Protocol

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A HUMAN PHASE II STUDY –

SAFETY AND EFFICACY OF

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)-

ASSISTED PSYCHOTHERAPY IN THE TREATMENT OF CHRONIC

POSTTRAUMATIC STRESS DISORDER (PTSD)

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Introductory Statement and General Investigational Plan

This application is for a Phase II pilot study into the use of 3,4-methylenedioxymethamphetamine (MDMA) to treat patients with chronic Posttraumatic Stress Disorder (PTSD). This study builds on FDA-approved research begun in the Phase 1 trials conducted at Harbor-UCLA Medical Center by Dr. Charles Grob (Grob et al. 1996), at The University of California, San Francisco by Dr. John Mendelson (Lester et al. 2000), and at Wayne State University by Dr. Manny Tancer and Charles R. Schuster, Ph.D**.** (Tancer, personal communication), and on ongoing Phase I research being done in Switzerland by Dr. Franz Vollenweider and his colleagues (Gamma et al. 2000; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2001b; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998; Vollenweider et al. 1999b) and in Spain by Drs. R. de la Torre**,** Jordi Cami and Magi Farre (Cami et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Mas et al. 1999; Pacifici et al. 2000; Pacifici et al. 1999; Pacifici et al. 2001).

On June 24, 1999, Dr. Cynthia McCormick chaired a teleconference between staff from the Division of Anesthetics, Critical Care and Addiction Drug Products (ACCADP) and Dr. Charles Grob, Dr. Rick Doblin, Loren Miller and Matthew Baggott (Memorandum of Telecon Meeting Minutes, July 23, 1999). The teleconference had been requested by Dr. Charles Grob and Dr. Rick Doblin, after FDA policy regarding MDMA research had been reviewed by Center-level policymakers. The purpose of the teleconference was "to discuss what preclinical studies, if any, would be required before further studies in humans would be permitted."

Dr. McCormick reported that the "Center has decided to allow the sponsor [MAPS] to undertake a proof-of-principle study without further pre-clinical data" and that the proof-of-principle study should be "a solid clinical trial capable of demonstrating efficacy." In response to a request by Dr. Rick Doblin "to begin with some pilot patients to allow the treatment team to develop their technique in administering the drug and concomitant therapy," Dr. McCormick stated that "a case could be made for a pilot study with controls, to establish the effect size in order to appropriately power the main study."

This protocol in patients with posttraumatic stress disorder (PTSD) involves a different patient population than the protocol discussed during the teleconference, which was in patients with terminal cancer. On the one hand, the acute risks associated with the administration of MDMA are less of a concern in PTSD patients than in cancer patients, due to the absence of significant physical disease in PTSD patients. On the other hand, the risks of long-term functional or behavioral consequences associated with the possibility of MDMA neurotoxicity are more of a concern in PTSD patients than in terminal cancer patients, due to the potentially longer life span of the PTSD patients. Based on the evidence presented in this protocol and the associated literature review, these risks are more than balanced by the potential benefits to the subjects.

This randomized double-blind placebo-controlled pilot study is designed to gather preliminary information about the safety and efficacy of MDMA-assisted psychotherapy

in stimulating therapeutic processing of traumatic experiences, with the goal of reducing or relieving symptoms of PTSD. If data from this pilot study reveals no unexpected safety issues, more definitive proof-of-principle studies will be submitted to FDA.

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 hallucinogen mescaline. MDMA does not cause hallucinations and other extreme changes in perception in the way that mescaline does. MDMA has some unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Shulgin, 1990, Greer and Tolbert, 1998). Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens (Nichols and Oberlender, 1990). The term refers to MDMA and similar substances that produce increased feelings of closeness to others, increased sensitivity to emotions and increased insights about the self, especially in the context of interpersonal relationships.
The drug is a white, crystalline powder and will be administered orally in capsule form (FDA Drug Master File 6293).

Before MDMA became a Schedule I drug, it was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists (Greer and Tolbert 1986: Saunders 1993; Stolaroff 1997). There are a number of published case reports and uncontrolled studies of its effects. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways: Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" (Greer and Tolbert 1998). Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. It has also been asserted that MDMA causes increased empathy for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience (Greer and Tolbert,1998, Holland, 2001).

To date, no study in this country has attempted to evaluate the safety, efficacy or mechanism of action of MDMA as an adjunct to psychotherapy in PTSD patients or in patients with any other psychiatric disorder. There is presently an ongoing study in PTSD patients in Spain, which is still in the very early stages of treating subjects.(Bouso Saiz and Sopelana Rodriguez, AEM Protocol #99-309).

This proposed experiment will involve twenty subjects. Patients are to be recruited through newspaper advertisements intended to attract patients who are not currently in treatment. Only chronic PTSD patients who have failed to benefit from or tolerate psychopharmacological or psychotherapeutic treatment will be included. The subjects in the experimental group will receive two MDMA treatment sessions (125 mgs./treatment)

3 - 5 weeks apart, while controls will receive an inactive placebo during the same sessions. Both groups will experience identical psychotherapeutic treatment during the experimental sessions. All sessions will be conducted in a carefully controlled setting in the presence of a male and a female therapist (a male psychiatrist and a female nurse) with whom the patient has previously had the opportunity to develop a therapeutic alliance during several introductory non-drug psychotherapy sessions. There will be follow-up non-drug psychotherapy sessions with the therapists between MDMA or placebo sessions to aid in further processing and integration of the experiences.

The subject population of chronic PTSD patients was selected in part because of patient and therapist reports as to the effectiveness of MDMA-assisted psychotherapy in treating PTSD, from treatments conducted prior to the criminalization of MDMA in 1985. The qualities that have been associated with MDMA in anecdotal reports (i.e. decreased defensiveness and enhanced therapeutic alliance) seem to have the potential to be particularly useful in the treatment of this disorder. PTSD is a condition that involves prominent fear responses. Revisiting traumatic experiences in psychotherapy is recognized to be of therapeutic value. Early clinical experience with MDMA is consistent with the hypothesis that it can increase therapeutic effectiveness in this population. It is also a disorder for which there is, to date, only one FDA-approved medication, and about which there are still many unanswered questions regarding psychological and pharmacological interventions (Montgomery and Beck 1999). The lifetime prevalence of PTSD in the general population may be as high as 10% (Meltzer-Brody et al. 2000), so the search for additional and more effective treatments is extremely important.

The rise in illicit, recreational use of "Ecstasy" (MDMA) since it became scheduled has contributed to concern about its toxicity. Given the widespread use by millions of people around the world, remarkably few related problems have come to clinical attention. Nevertheless, there have been some serious complications and even deaths associated with the use of "Ecstasy" (often containing substances other than MDMA) at raves, primarily due to hyperthermia, dehydration or hyponatremia. 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 illegal Ecstasy consumption have occurred in conditions of high ambient temperature, long periods of strenuous activity (dancing) and insufficient or uncontrolled fluid intake.

On the other hand, according to the data from several phase I trials conducted in the United States, Spain and Switzerland, when MDMA is used in therapeutic doses in a controlled setting, the risk/benefit ratio is favorable (Aghajanian and Lieberman 2001; Cami et al. 2000; de la Torre et al. 2000a; de la Torre et al. 2000b; Lester et al. 2000; Lieberman and Aghajanian 1999; Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Liechti et al, 2001: Mas et al. 1999; Vollenweider et al. 1998; 1999: See also data collected by CS Grob in Previous Human Experience and attached letters of support). There has been no evidence of significant or lasting toxicity in phase I studies. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e.g., Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle

neurocognitive changes may occur in a subset of repeated users of illicit MDMA and other drugs (e.g., Gouzoulis-Mayfrank et al. 2000; Gouzoulis-Mayfrank, attached letter of support). In contrast, our all available phase I data (published and yet unpublished) indicate that it is unlikely that the MDMA exposures proposed in this protocol cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Tests of neurocognitive function have found that performance is not affected by participation in clinical MDMA trials (Boone et al. in preparation, see also **Table 2.5** in Investigator's Brochure; Vollenweider et al. 2001; Vollenweider, attached letter of support). Vollenweider and colleagues (2000) recently presented positron emission tomography data at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine that found no change in estimated serotonin transporter binding sites four weeks after a dose of MDMA similar to our proposed dose of 125 mg was given to MDMA-naïve volunteers. Based on these data and an extensive review of the MDMA literature, we conclude that risks of neurocognitive, serotonergic, or other toxicity are low in the proposed protocol.

These low risks are more than balanced by the potential benefits to the volunteers. All participants have had at least one unsuccessful attempt at treatment with medications and psychotherapy and may find some relief associated either with MDMA-assisted psychotherapy or with the non-drug psychotherapy to be administered to the control subjects. Studies in humans and non-human animals suggest that ongoing symptoms and stress of untreated posttraumatic stress disorder may be neurotoxic in hippocampal areas (Bremner 1999; Ling 1981; Rauch 1996; Sapolsky 1990; Shin 1997; Wolkowitz, 1990). Hence the risks posed by MDMA-assisted psychotherapy are offset by the benefits of treating PTSD and its neurotoxic effects in one or more areas of the brain.

Based on these findings, which will be discussed further below in the section on Pharmacology and Toxicology, it is very unlikely that the doses we propose to administer in a controlled clinical setting will cause memory impairment or other neurological or physiological damage. These low risks are more than balanced by the potential benefits to the volunteers. All subjects have had at least one unsuccessful attempt at treatment with medications and/or psychotherapy and may find some relief associated either with MDMA-assisted psychotherapy or with the non-drug psychotherapy to be administered to the control subjects.

Rationale for Studying PTSD

A) Epidemiology of PTSD:

Posttraumatic stress disorder (PTSD) occurs in response to a traumatic event or events. Approximately 10% - 20% of people who experience a major trauma go on to develop PTSD, giving it an estimated 8% prevalence in the general population (Kessler et al. 1995). It is most likely to occur following an event involving perceived personal threat, such as rape or physical assault (Breslau 1998), and it develops approximately twice as often in women as it does in men. Vulnerability to PTSD is increased in people with a family or personal history of psychiatric illness, particularly anxiety or depression (McFarlane 1989). The most common comorbid conditions appear to be major depression, followed by generalized anxiety and substance abuse (Montgomery et al., 2000). In the National Comorbidity Study, 88% of men and 79% of women with PTSD reported a lifetime history of at least one other psychiatric disorder. Fifty percent of people with PTSD had 3 or more comorbidities. PTSD generally precedes most comorbidities, particularly affective and substance abuse disorders (Kessler et al., 1995). In addition to the psychiatric manifestations, individuals with PTSD have an increased incidence of physical problems and impairments in social and occupational functioning that lead to increased healthcare utilization and decreased quality of life (Brady et al. 2000: Kessler et al. 1999; Solomon and Davidson, 1997). PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. The search for more effective treatments and a wider array of treatments is crucial. In a recent update on PTSD by three experts in the field it was stated that,

"Pharmacologic agents and psychotherapeutic modalities are components of a multidimensional treatment strategy. …PTSD often responds slowly and may not completely resolve, even with prolonged intervention. Because PTSD can devastate nearly every aspect of life, refinements in diagnostic accuracy and management options are clearly needed… Leaving aside cost issues in the healthcare system, patients with PTSD suffer significant impairments of work productivity, relationships, and overall health. The effects on society are no doubt enormous" (Brady et al. 2000, p. 25).

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

treatments, such as MDMA-assisted psychotherapy, which have shown promise in anecdotal reports.

B) Biology of PTSD:

Although the biology of PTSD is not completely understood, animal models have been developed to study the neurobiology of the key PTSD symptoms, re-experiencing, avoidance/numbing, and hyper-arousal. The following two tables by Dennis Charney, MD (in Brady et al., 2000) summarize findings from the study of the conditioned-fear model in animals:

Table 1: Neurobiologic Changes in Animal Models of Conditioned Fear

Neuroanatomic:
4. Damage and/or cell death in the hippocampus
5. Stimulation of the amygdala
6. Stimulation of the red nucleus of the stria terminalis

Hypothalamic-pituitary-adrenal (HPA) axis
7. Elevated levels of corticotropin-releasing hormone (CRH) in the brain.

Neurotransmitters:
8. Elevated norepinephrine levels
9. Elevated serotonin levels
10. Elevated acetylcholine levels
11. Elevated dopamine levels in the prefrontal cortex

Other effects:
Reduced levels of messenger RNA (mRNA) encoding brain-derived neurotrophic factor

(Adapted by Charney from Rasmusson and Charney, 1997, and Davis 1999)

Table 2: Noradrenergic and Serotonergic Changes in Animal Models of Anxiety

Increased norepinephrine turnover: - amygdala - cerebral cortex - hippocampus - hypothalamus - locus coeruleus	Increased serotonin turnover - amygdala - lateral hypothalamus - nucleus accumbens - prefrontal cortex
Occurs in conjunction with Fear-associated conditioned Response	Occurs in conjunction with hyperirritability, hyperexcitability and hypersensitivity

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Adapted by Charney from Charney and Bremner, 1999

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

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. Ideally, treatment should reduce or reverse any hippocampal atrophy arising from post-traumatic stress disorder. One approach is to discover drugs that directly counteract these neurobiologic changes. Sertraline, currently the only drug with an FDA approved indication for treating PTSD, is known to affect the noradrenergic and serotonergic components of PTSD. It 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 neurobiologic effects 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 (Charney 1997, Davis 1999).

Investigators and Institutional Review Board

Principal Investigator:

Michael Mithoefer, MD is a practicing psychiatrist and Clinical Assistant Professor of Psychiatry at the Medical University of South Carolina. He is board certified in Psychiatry and was also board certified in Internal Medicine in 1981 and in Emergency Medicine in 1987. Dr. Mithoefer will be the primary therapist for all the patients and will be responsible for participant safety during protocol participation. He will be present during all MDMA sessions.

Additional Investigators:

Ann T. Mithoefer, BSN is a registered nurse who works with her husband, Michael Mithoefer, MD, as a psychiatric office nurse and as co-facilitator in their monthly Holotropic Breathwork groups. She completed training and certification in Holotropic Breathwork with Stanislov Grof, MD in 1997. Ann Mithoefer will be acting as co-therapist throughout the study, and she will be present during all MDMA sessions.

Mark T. Wagner, Ph.D. is an Associate Professor of Neurology at the Medical University of South Carolina, and is the Director of the Neuropsychology Section at the University. He is an expert in the assessment of cognitive and psychological function. His clinical work often involves assessment of patient response to pharmacological agents and assessment of efficacy of medical/surgical treatment modalities. He has an extensive research background and numerous publications related to the topic of neuropsychology.

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Institutional Review Board:

This research will be submitted to the Western I.R.B.

The I.R.B. can be reached at:

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The Investigator's Brochure

Please find the entire text in Volume 3 "The Investigator's Brochure."

The Protocol

Experimental Design and Methods

Study design:

The proposed project is a double-blind placebo-controlled Phase II pilot study designed to investigate the safety and efficacy of two MDMA-assisted psychotherapy sessions. The effects of 125 mg. of MDMA delivered within a controlled therapeutic setting to patients with chronic PTSD will be compared with placebo administered in otherwise identical sessions. All subjects will meet current criteria for PTSD. Subjects will be recruited through newspaper advertisement and referrals from physicians or psychotherapists. They will be screened through intake interviews, physical examinations, neuropsychiatric exams and psychiatric diagnostic interviews. Twelve of the twenty subjects will receive two MDMA-assisted therapeutic sessions scheduled 3 - 5 weeks apart, and the eight remaining subjects will receive inactive placebo. All subjects will also receive 13 – 14 hours of non-drug psychotherapy before and after the experimental sessions. Physical and psychological status will be continuously monitored throughout the test sessions. Subjects will be reassessed for physical status by the physician-investigator immediately following and weekly for at least 3 weeks after each session. Psychiatric status will be objectively reassessed 4 days after each session and 3 months following the first session (2 months following the second session). Neurocognitive status will be measured again at 2 months following the second MDMA session. A full medical exam and laboratory screening will be done before the study and 2 months after the second MDMA session.

Specific Hypothesis:

- There will be a trend for volunteers participating in MDMA-assisted therapy to experience a greater decrease in signs and symptoms of PTSD than will controls, with signs and symptoms measured by a change in the Clinician Administered PTSD Symptom Scale (CAPS-2: Blake et al. 1990), the Impact of Events Scale (IES: Horowitz et al. 1979) and the Symptom Checklist 90 (SCL-90-R) administered at study initiation and again at 4 days after each MDMA session and at 2 months after the second treatment session.

- Exposure to MDMA will not be associated with neurocognitive toxicity as measured by The Repeatable Battery for Assessment of Neuropsychological Status (RBANS), the Paced Auditory Serial Addition Test (PASAT) and the Rey-Osterrieth Complex Figure Test administered at study initiation and 2 months after the second MDMA session. Likewise, it will not be associated with hepatic, electrolyte or other metabolic toxicity as measured by biochemical profiles and serum electrolytes determined at study initiation and 4 days after the last treatment session. Subjects in the experimental group will not perform any differently than controls on measures of neurocognitive performance when measured three months after treatment administration.

Subjects:

Twenty subjects, including males and females, aged 18-65, will be recruited for study participation. Prospective subjects will be recruited through newspaper advertisements and referrals from physicians or psychotherapists. Subjects will be screened with intake interviews, physical examinations and psychological diagnostic testing. The first twenty who meet inclusion criteria without any exclusion criteria will be included in the study. All subjects will receive the treatment (MDMA or placebo) within an experimental setting (described below) designed to facilitate optimal trust, relaxation, and catharsis. Data from this initial set of twenty volunteers will be analyzed for preliminary information about safety and efficacy before any additional patients are treated in the context of a full-scale controlled clinical trial. Any volunteers who drop out or are excluded between the first and the second MDMA or placebo sessions will be replaced. Researchers will, nevertheless, attempt to collect outcome data on drop-outs and excluded volunteers.

Inclusion Criteria:

1. Subjects must meet DSM IV criteria for current PTSD (within the past 6 months) in response to crime victimization (CR-PTSD), including childhood sexual or physical abuse.

2. They must have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor, either alone or in the context of psychotherapy**.** Treatment will be deemed to have been unsuccessful if the patient continues to meet criteria for current PTSD following the treatment.

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

4. Subjects must also be willing to commit to medication dosing, therapy sessions, and follow-up sessions and to complete evaluation instruments.

5. Subjects must be willing to refrain from taking any psychiatric medications from the outset of the study until the final follow-up evaluation, which will occur two months after the second MDMA session. 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 then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). An exception to this may arise in the case of designated rescue medication

that may be administered in the event of a crisis during the MDMA or placebo treatment session.

6. Subjects 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 to communicate directly with the therapist, they 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 evaluation session 2 months after the second MDMA session.

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

8. Subjects must agree to take nothing by mouth except alcohol-free liquids after 12 A.M. (midnight) the evening before each MDMA 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.

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

<u>Exclusion Criteria:</u>

Potential subjects with the following conditions will be excluded:

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

2. Patients with a history of or current primary psychotic disorder or bipolar affective disorder type 1.

3. Patients with dissociative identity disorder or an eating disorder with active purging.

4. Patients with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Patients

with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).

5. Patients with hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of or existing hyponatremia.

6. Patients weighing less than 50 kg or more than 105 kg.

7. Patients with prior use of "Ecstasy" more than 5 times or at any time within the previous 6 months.

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

9. Patients requiring ongoing concomitant therapy with a psychotropic drug.

10. Patients meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.

11. Any subject who is not able to give adequate informed consent will be excluded.

Initial screening visit and diagnostic evaluation:

The purpose of the initial screening visit is to determine whether or not the potential subject fits the inclusion criteria and is free from any exclusion criteria. This visit will consist of:

The Clinician Administered PTSD Scale (CAPS-1: Blake et al. 1990: Appendix C) will be used to provide a DSM-IV CR-PTSD diagnosis. If the subject meets DSM-IV PTSD criteria, the rest of the SCID (First et al. 1994) will be administered for the purpose of ruling out patients for exclusionary Axis I diagnoses (i.e., exclusion criteria of substance dependence, psychotic disorder, eating disorder, or bipolar disorder).

DSM-IV criteria will be used as the diagnostic criteria for psychiatric assessment because they represent a standardized set of criteria that are easily interpreted and followed. They yield consistent diagnoses for treatment for research purposes across sites and between studies.

Any patient who appears at imminent risk for trauma and victimization as assessed by information gathered during the screening assessment will be evaluated by the PI or a study co-investigator. They will be counseled in specific risk-reduction strategies, and referred for immediate protection or care as needed. These subjects would not be eligible for study participation. Patients who do not meet eligibility criteria at this point or who do not wish to participate will be referred for alternative treatment.

Patients who meet the above psychiatric criteria and agree to participate in the study will receive further medical evaluation as follows:

- general medical history and physical exam
- EKG
- metabolic profile
- serum electrolytes
- thyroid hormone levels and TSH
- HIV serology (like all other results, these results will be kept confidential, and appropriate referral for counseling will be made if necessary)
- urine pregnancy test for females

Following this pre-study evaluation, patients who meet the study criteria as outlined above will be scheduled for a baseline assessment battery to be administered 14 days prior to their first MDMA session. They will also be scheduled for the two preparatory psychotherapy sessions that will occur within this same time period.

Baseline assessment visit:

An assessment battery will be performed during the 2 weeks prior to the first MDMA session in order to provide baseline measures of PTSD symptomatology, mood state and global functioning. Inter-rater reliability will be established on all clinician or research-administered rating instruments prior to the initiation of the trial as we have done for other clinical research projects. The assessment instruments to be used represent state-of-the-art instruments in PTSD and neuropsychology testing fields. They are outlined below. The baseline assessment battery should take approximately 2-3 hours to complete. The rationale for the use of these particular instruments and a detailed description is provided below:

A. Screening and diagnostic instruments:

1. SCID-IV (First et al. 1994). The SCID is a semi-structured interview, typically performed by a psychiatrist that permits accurate diagnosis of lifetime and current psychiatric disorders, using DSM-IV criteria. Tests for inter-rater reliability will be performed with SCID interviewers (Nunes et al. 1989; Drake and Walloch 1989).

2. 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. Form 1 of the CAPS allows for a current and lifetime PTSD diagnosis. This instrument will be used to determine current PTSD diagnosis. Form 2 allows the interviewer to assess PTSD symptom status

over time (CAPS-2). 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).

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

4. Subjective Units of Distress. This is a standardized subjective rating scale by which a subject can quickly rate comfort level throughout the session (l-7 scale). The parameters of the scale are explained at study initiations.

5. NEO Personality Inventory (Piedmont, 1998). The NEO is a well-established measure of personality with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. The factor structure includes the major domains of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each factor consists of six facet subscales that sample constructs such as anxiety, hostility, vulnerability, warmth, positive emotions, fantasy, compliance, self-discipline, etc. This model of personality structure provides insight as to the internal psychological forces that have resulted in Axis I psychopathology, or in this case, PTSD. The instrument consists of a series of items to which the subject responds via a (1) strongly disagree to (5) strongly agree Likert-type scale. This measure will be administered during the baseline, then repeated 4 days post session and then again at the final 3 month follow-up session.

6. Working Alliance Inventory (WAI) (Horvath and Greenberg 1989) is a 36-item self-report scale designed to assess the quality of working alliance existing between patient and therapist. Scale reliability has been reported to be adequate to high.

B. Neuropsychological Measures:

1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1997) has two parallel forms, with identical administration but different stimulus content, ideal for measuring change in a patient's neuropsychological status over time. The use of alternate forms eliminates content practice effects and simplifies interpretation of repeat test performance. Each version has one stimulus booklet and one record form with a shared manual. Examining multiple neurocognitive domains RBANS provides a quick sampling

of major neurocognitive domains, using subtest content. The RBANS is brief (20-30 minutes), portable, and hand-scorable. Only the easel-backed stimulus booklet and record form are required for administration and scoring. RBANS is used to support the broad-based assessment of multiple cognitive domains with index scores for the following neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory.

2. The Paced Auditory Serial Addition Task (PASAT) (Roman, Edwall, Buchanan, & Patton 1991) is a sensitive measure of information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction. Comparison of attention and working memory using the PASAT test and fMRI within the same individual has been shown to be valuable in grading response to drug therapy or in following the natural recovery of cognitive function in individuals with deficits. The test consists of a taped sequence of numbers. The subject's task is one of serial addition in 4 conditions of increasing complexity.

3. Rey-Osterrieth Complex Figure (Mitrushina, Boone, D'Elia, 1999) consists of a complex two-dimensional line drawing. The subject's task is to copy the design with pencil on paper. The Rey-Osterrieth assesses visuoperceptual skills, spatial organizational skills and memory. It has frequently been found to be sensitive to nondominant hemispheric functioning and right temporoparietal area integrity in particular.

4. Symptom Checklist 90-Revised (SCL-90-R): This is a standardized instrument used to measure subjective, feeling states. It gives subscales on several dimensions.

5. Subject Beliefs on Condition Assignment: All subjects will be asked to indicate whether they believe they have received MDMA or placebo during the experimental sessions.

Table 3: Assessment Timetable

	Pre-Study	Baseline Eval.	2nd Therapy Session	Session 1	Therapy Follow Up 1	Post session (4-Day) Follow-up	Session 2	Therapy Follow Up 2	Post session (4-Day) Follow-up	3-Mo. Follow-up
Inclusion / Exclusion	X									
Informed consent	X									
SCID	X									
Physical Exam & Medical History	X								X	
B-HCG	X			X			X			
EKG	X									
Metabolic Profile, HIV Thyroid Panel	X								X (metabolic only)	
Electrolytes	X			X					X	
Liver Enzymes	X								X	
Urine Drug Screen	X			X			X			
Vital Signs	X			X			X			X
Neuropsyc. Evaluation		X								X
CAPS-1		X								
CAPS-2						X			X	X
IES		X				X			X	X
SCL-90-R		X				X			X	X
WAI			X		X			X		

Psychological measures to be used on the day of the experimental (MDMA or placebo) session:

Subjective Units of Distress (SUD): Will be administered immediately before the MDMA or placebo is administered and every 60-90 minutes during the session. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

Dosing Plan: (See table 4)

A dose of 125 mg MDMA has been selected for use in this study on the basis of prior reports of therapeutic effectiveness and tolerability. Patient testimonials of the effectiveness of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that 125 mg MDMA is an appropriate dose for psychotherapeutic treatment. Doses equal to or greater than 125 mg have been well-tolerated in previous studies wherein MDMA was administered to humans (Cami et al, 2000; Grob et al, In preparation; Mas et al, 1999). Some prior clinical trials have employed dosing on an mg/kg basis, while others have used fixed amounts. With mg/kg dosing, milligram dosage can vary widely (see Appendix B). The use of a standard dosage of 125 mg was chosen in an effort to optimize the therapeutic dose while assuring safety.

The MDMA will be weighed into 125 mg doses and placed in gelatin capsules by a compounding pharmacist at The Prescription Center in Charleston, SC. The pharmacist will also place lactose into gelatin capsules of identical appearance.

Drug treatment will be randomly assigned to each subject, with therapists and subjects blind to treatment condition. Twelve subjects will be assigned to the MDMA condition and eight subjects will serve as controls.

See table 4, "Timing of Visits" and table 5 "Study Timetable Within-Session Evaluation" for a summary of what follows.

Following the initial screening and the baseline data visits, all subjects will receive two ninety-minute introductory sessions with the therapists. There will then be two individual drug treatment sessions conducted 3-5 weeks apart, each lasting approximately six to eight hours depending upon the subject's response.

A total of 11 sixty to ninety minute preliminary and follow-up therapy sessions will occur in the following schedule:

1) Two introductory sessions, ninety minutes each, will occur within the two weeks preceding the first drug treatment session. Informed consent will be obtained at this time. The WAI will be administered during the second introductory session.

2) First treatment session: One hour before the beginning of the treatment session, a urine specimen will be collected for a drug screen and, for females, a pregnancy test. These results must be negative for the subject to receive the treatment (MDMA or placebo) and to continue in the study. After the patient has acclimated to the environment and reviewed their intentions with the therapists the SUD will be administered. The patient will then receive either 125 mg of MDMA or placebo p.o. Therapists and subjects will be blind to treatment condition. The therapists will stay with the subjects during the entire period of the experience until the patient reaches a satisfactory point of resolution and initial integration of the experience. Blood pressure, heart rate and temperature will

be measured at regular intervals for subjects in both groups throughout the test session. The SUD will be repeated at 60-90 minute intervals and at the conclusion of the session. Serum electrolytes will be measured at the conclusion of session 1 (see table 3 and "Nature of Treatment Sessions" below).

3) There will be a ninety-minute follow-up session with the therapists on the day following the first treatment session and 3 or 4 sixty to ninety-minute additional sessions, at approximately weekly intervals between the first and the second treatment sessions. The WAI will be administered during the therapy follow-up session occurring 1 day after the MDMA or placebo session. (Whether there are 3 or 4 therapy sessions will depend on the length of time between MDMA or placebo sessions. A clinical judgment will be made as to whether the second MDMA or placebo session should occur 3 or 4 weeks after the first).

4) Psychological measures will be performed 4 days after the MDMA or placebo session.

5) Second treatment session: 3-5 weeks after the first drug session, the subject will again be administered placebo or 125 mg of MDMA p.o. One hour before the beginning of the treatment session, a urine specimen will be collected for a drug screen and, for females, a pregnancy test. These results must be negative for the subject to receive the treatment and to continue in the study. The therapists will again stay with the subjects during the entire period of the experience and until the patient reaches a satisfactory point of resolution with initial integration of the experience. Monitoring of BP, pulse, temperature and SUDS will be the same as in session 1. Serum electrolytes will not be measured if they were normal at the conclusion of session 1.

6) There will be a ninety-minute follow-up session with the therapists on the day following the second treatment session and 3 additional sessions at approximately weekly intervals. The WAI will be administered during the therapy follow-up session. There will be two additional sixty to ninety-minute follow-up therapy sessions at 3 months following the first MDMA or placebo session.

7) Psychological measures will be performed 4 days after the second MDMA or placebo session (See table 4). Serum liver enzymes and metabolic profile will be drawn during that visit, and serum electrolytes will be measured if necessary.

8) Three months after the first treatment session (approximately 2 months after the second MDMA or placebo session), an independent rater will assess the response to treatment using the instruments indicated below in table 4. Neuropsychological measures will also be repeated at this time.

Table 4 Timing of Visits

Time: d=days w=week m=month	**-14 d**	**0**	**+1-7 d**	**+7-13 d**	**+2 w (s. 1)**	**+2 w, 1 d**	**+2 w, 4 d**	**+3 w**	**+4 w**	**+5 w**	**+6 w (s. 2)**	**+6 w, 1 d**	**+6 w, 4 d**	**+7 w**	**+8 w**	**+9 w**	**+3 1/2 m**
Pre-Study Eval	X																
Baseline Eval.		X															
Psycho Therapy			X	X		X		X	X	X		X		X	X	X	X
MDMA Session					X						X						
Psycho Logical Measure		X					X						X				X
Neuro Psych. Measure		X															X
Metabolic profile	X												X				
Electro-Lytes	X				X								X				
Liver FCT	X												X				
Drug Screen & B-HCG	X				X						X						
Medical exam	X												X				
Working Alliance Measure						x						X					
Time from First MDMA session					0	1 d	4 d	1 w	2 w	3 w	4 w	4 w 1 d	4 w 4 d	5 w	6 w	7 w	+3 m

Nature of the treatment sessions: (See Appendix A. for additional details and table 5 for summary)

The two 90 minute introductory sessions with the therapists will be used to facilitate the therapeutic alliance, identify the subject's significant issues and concerns, prepare for the nature of the drug sessions, and set goals for the treatment. The Working Alliance Inventory (WAI), a measure assessing quality of the therapeutic alliance, will be administered during the second introductory session.

The experimental treatment sessions themselves will be supervised and facilitated by the male investigator/psychiatrist (M.C.M.) accompanied by an experienced female registered nurse (A.T.M.). Both therapists will be present throughout the sessions. The sessions will be conducted following the principles developed by Stanislav Grof, MD for LSD psychotherapy (Grof, 1980, pp. 123-147) and for Holotropic Breathwork (Grof, 2000: pp. 178-183) and adapted for MDMA-assisted psychotherapy by Metzner and by Greer and Tolbert (Metzner 1988; Greer & Tolbert 1998). (see Appendix A). Both therapists have been trained and certified in Holotropic Breathwork facilitation by Grof, and have years of experience working therapeutically with this model in non-drug Holotropic Breathwork sessions. M.C.M also has extensive experience treating PTSD in his psychiatric practice using both medications and psychotherapy. The treatment 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 medical offices of the primary investigator. The furnishings of the room will be arranged to create as comfortable and welcoming a setting as possible. The ambient temperature will be kept comfortably cool to decrease the likelihood of hyperthermia. Subjects will have had nothing by mouth except alcohol-free liquids since 12 AM the evening before. 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 subject his or her intentions for the session, including intentions regarding working with psychological issues related to their PTSD. The SUD will be measured just prior to the administration of placebo or MDMA. After the session begins, subjects will recline in a comfortable position with eyes closed or wearing blindfolds 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 subject has not spoken spontaneously, the therapists will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapists will engage with the subject to support and encourage emotional processing and resolution of whatever psychological material is emerging. The therapists will also encourage periods of time in which the subject remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of the 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 and pulse will be measured at the outset of each treatment session and then once every 15 minutes for 4 hours, and then every 30 minutes for 2 more hours. If at any time the blood pressure exceeds 160 systolic or 110 diastolic or pulse exceeds 110, measurements will then be taken every 5 minutes until the values fall below these levels. Temperature will be measured at the outset and then hourly for 6 hours. The physician may also call for more frequent measurements of pulse, blood pressure or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of hypertension, cardiovascular problems or hyperthermia. The SUD will

be repeated at 60-90 minute intervals. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process.

All treatment sessions will be audiotaped in their entirety**.** Sessions will last from six to eight hours, depending on when the subject feels that he or she has arrived at a point of completeness with the process and on the therapists' determination of the mental and physical state of the subject. Rides home will be pre-arranged so that subjects will not have to drive after the sessions. One of the investigator psychiatrists will be on call 24-hours a day, seven days a week to handle any concerns or emergencies related to the protocol.

Table 5 Study Timetable Within-Session Evaluation

TIME	
9:00 AM	Urine drug screen and pregnancy test, Patient acclimated to environment
9:45 AM	Baseline BP, Pulse, Temp, Subjective Units of Distress Rating (SUDS)
9:55 AM	2nd Baseline BP, Pulse, SUDS
10:00 AM	Drug Administration
10:15 AM	BP, Pulse
10:30 AM	BP, Pulse.
10:45 AM	BP, Pulse
11:00 AM	BP, Pulse, Temp, SUDS
11:15 AM	BP, Pulse
11:30 AM	BP, Pulse
11:45 AM	BP, Pulse
12:00 Noon	BP, Pulse, Temp
Every quarter-hour and as needed until 2:00 PM	BP, Pulse
Every half-hour and as needed after 2:00 PM	BP, Pulse,
Every 60-90 minutes	SUD, Temp

Nature of follow-up therapeutic sessions:

During the 90-minute follow-up sessions, the subjects will be encouraged to describe their experiences during the experimental sessions and to express freely any thoughts, feelings, questions or concerns they have. The WAI, the measure of quality of working alliance administered during the second non-experimental therapy session, will be administered again at each of the two therapy follow-up sessions. Subjects will also be

asked to indicate whether they believe they received MDMA or placebo at each follow-up session. The primary purpose of these sessions will be to support the subject in further processing, understanding and integrating the experience. It will also be an opportunity for the therapists to gather information, in an unstructured format, about the effects of MDMA or placebo and to evaluate whether the blind was maintained for subjects in either condition.

Methods of Evaluating Efficacy and Monitoring for Toxicity::

Research follow-ups:

The follow-up will begin 4 days after the first experimental (MDMA or placebo) treatment session. There will be a total of three research follow-up interviews. The first two will be done 4 days after the first and second experimental sessions respectively. A research follow-up will also be done at 2 months after the second experimental session. During these follow-up visits the CAPS-2, IES and SCL-90-R will be administered as outcome measures to be compared with baseline scores. The research and treatment intervention aspects of this project will be kept as separate and distinct as possible. The research assistants obtaining the follow-up information will not be involved in monitoring patients during the medication portion of the protocol. They will, therefore, be naïve to complaints of medication side effects.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from this dose of MDMA used in this kind of setting is very low. The three FDA-approved Phase I studies in this country have failed to demonstrate toxicity (Grob et al. 1996; Lester et al. 2000; Tancer, personal communication). Doses of up to 2.5 mg/kg were employed in one of these three studies, with eight subjects receiving doses equal to or exceeding the 125 mg. The same is true for studies that have been conducted in Switzerland and for ongoing studies that are being conducted there and in Spain (Vollenweider et al. 1998a; de la Torre et al. 2000b; Liechti et al. 2001a). Likewise, psychiatrists in the US and Europe used MDMA safely in a large number of patients before it became illegal (Greer and Tolbert 1986; Downing 1986; Gasser 1994).

In spite of this reassuring data, we intend to monitor closely for the unlikely possibility of an untoward reaction. A physician will be in attendance throughout each MDMA treatment session. In addition to the two co-therapists (a physician and a registered nurse), a currently practicing, board-certified, emergency physician and a currently practicing, emergency department nurse will be on-site in an adjoining room throughout the first five hours of the MDMA or placebo session. These two additional staff members, along with the two co-therapists, will provide a team of two experienced emergency physicians and two registered nurses that will assist in the treatment of serious adverse events upon request from the primary investigator.

The sessions will be conducted in an outpatient office setting where a crash cart and other emergency equipment will be immediately available. The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Available emergency medications include antihypertensive agents (such as nitroprusside and labetolol), pressor agents, anxiolytics, and intravenous fluids. In addition to drugs, the crash cart will contain a defibrillator (with telemetry capability), an oxygen tank, a 12-lead electrocardiogram (EKG) device, a suction device, a pulse oxometer, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). We will have equipment for placing an arterial line and monitoring arterial pressure. With these personnel and equipment, the researchers would be able to stabilize a patient in the office and then transport them by ambulance if hospital admission were required. The researchers have contacted the Charleston County Emergency Medical Services and learned that, in 2001, the average response time for an ambulance to arrive at a location in the sector of Mt. Pleasant where the research will be conducted was 8 minutes, 55 seconds. Transportation time to the nearest hospital should take no more than 10 minutes.

Blood pressure and pulse will be measured at the outset and then once every 15 minutes for 4 hours, and every 30 minutes for 2 more hours. Temperature will be measured at the outset and hourly for 6 hours. The physician may also call for more frequent measurements of pulse, blood pressure, or temperature in the event of clinically significant changes in any of the measurements or any other clinical signs of hypertension, cardiovascular problems or hyperthermia. After approximately eight hours, if all medical parameters are acceptable and the patient is alert, ambulatory and emotionally stable, the session will be ended. The patient will be given Dr. Mithoefer's pager number to call immediately if any problems occur. He or she will then be allowed to leave via a previously arranged ride from a friend or family member. We feel that these precautions and the contingency plans described below represent a very cautious approach to the remote possibility of a serious complication.

Hypertension and related cardiovascular complications:

> Blood pressure and pulse will be measured at the outset of each treatment session, then once every 15 minutes for the first 4 hours, and then every 30 minutes for the next 2 hours. If at any time the blood pressure exceeds 160 systolic or 110 diastolic or the pulse exceeds 110, measurements will then be taken every 5 minutes until the values fall below these levels. During this time the physician/ therapist will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. If needed, additional care will also be provided by the board-certified emergency room physician and licensed emergency room nurse who will be on standby in the next room. The physician-therapist will make a clinical judgment about whether additional monitoring or treatment is required. If a patient exhibits systolic BP > 220 or diastolic BP > 120, he or she will be considered to be in hypertensive crisis, and will receive immediate treatment to lower blood pressure. Reasons for moving a patient to the ICU would include, but not be limited to,

severe headache in the setting of hypertension, angina or neurologic deficits regardless of blood pressure. A crash cart will be immediately available and will contain nitroprusside and other antihypertensives in addition to the usual resuscitation drugs and equipment. This will allow any necessary emergency treatment to be instituted on site. The physician-therapist may, at any time, make a clinical judgment to transfer the patient to the ICU at the nearest local hospital for further observation and care.

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

Angina or Myocardial infarction

If a patient experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, they will receive oxygen and an IV and will be monitored as described above. They 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 they have had an acute myocardial infarction (AMI), the patient will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI (J Am Coll Cardiol 34:890, 1999).

Stroke

If any patient has neurologic deficits, whether or not they are associated with hypertensive crisis, they will receive oxygen and an IV and will be monitored as described above. They will be transported to the hospital for a head CT scan and further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the 3 hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines (Neurology 47:835, 1996).

Psychological Toxicity

During the preparatory sessions, patients will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during the MDMA 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 Appendix A, every effort will be made to help patients 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 patient is experiencing

severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an MDMA session then the physician-investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication". If a participant should become psychotic or suicidal, arrangements will be made for them to be admitted to the nearest inpatient psychiatric facility of their choice.

Hyperthermia:

Temperature will be taken every 60 to 90 minutes as described above. If the 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 patient. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, a cooling blanket will then be used, blood will be drawn for stat CBC, electrolytes, BUN, creatinine, glucose, CPK, PT, PTT, platelets, 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 patient will then be transferred to the ICU at the nearest hospital.

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

Dehydration:

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

Hyponatremia

Patients will be given electrolyte solutions such as Gatoraid 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, 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, then the patient will be admitted to the ICU at the nearest hospital for further monitoring and for water restriction and possibly hypertonic saline and furosemide administration if the symptoms are severe. Even in the absence of symptoms, as a precaution, serum electrolytes will be measured at the conclusion of the first MDMA session.

Liver toxicity:

Liver enzymes will be measured as part of the initial screening visit. Volunteers with preexisting abnormalities will be excluded from the study. Liver enzymes will be repeated 4 days after the second MDMA session. Any patient who shows abnormalities on any of the liver enzyme determinations will receive further evaluation and follow-up by a gastroenterologist.

Neuropsychological toxicity:

Psychological and neurological status will be clinically monitored by the therapists during the MDMA sessions and during therapy sessions at frequent intervals thereafter. Formal neuropsychological testing will not be done between sessions, but any patient who, on clinical examination during that period, is found to have cognitive deficits which persist for more than two weeks will not be given a second MDMA session. Any patient who develops mania or psychosis will not be given a second MDMA session and will receive appropriate psychiatric treatment. Neuropsychological effects will be formally measured by repeating neuropsychological testing 2 months after the final MDMA session using the RBANS, PASAT and Rey-Osterrieth Complex Figure tests.

Chemistry, Manufacturing and Control Information

Complete details on the chemistry, manufacturing and control of the MDMA HCl to be used are described in Drug Master file # 6293. As described in that file, MDMA was prepared for human consumption by David Nichols, Ph.D., Dept. of Medicinal Chemistry and Pharmacology, Purdue University. The identity and purity of this MDMA was confirmed using HPLC in 1997 as described in DMF # 6293 and was found to be 99.87% pure. There was no evidence of deterioration at that time, 12 years following original synthesis in 1985.

MDMA is a Schedule I compound and will be stored and handled in compliance with relevant Federal, State and University regulations. In accordance with DEA requirements, the principal investigator, Michael C. Mithoefer, MD, will be responsible for storing and dispensing the MDMA.

MDMA will be weighed into 125 mg doses (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules by a compounding pharmacist at The Prescription Center in Charleston SC.

Lactose will be used as a placebo, and will be prepared in gelatin capsules identical in appearance to the capsules containing MDMA. Placebo capsules will be prepared by a pharmacist at the Prescription Center in Charleston, SC.

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

Pharmacology And Toxicology

Primary Pharmacodynamics

Mechanisms of Action

MDMA interacts with plasma monoamine transporters and storage vesicles to increase extracellular levels of 5-HT, dopamine, and norepinephrine (Cozzi et al. 1999; Fitzgerald and Reid 1990; 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. Central dopamine and norepinephrine are also thought to regulate readiness for action and arousal, with dopamine possibly mediating behavioral readiness, and locus coeruleus norepinephrine mediating conscious registration of external stimuli (Clark et al. 1987; Robbins and Everitt 2000). Increasing these neurotransmitters may therefore place the individual in a state of alertness that is ideal for recalling or even re-experiencing state-dependent memories of stressful events. This potentially aversive state may be modified by MDMA effects on both the serotonergic system and postsynaptic α-2 adrenoceptors.

MDMA effects on the serotonergic system are likely important for its therapeutic effects. MDMA induces 5-HT release and is a 5-HT2 agonist. Serotonergic dysfunction is associated with anxiety, aggression, and depression. Increasing 5-HT release is thought to have opposite effects. For example, stimulation of 5-HT_{1A} and 5-HT_{1B} receptors decreases anxiety and aggression in rodent behavioral studies (Brunner and Hen 1997; Graeff et al. 1996) and likely contributes to reduced defensiveness and increased self-confidence reported after MDMA. 5-HT_{1A} receptors in the hippocampus have also been specifically hypothesized to enable disengaging from previously learned associations if they lead to adverse outcomes (Guimaraes et al. 1993). MDMA also has moderate 5-HT_{2A} activity (Nash et al. 1994), which leads to modest alterations in perception of meaning (Liechti et al. 2000b), possibly facilitating new ways of thinking. Case reports suggest increasing extracellular 5-HT levels may facilitate recovery of remote memories (Robertson 1997), a phenomenon that has been reported by psychotherapists administering MDMA to patients (Downing 1985). Thus, MDMA effects on the serotonergic system may decrease anxiety and aggression and create a state of mind that is conducive to psychotherapy.

Direct MDMA stimulation of postsynaptic α-2 adrenoceptors may modify this state by altering the balance of α-1 and α-2 stimulation, allowing the individual to remain emotionally calm

despite noradrenergic activation. MDMA is an α-2 agonist (Lavelle et al. 1999). Like other α-2 agonists, such as guanfacine and clonidine (Arnsten 1998), MDMA produces feelings of calmness and relaxation (Cami et al. 2000). It is worth noting that open label trials suggest that clonidine may be helpful for treating symptoms of PTSD (Harmon and Riggs 1996; Kinzie and Leung 1989).

Drug Activity Related to Proposed Indication

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection (Greer and Tolbert 1998; Grinspoon and Bakalar 1986). Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Cami et al. 2000; Liechti et al. 2000a; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998). These effects make it likely that MDMA would be useful in psychotherapeutic treatment of many different complaints.

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

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

Secondary Pharmacodynamics

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure. These acute effects of MDMA are well documented in the dose-response safety study described in Previous Human Experience and in placebo-controlled double-blind studies published in peer-reviewed journals (de la Torre et al. 2000a; de la Torre et al. 2000b; Gamma et al. 2000; Grob et al. 1996; Lester et al. 2000; Liechti et al. 2001a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Mas et al. 1999; Vollenweider et al. 1998). 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. Available data on maximum changes in heart rate and blood pressure are summarized in Table 3.1 in the Investigators' Brochure. In the currently proposed study, the effects of 125 mg MDMA are not expected to increase heart rate above 100 BPM and blood pressure above 170/100 mmHg. As described elsewhere, blood pressure and heart rate of volunteers will be monitored at regular intervals and appropriate action will be taken if clinically significant changes occur.

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocortictropic hormone concentrations (Grob et al. 1996; Grob et al. In preparation; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. 40 mg MDMA was found to acutely increase circulating levels of antidiuretic hormone (arginine vasopressin) in 8 male volunteers (Henry et al. 1998). Antidiuretic hormone reached maximum between 1 to 2 hrs 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.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifici et al. 2000; Pacifici et al. 1999; Pacifici et al. 2001). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutin A-induced lymphocyte proliferation. Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase the amount of Th2 cytokines measured in blood. These acute changes are unlikely to be of consequence in healthy individuals and are of a similar magnitude to changes produced by other pharmacological agents. For example, the CD4 T-cell count decrease was similar in magnitude to that produced by 0.8 g/kg oral ethanol (the equivalent of 4-5 drinks) in the same report (Pacifici et al. 2001). The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998). This immunomodulation is an acute effect of MDMA and is not likely to persist for more than 48 hours after MDMA administration.

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. These effects resolve within several hours. Lasting neurological effects have not been noted.

MDMA appears to produce modest acute changes in neurocognitive performance during peak drug effects. The acute effects of MDMA, generally at doses of either 125 mg or 1.7 mg/kg, have been assessed using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000), 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.

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) and by Vollenweider and colleagues (Vollenweider et al, 2001, Vollenweider, attached letter of support) 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. This has not been consistently found in studies and it appears that these changes are only associated with some conditions of use. In a retrospective study that did find some 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. 1998a). Similarly, a yet unpublished study failed to find decreased memory in ecstasy users reporting a lifetime dose of 20 to 40 tablets, with decreased memory function only appearing in ecstasy users reporting a lifetime dose of 80 or more tablets (Gouzoulis-Mayfrank, data presented at the 2001 National Institute on Drug Abuse MDMA Conference and described in attached letter of support).

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 (Dr. Alex Gamma, personal communication).

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 ug/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.

Abuse Liability

MDMA is classified as a Schedule I compound with a high potential for abuse, primarily because of its use in settings such as "rave" dance parties. 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, PTSD patients undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions and memories related to the original traumatic incident. As a result, it seems unlikely that PTSD patients undergoing this emotionally challenging psychotherapy will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings.

There is no evidence that MDMA-naïve healthy volunteers exposed to MDMA in previous Phase 1 clinical studies with MDMA have been motivated to seek out and use MDMA in non-medical settings. For example, Liechti et al. (2001) reviewed the effects of MDMA in 54 male and 20 female volunteers who had participated in clinical studies. Liechti et al. stated "none of the participants expressed any interest in taking MDMA as a recreational drug" after participation in an MDMA study.

There is known to be significant comorbidity for substance abuse among patients with PTSD, though specific data on the relationship between MDMA use and PTSD have not been reported. Currently, there is no definite evidence concerning the casual relations between the two disorders, and it is unclear whether posttraumatic stress disorder precipitates substance abuse or whether people with pre-existing substance abuse are at greater risk for PTSD. Currently, the most commonly accepted hypothesis for the

relationship between PTSD and substance abuse is that of self-medication (Meisler, 1996). Since individuals undergoing the proposed treatment will be encouraged to confront the traumatic events during MDMA-assisted therapy rather than defending against them or avoiding them, it seems likely that these individuals will subsequently be less inclined to choose to self-medicate through the self-administration of MDMA. If our hypothesis is correct that MDMA assisted psychotherapy will alleviate symptoms of PTSD, it is possible that subjects will be at reduced risk for substance abuse in general following MDMA treatment because they will have a reduced motivation to self medicate.

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

Pharmacokinetics/Toxicokinetics

Summary of Pharmacokinetic Parameters

MDMA Dose	**N**	**Cmax** *μg/l*	**Tmax** *H*	**AUC $_{0\text{-}24}$** *μg*h/l*	**AUC/dose** *μg*h/(l*mg)*	**Reference**
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8 .6	Mas et al. 1999
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	30.5 ± 11.2	de la Torre et al. 2000b
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
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	De la Torre et al. 2000a

The pharmacokinetics of MDMA, summarized above, have been primarily characterized by a group of Spanish researchers. Additional pharmacokinetic parameters for MDMA and metabolites are given in the papers cited in the table. 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 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 above, 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.

Absorption/Distribution/Metabolism/Excretion

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called alpha-methyldopamine), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

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

evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor in healthy individuals in a clinical setting.

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) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-enantiomer having a shorter elimination half-life and greater excretion that the R-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Ramcharan et al., 1998; Crifasi and Long, 1996). The stereoselective pharmacokinetics of MDMA are reflected in formation of MDA enantiomers. 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).

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

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

The urinary excretion of MDMA and its metabolites has been characterized by de la Torre and colleagues and is summarized in the table above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

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. Under these conditions, the most common serious adverse event involves hyperthermia, which often appears to be influenced by prolonged physical exertion (dancing) and other unsafe conditions of use. Reports of toxicity in illicit ecstasy users are summarized in the Investigator's Brochure. In addition to hyperthermic syndromes, other rare adverse events include dysphoric responses, hyponatremia, and hepatotoxicity. In the proposed clinical study, volunteers will be carefully monitored for signs and symptoms of these unlikely events, as discussed in the section on Monitoring for Toxicity. As described in Previous Human Experience, exposure to MDMA in a controlled clinical setting has not been associated with toxicity. As previously noted in the rationale section, the ongoing neurotoxicity of untreated PTSD is an important factor to weigh against any concerns regarding toxicity from MDMA exposure.

Published animal and *in vitro* studies have specifically investigated the possibility of 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.

Hepatotoxicity

Because hepatotoxicity has been noted in ecstasy users, three *in vitro* studies have examined the hepatotoxicity of MDMA. These studies show that MDMA can impair liver cell viability, but that this is very unlikely to occur in the proposed clinical study. The peak liver exposure to MDMA in the proposed clinical study should be approximately one-eleventh the concentration shown to impair cell viability in these *in vitro* studies.

In one study, MDMA caused increases in ALT, AST, and LDH activities in rat hepatocytes (Beitia et al. 2000). These increases were statistically significant with high concentrations of MDMA (1 mM for six hours) or lower concentrations for prolonged exposures (0.1 mM for 24 hours). Further evidence of MDMA-induced toxicity to hepatocytes came from moderate decreases in ATP (after three, but not one-hour incubation with 0.1 mM MDMA). A second *in vitro* study examined the possible pro-fibrogenic effects of MDMA on the liver by measuring expression of procollagen mRNA in a cell line of hepatic stellate cells (Varela-Rey et al. 1999). These cells produce the

collagen characteristics of a fibrotic liver. Expression of α1(I) procollagen mRNA was significantly increased by 0.5, but not 0.1, mM MDMA for 24 hr. This effect required sustained exposures, as 1 mM MDMA for 8 hr did not increase mRNA expression. A third *in vitro* study using mice hepatocytes showed that MDMA increases the lipid peroxidation and loss of cell viability produced by hyperthermic conditions (Carvalho et al. 2001). 1.6 mM MDMA slightly but significantly decreased cell viability but did not affect lipid peroxidation over 60 to 180 min under normothermic (37º C) conditions. When temperature was raised to 41º C, the hepatotoxicity of MDMA was dramatically increased. At this temperature, 1.6 mM MDMA approximately doubled lipid peroxidation after 180 min and decreased cell viability after as little as 60 minutes. A lower concentration, 0.8 mM MDMA, also decreased cell viability after 180 min at 41º C but not at 37º C.

Hepatotoxicity has not yet been reported to occur in any of the clinical studies where MDMA was administered to research subjects, and the drug exposures that can damage liver cells would not occur in the currently proposed clinical study. The lowest concentration that impaired cell functioning in these studies (0.1mM or ~19.3 mg/l MDMA) affected indices of cell viability after 24, but not 6, hours in the study by Beitia et al. This same concentration had no significant pro-fibrogenic effect after 24 hr in the study by Varela-Rey et al. This lowest toxic concentration is approximately 82 times higher than the expected peak MDMA plasma level (236.4 ± 57.97 μg/l MDMA) after 125 mg, the proposed dose in this study. Liver exposure to drugs is often higher than plasma levels. In an autopsy of a deceased ecstasy user, liver MDMA concentration was 7.2 times higher than femoral blood MDMA concentration (Rohrig and Prouty 1992). Thus, the peak liver exposure to MDMA in a clinical setting should be approximately one-eleventh the concentration shown to impair cell viability in these studies. This peak concentration would only be briefly sustained. Therefore it is unlikely that MDMA exposures in clinical studies will approach those demonstrated in these studies to impair rat liver cell viability or induce procollagen mRNA. Nonetheless, patients will be monitored for hepatotoxicity with liver panels performed before and after MDMA administration.

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.

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. Moreover, 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).

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [^{11}C]McN5652 before and after a single clinical MDMA exposure. This research was presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine, and is described in the attached letter of support. 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. The validation study found that, in most brain regions, PET tended to overestimate serotonin transporter changes (Scheffel et al. 1998). Given the small sample size in the study by Vollenweider et al., it is possible that a modest change in SERT density could have gone undetected. However, very little variance in ligand binding was found in baseline measures of ligand binding. 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. 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 125 mg MDMA is unlikely to lead to neurotoxicity in the proposed study.

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*.

In one study, exposure to MDMA for forty-eight hours dose-dependently decreased survival of cultured human placental serotonergic cells (Simantov and Tauber 1997). This decreased cell viability was accompanied by DNA fragmentation and cell cycle arrest (in the G2M phase). Forty-eight hour exposure to 0.4 mM MDMA decreased cell survival by 1.4 ± 4%, while 1.2 mM MDMA decreased cell survival by 61 ± 9%. In another study, the effects of MDMA on cultured rat neocortical neurons were studied at concentrations of 125 to 1000 μM MDMA and exposure times of 1, 24, and 96 hours (Stumm et al. 1999). Cell survival was not significantly affected by 125 μM MDMA at any exposure time. However, cell survival was decreased by 34.2 ± 11.4% at 96 hours after an average exposure of 500 μM MDMA. Stumm et al. also noted DNA fragmentation and altered expression of the bcl-x_{LS} 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.

It is unlikely that MDMA exposures in the currently proposed clinical study will approach those demonstrated to trigger programmed cell death in neurons. If MDMA levels in the brain are about 6 times higher than in plasma (Rohrig and Prouty 1992), then 125 mg MDMA should produce peak plasma levels of 236.4 ± 57.97 μg/l MDMA (de la

Torre et al. 2000b) and peak brain levels of 1.4 ± 0.3 mg/L. This estimated peak level is significantly less than the lowest drug concentration used in either apoptosis study. While 0.4 mM MDMA or 77.3 mg/L had modest effects in the first study, 125 μM or 24.2 mg/L had no significant effect in the second study. 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.

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 McEllhatton and colleagues are, in fact, the result of "ecstasy" consumption. Pregnant women will be excluded from participation in the proposed study and urine pregnancy tests will be performed before each drug administration.

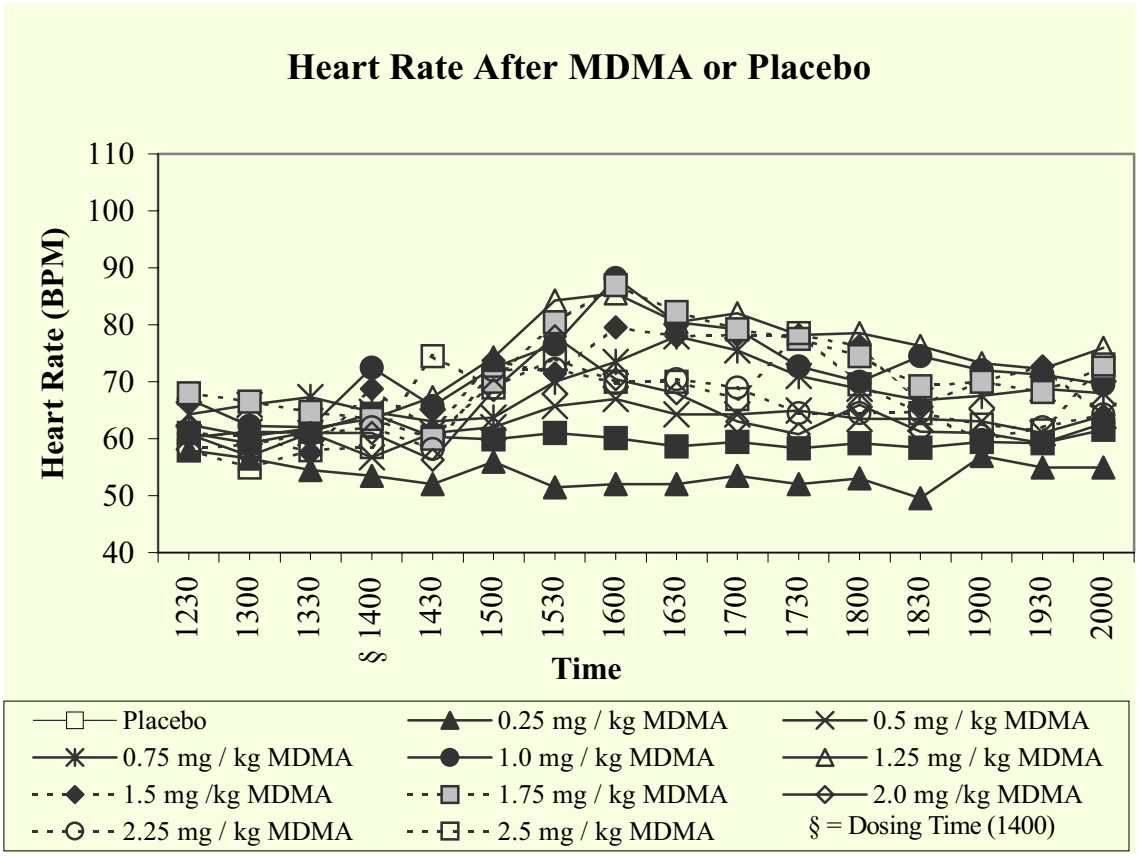
Previous Human Experience

Clinical MDMA research using healthy volunteers has been conducted by at least five research groups, including three in the United States. Double-blind placebo-controlled MDMA studies that have been published in peer-reviewed journals include a review of the physiological and self-reported effects of up to 1.7 mg/kg MDMA in 74 volunteers (Liechti et al. 2001a), an 8-volunteer study of cardiovascular effects of 0.5 and 1.5 mg/kg MDMA (Lester et al. 2000), a 16-volunteer positron emission tomography study of the effects of 1.7 mg/kg MDMA on cerebral blood flow (Gamma et al. 2000), a 13-volunteer study of the physiological and self-reported effects of 1.7 mg/kg MDMA (Vollenweider et al. 1998), an 8-volunteer study of the pharmacokinetics and physiological and neuroendocrine effects of 75 and 125 mg MDMA (Mas et al. 1999), a 6-volunteer study of the acute immunomodulating effects of 100 mg MDMA alone and in combination with ethanol (Pacifici et al. 2001), an 8-volunteer study of the pharmacokinetics and neuroendocrine effects of 40 mg MDMA (Fallon et al. 1999; Henry et al. 1998), and a 6-volunteer study of the physiological and neuroendocrine effects of 0.25 to 1.0 mg/kg MDMA (Grob et al. 1996). This research is discussed in the Investigator's Brochure, which presents information drawn from unpublished research data as well as from all published research reports. Structured abstracts of each published study are available as an appendix in the back of that document.

In summary, researchers have measured the cardiovascular, physiological, neuroendocrine, cerebrofunctional, psychiatric, and subjective effects of MDMA at doses ranging from 0.25 to 2.5 mg/kg. MDMA has been generally well tolerated in these studies, and we are aware of no serious adverse events. Participants with and without previous experience with MDMA reported that the effects of MDMA were mostly pleasant and otherwise tolerable (Cami et al. 2000; Grob et al. 1996; Grob et al. In preparation: Vollenweider, 1998). Occasionally, dysphoric responses to MDMA have occurred, but have always resolved within several hours. Clinically significant hypertension has occurred in several volunteers; these cases are discussed below. Researchers have not detected any evidence that exposure to MDMA in a clinical context produces neurocognitive changes, serotonergic neurotoxicity, or any other lasting toxicity. As shown in Table 2.5 of the Investigator's Brochure, Grob et al. did not detect any change in neurocognitive function in their volunteers. Similarly, Vollenweider et al. (2001) report that retrospective analysis of their studies did not detect any lasting effect of MDMA on psychological and neuropsychological measures, cerebral blood flow ($H_2{}^{15}O$-PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP). Most importantly, preliminary analysis using positron emission tomography (PET) and the radioligand McN-5256 revealed no significant changes in estimated serotonin transporter density four weeks after a single dose of MDMA (1.5–1.7 mg/kg) in MDMA-naive volunteers (Vollenweider et al. 2001). It is worth noting that MDMA was administered to hundreds of patients in the context of psychotherapy in the 1970s and 1980s (Greer and Tolbert 1998; Grinspoon and Bakalar 1986; Wolfson 1986) and more recently in Switzerland (Gasser 1994; Widmer 1997) without evidence of toxicity.

The remainder of this section will discuss the Phase I study conducted by Dr. Charles Grob and colleagues at the UCLA-Harbor Medical School with doses ranging from 0.25 mg/kg to 2.5 mg/kg. Eighteen healthy individuals (five females and 13 males) with histories of previous use of ecstasy received two doses of MDMA in a randomized, double blind placebo-controlled dose-response study. The doses administered to each volunteer differed by an increment of 0.25 mg/kg, with dosage in milligrams ranging from 16.6 mg to 204.8 mg. Eight out of 18 volunteers received at least one dose of MDMA that was equal to or greater than 125 mg, which is the proposed dose in the current study. (Appendix B gives complete information on individual doses.) Participants arrived at the laboratory at 700. The first physiological measures were made at 1230, and placebo or MDMA was administered p.o. at 1400, one and a half hour after the first measures were taken. Measures of heart rate, systolic blood pressure, diastolic blood pressure, and body temperature were taken at 30-minute intervals, before and for 6 hr after MDMA administration.

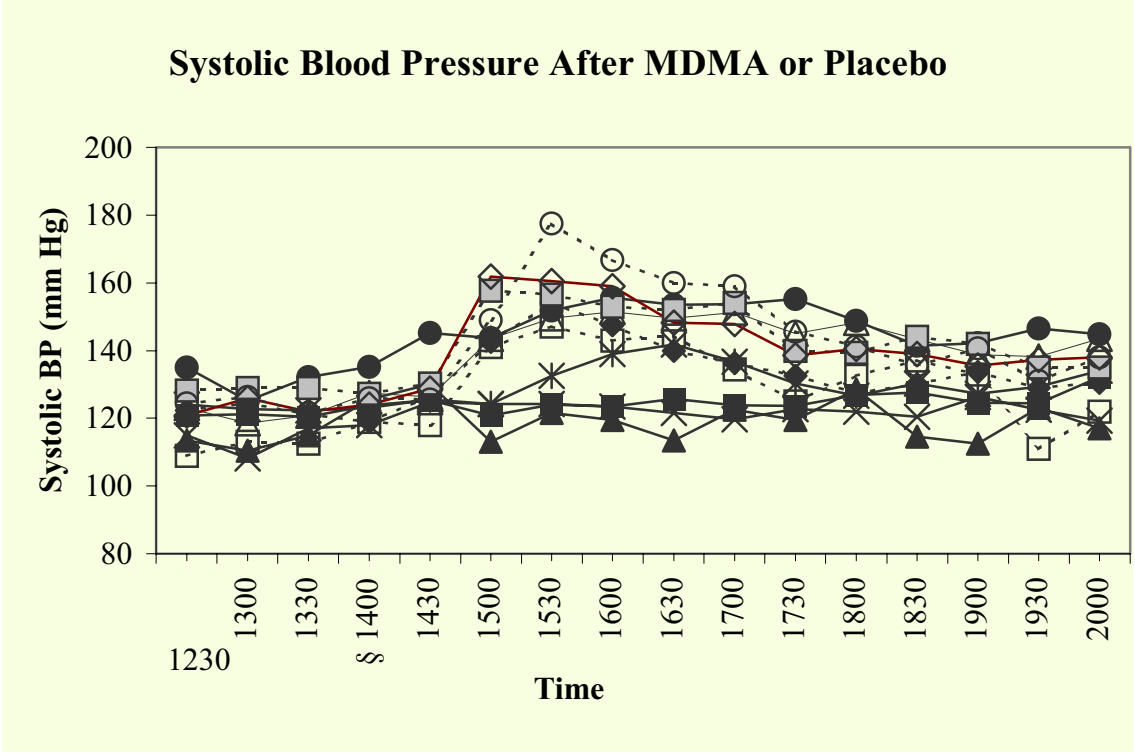
Safety data from this study are summarized in the following charts and tables depicting drug effects at each dose level. Individual data from each volunteer are shown in Appendix B. MDMA was well tolerated by all individuals participating in this study, and no adverse effects requiring medical intervention arose during any session. However, hypertensive urgencies occurred in two volunteers. Blood pressure was elevated above 200/100 in a 61-year-old male (subject #16) who received 2.25 mg/kg (162.0 mg) MDMA and in a 24-year-old male (subject #10) who received 1.75 mg/kg (204.8 mg) MDMA. Elevated blood pressure in the 24-year old male may have been related to undisclosed use of Ventolin (salbutamol/albuterol), an □-2-adrenergic agonist and CYP3A substrate (Manchee et al. 1996), on the morning of the study. Blood pressure returned to normal limits in both individuals within 20 minutes to 1 and a half hours, and neither individual required additional treatment to reduce blood pressure. Clinically significant hypertension after MDMA has been reported by other investigators, with clinical significance defined as being 220/130 or higher (see "Monitoring for Toxicity.") Vollenweider et al. (1998) conducted a 16-volunteer study employing 1.7 mg/kg MDMA. One volunteer, a 49-year-old male with no previous MDMA experience, displayed peak blood pressure values of 240/145 mm Hg (but no other signs of hypertensive crisis) for about 20 minutes. Plans for monitoring for and treating hypertension are described in the section on Monitoring for Toxicity.

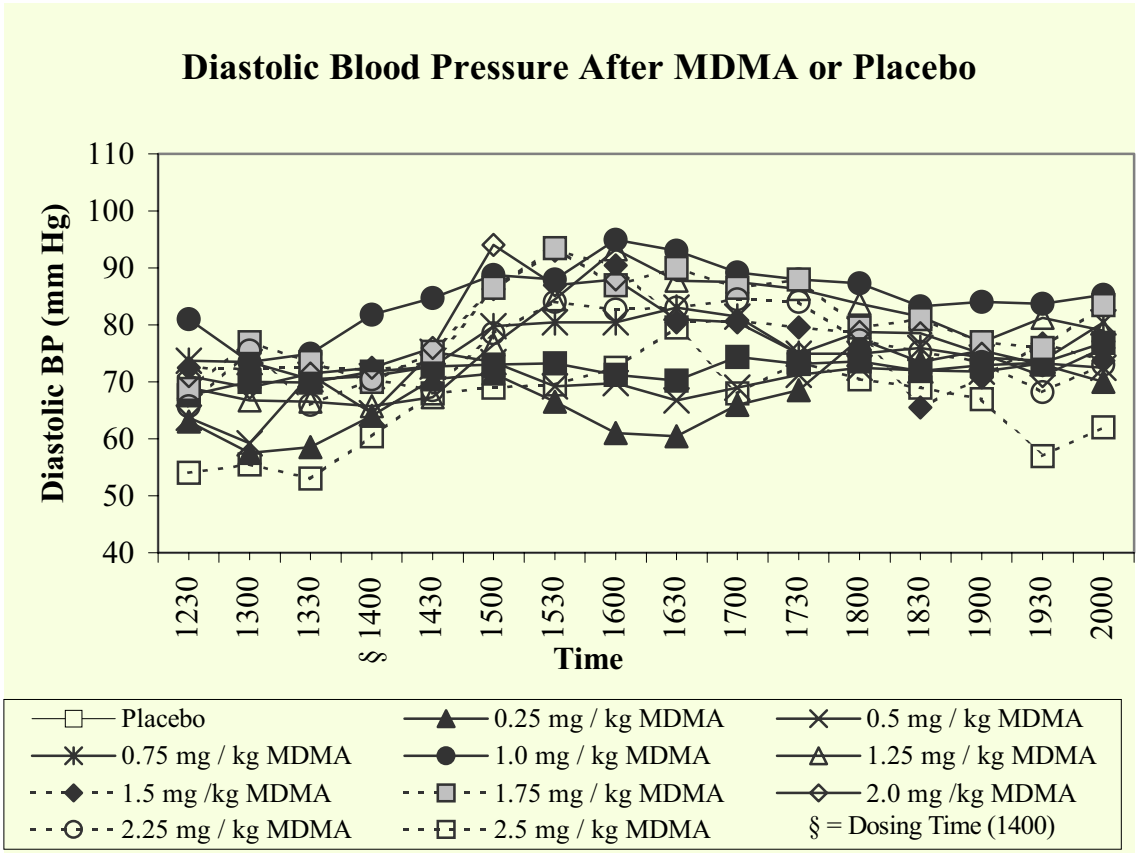


Heart Rate (BPM)

	Dose (mg / kg) MDMA										
Time	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	61.1	58.0	60.3	64.3	67.0	62.5	61.0	68.0	60.8	58.3	58.0
1300	59.2	56.5	61.3	66.0	62.3	60.5	60.5	66.5	57.0	59.0	55.0
1330	61.3	54.5	61.0	67.3	62.0	61.8	57.5	64.8	61.0	60.8	58.0
1400	64.3	53.5	56.8	64.8	72.5	63.5	68.8	63.5	61.0	62.0	58.5
1430	60.4	52.0	61.0	63.0	65.8	67.3	61.5	60.0	56.3	58.3	74.5
1500	59.9	56.0	62.0	63.8	72.5	74.3	73.8	70.0	68.5	72.0	69.0
1530	61.0	51.5	65.8	70.0	76.5	84.3	71.5	80.5	78.0	72.3	74.0
1600	60.1	52.0	67.0	73.5	88.3	85.5	79.5	87.0	70.5	69.8	70.0
1630	58.7	52.0	64.3	78.0	80.5	80.5	78.0	82.3	68.0	70.5	70.0
1700	59.4	53.5	64.3	75.5	79.3	82.0	78.3	79.3	63.0	69.0	67.0
1730	58.3	52.0	65.0	71.0	72.8	78.3	78.3	77.5	60.8	64.5	78.5
1800	59.2	53.0	63.5	68.8	70.0	78.5	76.3	74.5	66.0	64.5	69.5
1830	58.4	49.5	63.5	66.8	74.5	76.3	66.0	69.3	61.3	64.8	64.5
1900	59.4	57.0	63.0	67.5	72.0	73.3	70.0	70.0	61.0	59.8	62.5
1930	59.2	55.0	61.0	68.8	71.3	72.3	72.8	68.3	59.3	62.0	61.5
2000	61.6	55.0	64.0	68.0	69.5	76.0	64.0	72.5	62.8	64.3	73.0

n	18	2	4	4	4	4	4	4	4	4	2





Systolic Blood Pressure (mm Hg)

	Dose (mg/kg) MDMA										
Time	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	120.9	113.5	115.0	124.0	135.0	123.0	122.3	128.3	120.8	124.5	109.0
1300	121.1	110.5	108.3	122.8	125.3	118.5	124.5	129.0	126.0	126.3	113.0
1330	120.5	115.0	117.0	122.3	132.3	120.8	121.3	129.0	122.0	121.5	112.5
1400	123.8	125.5	118.0	123.0	135.3	127.5	119.0	127.3	124.0	126.0	119.0
1430	125.3	130.0	124.8	125.5	145.3	126.3	126.5	130.3	128.8	125.5	118.0
1500	120.9	113.0	124.3	124.3	143.8	143.5	142.5	157.8	161.8	149.0	141.0
1530	124.1	121.5	124.3	132.5	151.8	149.5	154.0	156.5	160.5	177.5	147.0
1600	123.6	119.5	123.5	139.0	155.5	151.5	147.5	153.0	159.0	166.8	143.0
1630	125.8	113.5	121.5	141.8	153.5	149.5	140.0	152.0	148.3	160.0	144.5
1700	123.8	122.5	119.8	136.8	153.8	151.3	136.3	154.0	147.8	159.0	134.5
1730	123.7	119.5	122.8	130.3	155.3	145.0	132.5	140.0	138.5	145.5	125.0
1800	126.8	128.5	122.0	126.8	148.8	148.3	127.5	139.3	140.5	141.3	132.5
1830	127.7	114.5	120.5	130.3	141.5	143.3	130.0	144.0	139.0	135.5	137.0
1900	124.7	112.5	126.3	127.3	142.3	138.8	133.8	142.0	135.5	140.8	133.0
1930	124.5	123.0	122.5	129.3	146.5	138.3	129.0	135.0	137.3	131.0	111.0
2000	132.2	117.0	119.3	134.0	144.8	143.5	130.5	135.0	138.0	138.0	122.0
n	18	2	4	4	4	4	4	4	4	4	2

Diastolic Blood Pressure (mm Hg)

	Dose (mg/kg) MDMA										
Time	0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2.0	2.25	2.5
1230	67.6	63.0	63.8	73.8	81.0	69.0	72.5	68.8	71.0	65.8	54.0
1300	70.0	57.5	59.3	73.5	73.5	66.8	72.3	77.0	69.0	75.5	55.5
1330	69.8	58.5	71.3	70.5	75.0	66.5	72.8	73.5	71.5	66.0	53.0
1400	71.8	64.0	64.5	71.0	81.8	65.8	72.0	70.0	72.5	70.5	60.5
1430	72.7	70.5	75.3	72.8	84.8	67.3	73.5	75.3	76.0	68.5	68.0
1500	73.1	71.5	73.5	79.8	88.8	76.5	86.3	86.5	94.0	78.5	69.0
1530	73.2	66.5	69.3	80.5	88.0	84.5	93.0	93.5	87.0	84.0	69.5
1600	71.3	61.0	69.8	80.5	95.0	93.3	90.5	87.0	88.0	82.8	72.5
1630	70.2	60.5	66.8	83.0	93.0	87.8	80.5	90.0	81.0	83.0	79.5
1700	74.4	66.0	69.0	81.5	89.3	87.5	80.8	86.5	80.5	84.5	68.0
1730	73.2	68.5	71.3	75.0	88.0	86.3	79.5	88.0	75.0	84.0	73.5
1800	73.6	77.5	72.5	75.0	87.3	83.8	78.5	79.5	78.8	77.3	70.5
1830	71.9	73.5	72.0	76.0	83.3	81.5	65.5	81.0	78.5	75.3	69.0
1900	72.9	75.5	71.8	74.3	84.0	77.0	70.8	77.0	75.0	73.5	67.0
1930	73.4	73.0	73.3	73.8	83.8	81.3	76.8	76.0	71.0	68.3	57.0
2000	76.9	70.0	72.5	80.5	85.3	79.0	73.8	83.5	76.0	73.0	62.0
n	18	2	4	4	4	4	4	4	4	4	2

Appendix A: Method of Conducting the MDMA or Placebo Session

Method of conducting MDMA psychotherapy: The therapeutic method to be used was developed and has been practiced extensively by Stanislav Grof, MD, first in LSD psychotherapy research and later in non-drug Holotropic Breathwork. (Grof 1980, pp.123-147; Grof 2000: pp. 178-183). The adaptation and use of this method for MDMA assisted psychotherapy has been described by Ralph Metzner, PhD and by George Greer, MD and Requa Tolbert, MSN. (Greer and Tolbert 1998; Metzner 1988). The therapy will be done by a male-female team in accordance with Grof and Greer and Tolbert's recommendations.

The preparation period:

All the above authors stress the importance of adequate preparation time during non-drug therapy sessions preceding drug-assisted psychotherapy. In the present study this will be accomplished during the two 90-minute sessions in the weeks preceding the MDMA session and will be reinforced during the first hour of the MDMA session before the drug is ingested. The goals of the preparation process will be:

2. To establish a therapeutic alliance between therapists and patient.

   The development of an adequate level of trust and understanding between therapists and patient is critical, and will be the primary focus to the preparation process. In the course of developing a therapeutic alliance, several specific agreements will be made: The patient will agree not to leave the treatment area before the therapists have declared the session over, and to accept a pre-arranged ride home after the session. The therapists will likewise both agree to stay until the end of the session. In addition, they will both be in the room with the patient during the vast majority of the time and at least one of them will be with the patient at all times. The subject of touch will be discussed. The patient will be told that there may be times during the session when they would like to ask for nurturing touch in the form of hand holding or being held. The therapists will agree to provide this nurturing touch if the patient desires and to immediately discontinue any physical contact if the patient says "stop". The patient will be told that they may experience sexual feelings as a normal part of the experience and that the therapists will support them in expressing these feelings but will not have any form of sexual contact with them.

3. To answer any questions and address any concerns, fears or doubts the patient may have about any part of the study protocol.

   In particular this will involve conveying to the patient therapists' commitment to providing a safe setting and to supporting the patient in working therapeutically with whatever experience arises.

4. To familiarize the patient with the general approach to be taken during the MDMA sessions.

   The therapists will describe the physical setting, and explain the following: Patients will start the session lying down with eyes closed and with music playing. They will be encouraged to direct their attention toward their inner experience. As the MDMA takes effect, they may notice a sense of stimulation or increased autonomic arousal. They will be taught diaphragmatic breathing as a tool to use if they experience anxiety or other discomfort at this stage or at any time during the session. It will be recommended that the general stance toward any emotional difficulty that arises should be to use the breath as an aid to experiencing and moving through, rather than away from, whatever is coming into consciousness. The stance that will be taken toward verbal interaction will be consistent with the recommendations of Grof, Metzner and Greer and Tolbert: Patients will be welcome to open their eyes and talk to the therapists at any point. If they have not done so after an hour, the therapists will ask them to describe briefly what they're experiencing. The therapists will continue to check in with the patient in this way throughout the session each time vital signs are being taken. On the other hand, it is also possible for talking to become a distraction from the inner experience. For this reason the therapists may at times suggest that the patient close their eyes and silently redirect their attention toward their inner process for a period of time before resuming verbal interaction.

5. To discuss the patient's intention or purpose for the session.

   Patients will be encouraged to include working with PTSD related material as part of their intention. They will also be introduced to the concept that the specific course of their therapeutic process related to PTSD may be different from what might be predicted by the intellect. They will be instructed that it may be helpful to set aside specific expectations and to open themselves to working with the experience in whatever way it unfolds.

5. For the therapists to become familiar with the patient's history, present life situation, symptoms, and personality.

<u>The Experimental (MDMA or Placebo) session:</u>

On the morning of the experimental session, the therapists will arrive at the General Clinical Research Center before the patient in order to prepare the room. This will involve assuring that the equipment for medical monitoring is present and taking steps to arrange and decorate the room to make it as comfortable, welcoming and aesthetically pleasing as possible. (As has been noted in the clinical observations of

Grof, Metzner, and Greer and Tolbert, attention to the nature of the physical setting is an important aspect of the therapy sessions). When the patient arrives, urine will be collected and sent to the laboratory for drug screen and (for females) a pregnancy test. While waiting for the urine results, the therapists will talk with the patient to answer any remaining questions and to complete preparation for the session as described above. If the urine tests are negative, the patient will be administered 125 mg. MDMA p.o. and will be asked to lie down, to close their eyes (with or without an eye shade according to their preference). At that time, music will be started. The music to be played will be the same for each patient, with the exception that the therapists may move ahead in the program at their discretion according to the nature of the patient's experience. In addition, a patient's request to discontinue a particular piece of music or to have a period of silence will be respected. The musical program will have been selected beforehand by the therapists. Music will be chosen to support emotional experience while minimizing suggestion. For this reason the music will not contain English words, and well known music to which people are likely to have strong associations will be avoided. The music program will have a trajectory designed to match the likely trajectory of the MDMA experience. In the beginning, it will be soothing and relaxing. Toward the end of the first hour it will become somewhat more energetic and supportive of emotions, and toward the end of the session it will become quieter and supportive of integration.

When there is verbal interaction with the patient, the therapists' responses will be oriented toward following and supporting the way in which the patient's experience is unfolding rather than toward directing the experience. As appropriate, the therapists may offer insights or ask questions to help the patient track and further explore the experience. Often, however, the therapists' role will be to listen carefully and empathically. If difficult material arises, they will help the patient keep the perspective that it is being presented by the psyche as part of the healing process. With this perspective, which tends to be strongly enhanced by the effects of MDMA, the re-experiencing of traumatic events can be profoundly healing rather than re-traumatizing. Toward the end of the session, the patient will be encouraged to talk about the experience in as much detail as they are ready to communicate. During this period, particular attention will be paid to any residual emotional or physical discomfort and the therapists will help the patient to further process, understand and integrate the experience.

Throughout the session, medical monitoring will be maintained as outlined in the protocol. After approximately eight hours, if all medical parameters are acceptable and if the patient is alert, ambulatory and emotionally stable, the session will be ended. The patient will be given an appointment time for a follow-up visit the following day and will be given Dr. Mithoefer's pager number to call immediately if any problems occur. He or she will then be allowed to leave via a previously arranged ride from a friend or family member.

Appendix B: Individual Safety Data from Phase 1 Ascending Dose Study

This appendix summarizes individual acute safety data from the Phase I study conducted by Dr. Charles Grob and colleagues at the UCLA-Harbor Medical School with doses ranging from 0.25 mg/kg to 2.5 mg/kg MDMA. Eighteen healthy individuals (5 females and 13 males) with histories of previous use of ecstasy received two doses of MDMA in a randomized, double blind, placebo-controlled, dose-response study. The doses administered to each subject differed by an increment of 0.25 mg/kg, with dosage in milligrams ranging from 16.6 mg to 204.8 mg. Participants arrived at the laboratory at 700. The first physiological measures were made at 1230, and placebo or MDMA was administered p.o. at 1400, one and a half hour after the first measures were taken. Measures of heart rate, systolic blood pressure, diastolic blood pressure, and body temperature were taken at 30-minute intervals, before and for 6 hr after MDMA administration.

As can be seen, MDMA was generally well tolerated. MDMA dose-dependently increased heart rate and blood pressure. At the highest doses tested, these changes were robust but not clinically significant. Two volunteers (subjects #10 and #16) experienced clinically significant hypertension but were without other signs of hypertensive crisis. These episodes resolved spontaneously within 20 minutes and 2 hours, respectively.

MDMA Doses (in mg) Used in Phase I Study

Subject	Session 1	Session 2		Session 3	
	mg/kg	mg	Mg/kg	mg	mg/kg
1	0.0	16.6	0.25	33.2	0.5
2	0.0	28.2	0.25	56.3	0.5
3	0.0	46.1	0.5	69.2	0.75
4	0.0	29.6	0.5	44.4	0.75
5	0.0	55.5	0.75	74.0	1.0
6	0.0	60.0	0.75	80.0	1.0
7	0.0	88.0	1.0	110.0	1.25
8	0.0	99.0	1.0	123.8	1.25
9	0.0	94.3	1.25	113.1	1.5
10	0.0	**175.5**	1.5	**204.8**	1.75
11	0.0	112.5	1.25	**135.0**	1.5
12	0.0	115.5	1.5	**134.8**	1.75
13	0.0	97.0	1.75	110.8	2.0
14	0.0	**125.3**	1.75	**143.2**	2.0
15	0.0	**156.0**	2	**175.5**	2.25
16	0.0	**144.0**	2	**162.0**	2.25
17	0.0	**137.3**	2.25	**152.5**	2.5
18	0.0	**172.8**	2.25	**192.0**	2.5

Doses of 125 mg or above have been bolded.

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