientation and creating a safe psychological and physical space:

Two introductory 90 minute sessions will be used to establish a positive therapeutic alliance and to create an atmosphere and a space of complete safety and trust permitting the patient to let the MDMA-experience unfold and to confront himself or herself with the traumatic experiences that are the basis of his or her PTSD. Information about the traumatic experiences, previous treatments, previous use of drugs and psychedelics, expectations, motivations, fears and concerns about the MDMA sessions are gathered to get as much relevant information as possible in order to create a sufficient understanding of the patient and his problems. The patient is informed about the setting, how the MDMA-assisted sessions proceed, how psychological difficulties are dealt with, how the participant will be supported and what safety measures will be provided. Goals and intentions for the session are discussed.

Phase 2: MDMA-Sessions:

Before ingestion of the MDMA the goals, intentions and concerns are reviewed. The participant is reminded of the effects of MDMA which include enhanced positive mood, changed thoughts of

meaning, increased access to distressing thoughts and memories, reduced anxiety, reduced self-blame and judgement, as well as increased feelings of closeness to others. Onset of MDMA-effects is after 30 to 60 minutes after ingestion. The main psychotherapeutic effective elements induced by MDMA are: prolonged spontaneous reliving of and confrontation with traumatic memories and emotions; cognitive restructuring, processing of difficult emotions, release of tension and somatic symptoms, increased awareness of past and present positive experiences, new perspectives and changes of meaning. The therapeutic approach is non directive, following and encouraging the MDMA-induced process. Discussions between therapist and participant are only intermittent. The therapists may employ other techniques, including focused body work and anxiety management techniques. Focused body work employs nurturing touch (hand-holding or hugging) and touch aimed at intensifying and thereby releasing body tension and pain by giving resistance for the participant to push against. Focused body work is always performed with explicit consent from the participant and respecting boundaries and

vulnerabilities of the patients. Transference is not a main focus and is addressed openly in early stages if necessary. Subsequent MDMA-assisted sessions lead to deeper emotional experiences, building on the experiences and results from the previous sessions.

Phase 3: Follow-up and Integration Sessions:

A 90-minute non-drug follow-up talk session the day after the MDMA experience and 2-4 sessions one week apart ensure the understanding, acceptance and integration of the insights and experiences from the MDMA-sessions. Goals and intentions are evaluated and reconsidered for the following MDMA sessions. The MDMA-induced shift of self- and other related cognition and emotion helps the patient gain a new perspective and meaning of his symptoms and life with a new sense of safety and control. Expressive techniques such as writing or drawing are encouraged. Therapist also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced on MDMA sessions to emotionally threatening everyday situations. Therapist attitude is supportive, validating the MDMA experience and facilitating understanding and emotional clearing. Therapists are accessible any time the participant needs support outside the scheduled integration sessions.

2.8.5.1. Details of MDMA-assisted Experimental Sessions

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 the office of Dr. Oehen in Biberist, Switzerland. There will be sufficient equipment for assessing blood pressure, pulse and body temperature, and for dealing with potential adverse events, such as hypertension. In case of a hypertensive crisis the next hospital with emergency room and ICU is 5 minutes away from the office (Bürgerspital Solothurn). 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.

Blood pressure, pulse and temperature will be measured according to Table 3. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

Approximately 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. 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.

Table 3. Schedule of Procedures and Measures for Experimental Sessions

TIME	Procedure or Action
9:00	Urine drug screen and pregnancy test. Participant acclimated to environment
9:45	Baseline BP, Pulse, Temp, Subjective Units of Distress Rating (SUDS)
9:55	2 nd Baseline BP, Pulse, SUDS
10:00	Drug Administration, begin audiotaping
10:30	BP, Pulse.
11:00	BP, Pulse, Temp, SUDS
11:30	BP, Pulse
12:00	BP, Pulse, Temp
12:30	BP, Pulse, SUDS
13:00	BP, Pulse, Temp
13:30	BP, Pulse,
14:00	BP, Pulse, Temp, SUDS
Every hour, and as needed	BP, Pulse,
Every 60-90 minutes	SUDS, Temp

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 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 at Dr.Oehen's office where the MDMA-assisted therapy session will take place. The office is located right next to the house of Dr. Oehen. He will check on the participant before he leaves for the night. He is available on all times during the night following the experimental session if requested to do so by the participant or the designated support person. 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. Oehen will remain available to participants via 24-hour cellular phone.

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, pending approval from Dr. Oehen after he has met this support person and has discussed the possible advantages and pitfalls with the study subject.

2.8.5.2. Details of Non-Drug Psychotherapy 24 Hours Post-Experimental Session

The scheduled sixty to ninety-minute therapy session will take place in the morning after the experimental session. After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the participant due to unforeseen events, the investigators will assist the participant in finding an alternative means of returning home.

The therapist-investigators and the participant will discuss the experimental session and any 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 participant's psychological well-being during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study.

2.8.5.3. Outcome Measure Administration

The assessment of PTSD symptoms as described under 2.8.2 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 any of the experimental sessions. He or she will, therefore, be naïve to complaints of medication side effects. Outcome measures may be administered at the same office 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.

2.8.6. Open Label Continuation for Active Placebo Patients ("Stage 2")

After each participant completes all outcome measures on the session scheduled 3 weeks after the third experimental session (T2), 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 three experimental sessions scheduled two to four weeks apart. Outcome measures administered three weeks after the third 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.

2.8.7. Open Label Continuation for Full Dose Patients ("Stage 3")

Participants who have completed Stage 1 or Stage 2 of the study and showed insufficient clinical response to the fully active dose of 125mg MDMA followed by a supplemental dose of 62.5mg 2.5 hours later, will be offered the opportunity to enroll in the open label continuation of the study referred to as "Stage 3". The possibility of participating in phase 3 will not be disclosed to participants until "non-response" has been determined at T3. This is to ensure that participants are not influenced by this information during phase 1 and phase 2 respectively of the trial. Participants will receive separate informed consent forms for phase 3.

Response will be considered clinically insufficient on the basis of the PI's and patient's subjective impression of the lack of significant improvement. CAPS change scores (T0: baseline to T3: 2 months after the third experimental session) \leq 15 points (Weathers 2001, Schnurr 2007), CAPS item #25 \geq 3 and overall CAPS score still \geq 50 points at outcome measurement 2 months after the third experimental session (T3) as assessed by the independent assessor will serve as additional guidelines for the assessment of clinical insufficient response. A strict definition of non-response is presently not possible since the magnitude of placebo reactions as well as the length of persistence of CAPS score reductions is not known yet. Factors such as obsessive-compulsive personality traits (Grof 1980, Styk 2007), high levels of anxiety or distrust are known to be associated with clinical insufficient response. Higher doses of up to 187.5 mg MDMA in a single administration have been used prior to the scheduling of MDMA in therapeutic contexts (Stolaroff 2004). Charles Grob administered single doses over 150 mg on eight occasions to four participants in his FDA-approved Phase 1 MDMA safety study without any Serious Adverse Events (SAEs)

The subject will be required to give written informed consent to take part in Stage 3 of the study, with consent given separately from the initial consent. If the participant consents to take part in Stage 3 of the study, he or she would receive an initial dose of MDMA that will either be identical to that used in Stage 1 and 2 or that of 150 mg, followed by a supplemental dose of up to 75 mg 2.5 hours later, during two experimental sessions scheduled two to four weeks apart. The investigators will use clinical judgment as the basis for determining initial and supplemental dose for each of the two Stage 3 sessions, and they may use their judgment to employ a different dose during the second session on the basis of their experience during the first Stage 3 session. Outcome measures administered 2 months (T3) after the third experimental session will serve as baseline measures for Stage 3. 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 stage 1 of the 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.

2.8.8. 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 280 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; Freedman et al. 2006; Gamma et al. 2000; Frei et al. 2001; Grob et al. unpublished; Grob et al. 1996; Harris et al. 2002; Johanson et al. 2005; Hernandez-Lopez et al. 2003; Kuypers and Ramaekers 2005; Kuypers and Ramaekers 2006; Kuypers and Ramaekers 2007A; Kuypers and Ramaekers 2007B; Lester et al. 2000; Lamers et al. 2003; 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; Ramaekers and Kuypers 2006A; Ramaekers and Kuypers 2006B; Segura et al. 2001; Segura et al. 2005; Tancer and Johanson 2001; Tancer and Johanson 2003; Tancer and Johanson 2007I; Vollenweider et al. 1998; Vollenweider et al. 1999; Vollenweider et al. 2005). 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 basic emergency equipment will be immediately available. Dr. Oehen's office is located five minutes from the next hospital, the Bürgerspital Solothurn, which has an emergency room and an intensive care unit. The hospital will be informed in advance about the nature of this study.

Hypertension and related cardiovascular complications:

Blood pressure and pulse will be measured at regular intervals (see table 3). If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. During this time the principal investigator will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. The principal investigator will make a clinical judgment about whether additional monitoring or treatment is required. Reasons for moving a patient to an ICU would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. This will allow treatment to be instituted without transferring the participant if that should become necessary. The investigator may, at any time, make a clinical judgment to transfer the participant to the ICU for closer monitoring and additional treatment. Any participant who experiences sustained blood pressure of > 220 systolic or > 120 diastolic or heart rate > 75% predicted maximum during an experimental session will not be given a subsequent 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.

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 further assessment and management.

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 research facility for the night after each experimental session. The investigator will be able to attend to the participant if there is a need to deal with continued psychological distress.

If, by the end of 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 designated support person 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. Oehen may make the clinical judgment to proceed to option B.

B. Hospitalization for stabilization

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

Hyperthermia:

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 or second 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 any subsequent experimental sessions.

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 any subsequent experimental sessions 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 pre-existing abnormalities will be excluded from the study. If a participant exhibits signs of liver toxicity after an experimental session, then he or she will not receive a subsequent experimental session.

Neuropsychological toxicity:

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

Abuse and dependence:

Although the likelihood for abuse or MDMA dependence triggered by the participation in this study is assumed to be very low (see 6.), the consumption of drugs of abuse outside of the study will be monitored carefully: Participants meeting the criteria for substance abuse or dependence 60 days prior to the screening will be excluded. Urine drug testing will be done before each experimental MDMA-session, once at random during the treatment phase as well as at the assessments T2-T5 by the

independent rater. The relevant modules of the SCID-II will be administered at the assessments T1-T5. The researchers will be alert to the question of MDMA abuse during the treatment phase and will explicitly address this point at the closing visit.

Part 2: MDMA

3. Chemistry, Manufacturing and Control Information

The drug product is d,l(3,4)-methylenedioxymethamphetamine HCl, 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. The product to be used in this study was synthesized by Lipomed AG, Switzerland in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On 30.01.06 a quality control was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94. 1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

The encapsulation will be performed by the Laboratory Dr. Bichsel in Interlaken, Switzerland. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, mannitol or a similar inactive compound used to ensure that all capsules have similar weights. The lowest dose contained in one capsule will be 12.5 mg, which is the supplemental dose offered to participants in the 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.

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

4. Pharmacology and Toxicology

4.1. Primary Pharmacodynamics

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 D₂ 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 mild 5-HT_{2A} 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 1986). 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 (Franowicz 1998), MDMA produces feelings of calmness and relaxation (Cami et al. 2000). 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.

4.1.1. 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 D₂ 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.

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4.1.2 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; Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Tancer and Johanson 2001; Tancer and Johanson 2003; 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 (Saunders 1993). In 2000, an MDMA/PTSD therapy study was approved in Spain (AEM #99-309), but has unfortunately 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).

4.2. 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 from previous reports. Pre-treatment with 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 D₂ 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 (de la Torre et al. 2000; Farre et al. 2004; Johanson et al. 2005; 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). The initial dose of 125mg and the supplemental dose of 62.5 mg are identical to the doses used in the FDA and IRB-approved MAPS-sponsored study of MDMA-assisted therapy in people with anxiety associated with advanced-stage cancer (IND 63,384). The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 2.5 h 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. It is expected that elevation in blood pressure and heart rate may be greater than 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. Likewise, an initial dose of 150 mg with a supplemental dose of 75 mg are likely to elevate blood pressure and heart rate to a greater degree than 125 mg and closer to those seen after 2 or 2.5 mg/kg.

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 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 immunomodulation is unclear but may be at least partly due to increased glucocorticoid levels or sympathomimetic activity, and activity at alpha adrenergic receptors (Connor et al. 2004). Serotonin release probably plays a role in these changes, since paroxetine pretreatment attenuated and in some cases eliminated immunological effects of MDMA (Pacifici et al. 2004) while only partially reducing elevated cortisol. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 2004). This immunomodulation is an acute effect of MDMA and is not likely to persist for more than 48 hours after MDMA administration.

4.3. Safety Pharmacology

4.3.1. *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. The acute side effect profile of a dose of 150 mg is expected to increase with the higher dose.

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 task (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. A study assessing impulsivity after 75 or 100 mg MDMA alone or in combination with alcohol found that MDMA improved performance on one measure of impulsivity while neither improving nor impairing performance on the other measures.

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; Sumnall et

al. 2004; Thomasius et al. 2003). A meta-analytic examination found that ecstasy use was significantly associated with self-reported depressive symptoms (Sumnall et al. 2005), but also remarked on the difficulty of separating self-reported depressive symptoms from sub-acute effects of ecstasy. When assessed via diagnostic interview, ecstasy users were not more likely to have affective disorders than controls (de Win et al. 2004; Thomasius et al. 2005). Given the tenuous link between repeated ecstasy use and psychiatric symptoms, it is not expected that three 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 [$H_2^{15}O$]-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).

4.3.2. *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-HT_{2B} receptors, which stimulate heart valve cell growth (Setola et al. 2003). 5-HT_{2B} 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. Valvular heart disease is associated with daily use of fenfluramine, whereas MDMA will not be administered on a daily basis in this study.

4.5. *Pharmacokinetics/Toxicokinetics*

The pharmacokinetics of MDMA, summarized 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.

Table 4. MDMA Pharmacokinetics

MDMA Dose	N	C_{max} $\mu\text{g/l}$	T_{max} H	AUC₀₋₂₄ $\mu\text{g}^*\text{h/l}$	AUC/dose $\mu\text{g}^*\text{h/(l*mg)}$	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
100	7	232.9 ± 45.3	1.5	Not reported	NA	Segura et al. 2005
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	de la Torre et al. 2000a

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

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 $232.2 \pm 39 \mu\text{g/L}$, $AUC_{(24-48)}$ was $2564 \pm 762 \mu\text{g}^*\text{h/L}$, $T_{max(24-48)}$ was $25.5 \pm 0.33 \text{ h}$, and AUC/dose was $25.64 \pm 7.6 \mu\text{g}^*\text{h/l*mg}$. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), probably as a result of non-linear pharmacokinetics. 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} .

4.5.1. Summary of Pharmacokinetic Parameters

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxymphetamine (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-methylenedioxymethylacetone, and N-hydroxy-3,4-methylenedioxymphetamine (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 methylenedioxyl 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 demethylation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylation, including CY1A2 and CYP3A4.

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 (de la Torre et al. 2005; 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. A comparison of MDMA metabolism in the poor metabolizer and extensive metabolizers with and without a dysfunctional CYP2D6 gene, finding that reduced CYP2D6 function was associated with higher MDMA AUC after the first of two doses of MDMA, but similar levels of MDMA and metabolites after the second dose (De la Torre et al. 2005). 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 than the R-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (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)

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

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Segura et al. 2001; Segura et al. 2005; 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).

4.6. 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 2003 update of the Investigator’s Brochure (Jerome 2004). In addition to hyperthermic syndromes, other rare adverse events include anxiety, dysphoria or psychosis (psychiatric problems), 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.

4.6.1. Hyperthermia

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; Darvesh et al. 2004; Green et al. 2004; Malberg et al. 1998; O’Shea et al. 2005) promotes a hyperthermic reaction to MDMA. It is expected that hyperthermia will be very unlikely to occur 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 and ambient temperature during the course of the study.

4.6.2. Hepatotoxicity

Because hepatotoxicity has been noted in ecstasy users, *in vitro* and *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 vitro studies found that high to very high concentrations of MDMA increased ALT, AST and LDH activity (Beitia et al. 2000), increased pro-fibrogenic activity in cultured stellate cells (Varela-Ray et al. 1999) and slightly reduced cell viability without producing lipid peroxidation (Carvalho et al. 2001). Incubating cells with slightly smaller concentrations of MDMA at high temperatures further reduced cell viability (Carvalho et al. 2001; Montiel-Duarte et al. 2002), with apoptosis (cell death)

seen when concentrations of MDMA approximately eleven times those seen in humans were incubated at high temperatures (Montiel-Duarte et al. 2002). Hepatotoxicity is probably the result of oxidative stress (Carvalho et al. 2004; Montiel-Duarte 2004), with antioxidants preventing or reducing hepatotoxicity, and the MDMA metabolite α -methyl-dopamine (α -MeDA) may also be involved in producing hepatotoxicity (Carvalho et al. 2004). In vivo studies in mice indicate that oxidative stress and high ambient temperature influence hepatotoxicity in mice (Carvalho et al. 2004; Johnson et al. 2002). MDMA given at higher doses and at high ambient temperature was associated with signs of oxidative stress and liver abnormalities (Carvalho et al. 2002), and repeated injections of 10 mg/kg, but not 5 mg/kg, S-(+)-MDMA, 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. Studies in rats also found a dose dependent increase in signs of oxidative stress in the liver (Ninkovic et al. 2004; Rusinyak et al. 2004).

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 \sim 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 ($236.4 \pm 57.97 \mu\text{g/l}$ 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 study begin and at the time of medical examination at the 2 month follow-up (see Table 2 above).

4.6.3. 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; Jerome 2005).

Two studies performed by the same team of researchers comparing MDMA administration (three 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) and heat shock protein (HSP), markers of neuronal injury (Wang et al. 2004; Wang et al. 2005). MDMA lowered brain serotonin and serotonin transporter binding without altering levels of serotonin transporter, GFAP or HSP, suggesting a dissociation between brain serotonin levels and other presumed markers of neurotoxicity. The study conducted in 2005 failed to find differences

in distribution of serotonin transporter, an indicator that transporter functionality has not changed as a result of altered distribution. 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 proline, used as a measure of axonal neurotoxicity (Callahan et al. 2001). Rhesus monkeys given 10 mg/kg MDMA exhibited plasma MDMA levels ten times higher than those seen in human volunteers given MDMA (Bowyer et al. 2003), and a recent study that plasma MDMA in squirrel monkeys given from 2.4 to 8.6 mg/kg MDMA were far higher than expected via interspecies scaling. A commonly used means of calculating human-equivalent doses in other species (Mechan et al. 2005). These recent findings raise issues concerning the interpretation of previous studies of MDMA neurotoxicity that used doses based on interspecies scaling. 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, the above described studies in squirrel and 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 [¹¹C]McN5652 before and after a single dose of MDMA (Vollenweider et al. 2000, data presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine). Vollenweider and colleagues were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in a pilot study with six MDMA-naive healthy volunteers and in a second study with 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.

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. Two research teams imaged the brains of ecstasy users with the same ligand (McCann et al. 1998; Buchert et al. 2003; Buchert et al. 2004; Buchert et al. 2005), and two used different ligands (Reneman et al. 2001; McCann et al. 2005). The most recent study compared images with McN5652 and [¹¹C]DASB, a newly developed ligand (McCann et al. 2005). All studies found lower ligand binding, considered an estimate of serotonin transporter binding, in the brains of current ecstasy users. It is worth noting that recent studies (Buchert et al. 2004; McCann et al. 2005) report a lesser degree of reduction in estimated serotonin transporter sites than seen in the initial report (McCann et al. 1998). A longitudinal study in current and abstinent ecstasy users (Buchert et al. 2005), and two cross-sectional comparison studies of current and former ecstasy users (Buchert et al. 2003; Buchert et al. 2004; Reneman et al. 2001) found that estimated serotonin transporter sites increased as period of abstinence increased (Buchert et al. 2005), and that estimated transporter binding was similar to levels seen in controls (Buchert et al. 2004; Reneman et al. 2001). The study using the newly created ligand DASB failed to find a significant relationship between period of abstinence and estimated serotonin transporter sites

(McCann et al. 2005). Two research teams using different ligands found reduced binding in women (Buchert et al. 2004; Reneman et al. 2001), though 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.

4.6.4. 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 $1.4 \pm 4\%$, while 1.2 mM MDMA decreased cell survival by $61 \pm 9\%$. In another study, the effects of MDMA on cultured rat neocortical neurons were studied at concentrations of 125 to 1000 μ M MDMA and exposure times of 1, 24, and 96 hours (Stumm et al. 1999). Cell survival was decreased by $34.2 \pm 11.4\%$ at 96 hours after an average exposure of 500 μ M MDMA, but not after 125 μ M 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. 2004).

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 $236.4 \pm 57.97 \mu\text{g/l}$ MDMA (de la Torre et al. 2000b) and peak brain levels of $1.4 \pm 0.3 \text{ mg/L}$. 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 μ M 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.

4.6.5. 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. Though results were likely hampered by the extremely low use of ecstasy by pregnant women, a more recent case control study also failed to find an association between ecstasy use in pregnancy and a heart defect (Bateman et al. 2004). 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.

5. Previous Human Experience

Clinical MDMA research using healthy volunteers has been conducted by at least seven research groups, including one in Switzerland. 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; Gamma et al. 2004; Liechti et al. 2000a; Liechti et al. 2000b; Liechti et al. 2001a; Liechti et al. 2001b; Liechti and Vollenweider 2000a; Liechti and Vollenweider 2001b; Vollenweider et al. 1998; Vollenweider et al. 1999; Vollenweider et al. 2005). The Zurich researchers have also published a review of the data that notes gender differences in MDMA effects (Liechti et al. 2001a), 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; de la Torre et al. 2005; Navarro et al. 2001; Pichini et al. 2002; Pichini et al. 2003; Pizarro et al. 2002; Pizarro et al. 2003; Segura et al. 2002; Segura et al. 2005). While it appears that the researchers reported data from 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), sought to replicate rodent drug discrimination findings in 8 volunteers given 1 and 1.5 mg/kg MDMA (Johanson et al. 2005), examined the effects of ambient temperature and 2 mg/kg MDMA in ten participants and fluoxetine pre-administration in eight participants (Freedman et al. 2006; Tancer and Johanson 2007). The Wayne State researchers have presented data from studies of ambient temperature and 2 mg/kg MDMA in ten subjects, and co-administration of fluoxetine with 1.5 mg/kg MDMA in eight subjects (Freedman et al. 2006; Tancer and Johanson 2007). 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 related to driving skills. The same team has performed several investigations into the acute effects of MDMA in ecstasy-experienced participants, including a study of 75 and 100 mg MDMA on impulsivity in 18 men and women (Ramaekers and Kuypers 2006A), acute effects on verbal memory in 18 participants (Kuypers and Ramaekers 2005), visual memory in 18 participants

(Kuypers and Ramaekers 2007A), driving-related skills in two studies in 18 participants (Kuypers and Ramaekers 2006; Ramaekers and Kuypers 2006B) and the effects of MDMA administered nocturnally in 14 participants (Kuypers and Ramaekers 2007B). 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. 2002; Forsling et al. 2001; Henry et al. 1998). 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 three successive revisions to the IB (Jerome and Baggott 2003; Jerome 2004; Jerome 2005).

Clinically significant hypertension has occurred in 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 or three 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. The study was later amended to include the use of a supplemental dose of 62.5 mg 2 to 2.5 hours after the initial dose and also a third session. Fifteen participants have completed the study., Three participants who received placebo have undergone two open-label sessions of MDMA-assisted psychotherapy, and one has undergone three sessions. Ten had received MDMA, and five received placebo. A psychologist assessed participants with the CAPS, the Impact of Events scale (IES) and SCL-90-R,. All ten participants who received MDMA-assisted therapy had improved CAPS scores two months after the second experimental session, and three of five participants who received placebo-assisted therapy had improved CAPS scores. The other placebo participants showed worsening PTSD symptoms (Mithoefer 2007). The psychologist also assessed cognitive function at the start of the study and two months after the experimental session, and failed to find significant differences in cognitive function between participants who received MDMA and those who receive placebo.

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.

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 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 drug-related 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-naïve 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.

6. Drug Dependence and Abuse Liability

MDMA is classified as a Schedule I compound (in Switzerland “Betäubungsmittel”) with a high potential for abuse, primarily because of its use in settings such as “rave” or 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, 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.

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.

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. 1999 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. 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. 2003; Wakonigg et al. 2004) and non-human primates (Beardsley et al. 1986; Fantegrossi et al. 2002; Fantegrossi et al. 2004; Lamb and Griffith 1987; Lile et al. 2005) 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-naïve rat descended a runway to obtain an injection of MDMA also found that descent was more rapid 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, either previous to the study or with cocaine offered before MDMA. 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. Rhesus monkeys were willing to work to self-administer MDMA, but they were willing to work harder to self-administer cocaine (Lile et al. 2005). 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 without any major psychiatric illnesses who were taking part in clinical trials of 1.5 to 1.7 mg/kg MDMA conducted in a non-psychotherapeutic setting reported that they had no interest in self-administering the drug outside the confines of a controlled laboratory setting (Liechti et al. 2001).

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 causal 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, then 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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