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1.0 List of Abbreviations

ACLS	Advanced cardiac life support
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
ARCI	Addiction Research Center Inventory
ASC (OAV)	Altered States of Consciousness (measure)
AST/SGOT	Aspartate aminotransferase
BLS	Basic Life Support
BSI	Brief Symptoms Inventory
C	Celsius
CAPS	Clinician Administered PTSD Scale
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HRS	Hallucinogen Rating Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LSD	d-lysergic acid diethylamide
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
NEO	Neuroticism-Extroversion-Openness Personality Inventory
NK	Natural Killer
POMS	Profile of Mood States
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty

PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
VAS	Visual analog scale(s)
WBC	White Blood Cell Count

2.0 Background Information

2.1 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization which has opened IND#63-384 for MDMA. MAPS is currently sponsoring a series of Phase 2 studies designed to gather preliminary evidence about the potential safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD). Encouraging data has been obtained and submitted to the FDA from MAPS' recently completed United States (U.S.) MDMA/PTSD pilot study, Protocol #63-384 (MP1). MAPS is currently sponsoring other Phase 2 MDMA/PTSD pilot studies in Switzerland and Israel, with additional pilot studies planned to start in the near future in Canada and the U.S and Jordan. These studies are laying the groundwork for possible Phase 3 multi-site MDMA/PTSD research studies.

This protocol submission is for a Phase 1 study for up to twenty people, "A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers." The information gathered during this study may help us better understand the psychological effects catalyzed by MDMA and how those effects can more effectively be used within a therapeutic context with PTSD patients. Additional safety data will also be gathered by the investigators who will monitor for suicidality using a standardized scale.

The study will consist of two day-long experimental sessions. One session will employ inactive placebo, and the other will employ MDMA. Each session will be followed a day later by a follow-up or integrative session. Experimental sessions will be conducted in a therapeutic setting over a five-day period supervised by Michael Mithoefer, MD and Annie Mithoefer, B.S.N. The dose of MDMA will be 125 mg, followed an hour and a half to two and a half hours later by 62.5 mg. The second dose will be administered only if both the subject and the two co-therapists agree to it. The first experimental session will be preceded the day before by a 90-minute preparatory session with both investigators, with approximately 40 minutes of testing before and after the session. One day after each experimental session, there will be a 90-minute integrative session, also with both investigators. There will also be daily telephone contacts between the investigators and the subject for a week after the second experimental session, for integrative purposes, as well as integrative follow-up phone calls one and two months after the MDMA sessions.

Previous research in healthy volunteers in clinical or neuropsychiatric laboratory settings have investigated alteration of consciousness and mood throughout the duration of drug effects, and on rare occasion up to eight hours afterwards [1-3]. This Phase 1 study will examine mood and symptoms both during the duration of the drug effects and at a number of various time points beyond eight hours, all within a therapeutic setting. More stable human characteristics, such as personality, have not yet been assessed in healthy volunteers before and after MDMA administration. Personality factors have been assessed in subjects with PTSD in the sponsor's recently completed Phase II trial of MDMA-assisted psychotherapy in people with PTSD, with some evidence of changes as a result of expo-

sure to MDMA-assisted psychotherapy. The same personality measure will be used in this Phase 1 study.

A key limiting factor in MAPS' drug development plan is the need to train 20–30 male/female co-therapist teams to conduct MDMA/PTSD psychotherapy research in accordance with MAPS' treatment method [4]. MAPS is developing group and individual training programs to teach potential research teams standardized techniques and procedures for MDMA-assisted psychotherapy for use in MAPS-sponsored clinical trials with PTSD patients. MAPS' training programs are designed to support and expand the knowledge and skills of current and potential co-therapists conducting MDMA-assisted psychotherapy research.

Enrollment in this protocol (MT-1) is limited to people who meet the inclusion/exclusion criteria and who have completed a sponsor-developed co-therapist training program. In addition to measuring psychological effects of MDMA in this setting, this protocol will provide members of the co-therapist teams an additional, optional training opportunity to experience MDMA in a therapeutic context. The MDMA-assisted psychotherapy session used in this Phase 1 protocol will employ techniques learned in the initial training program. Receiving MDMA under the direction of investigators will provide participants with an in-depth understanding of how to maximize the therapeutic effects of MDMA. It will also allow participants to better draw distinctions between common, self-limited side-effects of MDMA-assisted psychotherapy and those effects that require intervention.

The MDMA session will not be offered until appropriate Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and other authorities, if applicable, will be informed of protocol amendments in accordance with local legal requirements.

Experimental sessions will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines, and applicable standard operating procedures (SOPs). The session will be conducted under a protocol reviewed and approved by an IRB; the introductory, MDMA and integrative sessions will be conducted by scientifically and medically qualified persons; the benefits of the protocol are in proportion to the risks; the rights and welfare of the participants will be respected; the investigators conducting the trial do not find the hazards to outweigh the potential benefits; each participant will give written informed consent before any protocol-driven tests or evaluations are performed.

A comprehensive review of MDMA research is contained in the Investigator's Brochure supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

2.2 Protocol Purpose

One purpose of the protocol is to collect quantitative data on mood, psychological symptoms, personality traits and self-reported interpersonal closeness in up to twenty healthy volunteers after placebo and MDMA administration within a therapeutic setting through use of established measures of mood state, symptoms and personality. This exploratory study will permit an understanding of the acute effects of the drug in a specific and relevant setting for use in therapy and will include comparison with placebo, and it may permit comparison between personality assessment in people with PTSD and healthy volunteers before and after MDMA administration.

Only three human trials of MDMA have attempted to assess empathy or interpersonal closeness, an affect of potential relevance within a therapeutic setting. When given in a different context, it is probable that MDMA will produce different effects. A psychotherapeutic context possesses several features that differentiate it from a clinical laboratory setting, including a focus on introspection and relatively unstructured interactions with the investigators. This Phase 1 study is designed to examine the specific effects of MDMA on interpersonal closeness during the acute phase of the drug effects when administered in a psychotherapeutic setting in healthy volunteers. Interpersonal closeness will also be assessed a day after administration. A novel measure developed by Lisa Jerome PhD will be used to measure interpersonal closeness.

In addition, this protocol will provide participants who have completed the sponsor-developed training program with the optional opportunity to gain first-hand experience of the effects of MDMA administered in a therapeutic setting.

Currently, there are no training programs designed to teach MDMA-assisted psychotherapy. June May Ruse, Ph.D. and Michael Mithoefer, M.D., with the assistance of Lisa Jerome, Ph.D., Rick Doblin, Ph.D., Ann Mithoefer, B.S.N., and Elizabeth Gibson have developed a treatment manual describing the core elements, procedures and techniques of MDMA-assisted psychotherapy [4]. The treatment manual details descriptions of methods for therapists to provide guidance and support during MDMA-assisted sessions. The sponsor is developing training programs in which trainees will be taught the requisite skills and techniques to perform MDMA-assisted psychotherapy research in patients with PTSD. MAPS' treatment method can be conducted by therapists and researchers without any prior personal experience with MDMA, and MAPS will not require therapists conducting studies to have such experiences. Nevertheless, MAPS believes that a personal experience with MDMA, in a therapeutic setting similar to that used in clinical trials, is likely to make a significant contribution to a therapist's effectiveness conducting clinical trials with MDMA, and to offer a valuable opportunity to broaden our knowledge of MDMA effects relating to the safety of MDMA.

2.3 Supporting Information

Research into the subjective effects of MDMA has been spurred in part by the widespread use of Ecstasy (material represented as containing MDMA) in recreational settings. Early trials investigated alterations of consciousness and mood after MDMA [5, 6], and subsequent investigations assessed the subjective effects of MDMA with measures specifically

designed to assess alterations in consciousness, such as the Addiction Research Center Inventory, Altered States of Consciousness Scale or Hallucinogen Rating Scale [e.g. 2, 3, 7, 8]. Assessments of mood occurred in medical or neuroscience laboratory settings often involving cognitive tasks, imaging or physiological assessment, and assessment of mood was conducted immediately before and during MDMA administration. Such studies report consistent findings of elevated positive mood, anxiety and slight alterations in perception, and reported feeling more talkative, friendly and energetic but also more tense and anxious over loss of control [1, 2]. It is notable that MDMA tends to produce elevations on most or all scales of alteration of consciousness, but that these measures do not permit specific or directional assessment of mood. Subjective effects reported in clinical trials differ from the richer reports provided from retrospective surveys of people using ecstasy in various recreational settings, where people are more likely to report increased closeness to others or greater acceptance of self or others as well as positive mood, anxiety, and slightly altered perception [e.g. 9, 10-12].

Some researchers have specifically assessed the acute effects of MDMA with the Profile of Mood States [3, 5, 8]. Of these studies, only one has assessed mood the next morning after nocturnally administered MDMA [3]. A few investigators have examined sub-acute effects, but generally as self-reported side effects, and not effects on mood [2, 13]. To date, there are no trials that have investigated the effects of mood approximately 24 hours after MDMA administration.

A psychotherapeutic context differs from clinical trials and nonmedical settings in a number of ways. Participants are specifically prepared for the experience prior to drug administration with the expressed goals of introspection and communication with the therapists about their inner experience, including giving attention to any emotionally intense or upsetting material that may arise. In MDMA-assisted psychotherapy for PTSD, for example, people are expected to engage with trauma-related thoughts and memories in a nondirective but focused manner, with intermittent support from the therapists. Listening to music is often part of the experience, as is the option to use eyeshades during the session. Participants remain at the study site overnight and work with the therapists on the morning after a session, continuing to discuss and address their experience of the previous day. Hence the psychotherapeutic setting provides more structure than most recreational settings but less engagement and task completion than a laboratory setting, increasing the likelihood of intense emotions and allowing the opportunity to process them if they occur.

Personality measures have not been used in clinical trials of MDMA in healthy volunteers. These measures are intended to measure cross-situationally stable facets of personality, such as degree of extroversion or neuroticism. There is some evidence of age-related changes in at least some personality factors [14, 15], and preliminary evidence of changes in the NEO in people with PTSD after MDMA administration in a Phase 2 clinical trial. Hence it is possible that MDMA administration could have an effect on personality scores in healthy volunteers.

Narrative reports of the effects of MDMA, including reports from therapeutic use, describe increased empathy and acceptance for the self and others, and increased feelings of closeness toward others [10, 11, 16]. Changes in empathy, interpersonal closeness or acceptance may play a role in the therapeutic effects of MDMA. Only three human trials of MDMA have attempted to directly assess self-reported empathy or sociability, in all cases through a subset of items on surveys of subjective effects [13, 17, 18], with two of three finding an increase in sociability or closeness to others. While there are a number of instruments measuring trait empathy or compassion [e.g. 19] [20], few assess state empathy. A study in healthy volunteers demonstrating the prosocial effects of MDMA through a less direct measure, as through a nonverbal measure of perceived social distance, may be able to discover the presence and degree of changes in interpersonal closeness experienced after MDMA.

This exploratory protocol will use the Profile of Mood States, an established measure of current mood states employed in human MDMA trials [3, 5, 8] as well as the NEO Personality Inventory, an established measure of personality. The protocol will examine mood in healthy participants both shortly before drug administration and as drug effects are waning, as well as during the days before and after the session. The protocol will also examine potential changes in scores on a well-known measure of personality, the NEO Personality Inventory.

Enrollment in this protocol will be limited to a maximum of twenty co-therapists learning to conduct MAPS-sponsored MDMA-assisted psychotherapy studies. There is a precedent for the view that it is valuable for therapists to have personal experience with the specific therapeutic techniques they are being trained to employ. Various therapeutic schools have a model of psychotherapy training that requires psychotherapists in training to undergo some or all elements of psychotherapy [21]. While currently there is controversy as to the significance and benefits of these experiences, sometimes referred to as “personal psychotherapy,” specific features of using psychoactives as adjuncts to psychotherapy support such experiences [22].

Personal experience is considered beneficial by practitioners of psychotherapeutic methods such as hypnosis and psychoanalysis, and by teachers of meditation and yoga. However, in the case of present-day MDMA research, personal experience with MDMA can only be obtained legally through participation in a government-approved protocol. Some researchers currently conducting MAPS’ MDMA/PTSD studies have expressed the opinion that it would enhance the treatment that they are able to provide to study participants if they were able to experience MDMA within a controlled protocol such as this one.

The potential value placed on personal experience is consistent with the views expressed by many of the early psychedelic therapists and researchers from the 1940s to the early 1970s, who used psychedelic sessions to train therapists. At least some therapists who underwent personal therapy reported a better understanding of their patients’ experience, including both the negative and positive effects of therapy. People who are unfamiliar with the effects of a given compound in a specific setting may hold inappropriate expectations or be unaware of aspects of the setting that may enhance or hinder therapeutic ef-

fects. Investigators who administered LSD in the course of psychotherapy reported that therapists who took LSD gained better insight into their patients' experiences during LSD-assisted psychotherapy and were thus better able to aid them [23-25]. One hundred and eight people with pastoral and counseling jobs received LSD up to three times in a therapeutic context as part of the "Training Project for Mental Health Professionals" conducted at the Maryland Psychiatric Research Center as part of Dr. Albert Kurland's IND for d-lysergic acid diethylamide [26] initiated in order to enhance the ability of mental health professionals to work with people who discussed LSD experiences with them. Daniel Helminiak STL, Ph.D., Ph.D., LPC, a Professor of Psychology at the University of West Georgia, one of the original participants in the "Training Project for Mental Health Professionals", reported long-term benefits to his ability as a therapist from undergoing a supervised experience with LSD [27].

2.4 Previous MDMA Research

To date, MDMA has been administered to approximately 412 research participants, in both Phase 1 and Phase 2 studies, without any occurrences of drug-related Serious Adverse Events (SAEs) [1, 3, 28-38].

The initial and supplemental doses of MDMA to be used in this protocol are identical to those in use in the studies of MDMA-assisted psychotherapy research completed or currently underway in the U.S., Switzerland and Israel. Previous researchers have also used doses within this range [2, 7, 13, 28, 35].

Only three human trials of MDMA have attempted to assess empathy or interpersonal closeness, an affect of potential relevance within a therapeutic setting. When given in a different context, it is probable that MDMA will produce different effects. A psychotherapeutic context possesses several features that differentiate it from a clinical laboratory setting, including a focus on introspection and relatively unstructured interactions with the investigators. This Phase 1 study is designed to examine the specific effects of MDMA on interpersonal closeness during the acute phases of drug administration when administered in a psychotherapeutic setting in healthy volunteers. Interpersonal closeness will also be assessed a day before and a day after administration.

3.0 Protocol Objectives

The objectives of the protocol are to collect psychological effects of MDMA in healthy volunteers through a randomized, double-blind, placebo-controlled crossover design, assess safety, and to expand the knowledge of therapists training to conduct MDMA-assisted psychotherapy research.

3.1 Primary Objectives

The protocol will meet the following primary objectives:

- To assess changes in current mood state as measured by POMS before, during, and after MDMA and placebo experimental sessions. Measurements will be made before, during the latter part of, and one day after each experimental session.

Comparisons will be made in scores over time with each condition and between scores during and after MDMA and placebo sessions.

- To assess personality traits at baseline and two months after MDMA administration using the NEO Personality Inventory (neuroticism, extroversion, openness, conscientiousness and agreeableness).

3.2 Secondary Objective:

The protocol will meet the following secondary and exploratory objective

- To assess current interpersonal closeness before, immediately after and one day after each experimental session with an investigator-derived non-verbal self-report measure. Then protocol will compare interpersonal closeness after MDMA administration with interpersonal closeness assessed after placebo administration.

The protocol is designed exclusively for subjects who meet the medical and psychiatric inclusion criteria and who have successfully completed a training program conducted by the sponsor to expand the knowledge and skills of co-therapists conducting or wishing to conduct MDMA-assisted psychotherapy research. A secondary objective of this protocol is that after the experimental sessions, subjects are expected to grasp more completely the effects of the study drug as experienced by patients in a therapeutic setting.

3.3 Safety Objective

To monitor and assure the safety of participants during each experimental session and throughout the clinical protocol by monitoring physiological drug effects, psychological symptoms, suicidal thoughts or behavior and adverse events.

- To assess psychological symptoms at the same timepoints as mood assessment, using the BSI.
- Suicidal ideation and behavior will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) before and after each experimental (MDMA or placebo) session and throughout the follow up period.
- SUDS and vital signs (blood pressure, heart rate and temperature) will be measured during each experimental session. Comparisons will be made for SUDS and vital signs during and after MDMA administration and during and after placebo administration.
- Adverse events and side effects will be collected during and after each experimental session.
- The protocol will assess psychological symptoms before, immediately after and one day after each experimental session with the BSI.

4.0 Investigational Product

4.1 MDMA Activity Related to Proposed Action

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to

reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [39, 40]. In the first completed study of MDMA-assisted psychotherapy in people with PTSD, the principal investigator of this protocol reported reduction in PTSD symptoms, as assessed by an independent rater, in people who received MDMA with psychotherapy instead of placebo [41]. Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion [2, 6-8, 13, 17, 42, 43]. Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example [7] versus [6]). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that anxiety is reduced without depressing the sensorium, and that patients can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit patients to explore usually upsetting thoughts, memories or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

4.2 MDMA Description

The active compound to be used in this protocol is MDMA. This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor [44-46]. Its direct actions on serotonergic, adrenergic and other receptors are considerably lower. Lactose will serve as the inactive placebo.

4.3 MDMA Compounding, Doses and Labeling

This study employs a randomized, double-blind crossover design. Participants will receive an initial dose of 125 mg of MDMA followed in one and a half to two and a half hours by an optional supplemental 62.5 mg dose during one of two experimental sessions. During the other experimental session they will receive capsules containing an equivalent weight dose of lactose (225 mg for the initial dose, 62.5 mg for the supplemental dose) intended to maintain identical visual appearance. MDMA in bulk will be sent to the investigator who will take it to the pharmacist for compounding. The pharmacist will provide bulk lactose for compounding placebo capsules. MDMA will be weighed into 125 and 62.5 mg doses (calculated as the weight of the hydrochloride salt) and placed in gelatin capsules along with additional lactose to ensure weight and appearance identical to the placebo capsules. Capsules for initial dose will be a different color from capsules used for the supplemental dose. Lactose, in doses of equivalent dry weight, will be placed into gelatin capsules of identical appearance to those used for initial and supplemental dose MDMA.

Initial and supplemental doses for each experimental session (first and second experimental session) will be stored in four separate containers, with each container holding a single capsule that will either be an initial or supplemental dose for the first or second experimental session. Initial doses will be 125 mg MDMA or an equivalent weight of lactose, and supplemental doses will be 62.5 mg MDMA or an equivalent weight of lactose. Con-

tainers will be labeled with the protocol number, drug name, lot number, dosage, inactive drug name, weight, the sponsor name and a statement that the drug is for clinical-trial-use only. Because the investigator is blind to condition (either MDMA on first experimental session or placebo on first experimental session), it will be indicated on each container that there is a 50% chance that it contains MDMA, and a 50% chance that it contains lactose. Labels for each dose and each subject will be provided by the sponsor and applied by the pharmacist. All packaging and labeling will all be done in the presence of the investigator.

Example of a container and label that will contain all doses for a participant

Box label

MAPS Study # MT-1

Investigational Product MDMA and Placebo

Randomization # 51

Subject # _____

Administer as per protocol

Caution-Limited by United States law to Investigational Use

An example of planned drug labeling is provided below
Label for each individual container assigned to a participant

Container label	Container label	Container label	Container label
MAPS Study # MT-1			
Experimental Session #1	Experimental Session #1	Experimental Session #2	Experimental Session #2
Dose 1: XXX mg	Dose 2: XX mg	Dose 1: XXX mg	Dose 2: XX mg
Randomization # 51	Randomization # 51	Randomization # 51	Randomization # 51
Subject # _____	Subject # _____	Subject # _____	Subject # _____
Administer as per protocol			

4.4 MDMA Accountability

Forms will be provided to track drug accountability and administration throughout the study. Drug accountability will be reviewed during routine monitoring visits.

4.5 MDMA Storage and Handling

MDMA is a Schedule 1 compound and will be stored and handled in compliance with relevant Federal and State regulations. In accordance with Drug Enforcement Administration (DEA) requirements, the principal investigator will be responsible for storing and dispensing the MDMA. It will be stored in a safe mounted to the floor, that has been inspected and approved by the DEA for this purpose. Only the principal investigator with the Schedule 1 license will have the combination to the safe. The room in which the safe is mounted has an alarm system and will be locked whenever the investigator or his nurse is not present.

Investigational product will only be removed from the safe for one subject at a time at the time of the session and the MDMA will not leave the premises. MDMA will be administered orally with a glass of water. All doses administered will be recorded on the appropriate accountability logs.

Records pertaining to the use of Schedule 1 compounds will be maintained in accordance with relevant Federal and State Regulations. They will be kept separate from other records and will be maintained in a locked cabinet mounted to the wall in a locked office with an alarm system.

4.6 MDMA Stability

Complete details on the chemistry, manufacturing and control of the MDMA Hydrochloride (HCl) to be used are described in Drug Master file (DMF) # 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 in 1985. The identity and purity of this MDMA was confirmed using High Performance Liquid Chromatography (HPLC) in 1997 as described in DMF # 6293 and was found to be 99.87% pure. On August 12, 2002, Chemic Laboratories reanalyzed the MDMA at the request of the sponsor in relation to the study of MDMA-assisted psychotherapy in people with PTSD, the analysis found it to be more than 99.7% pure. A more recent analysis performed by Nichols at the request of researcher Dr. Carl Hart on February, 2006 continued to find a high degree of purity. This analysis found the MDMA in question to be 99.9 pure.

5.0 Protocol Design

This study protocol will use a randomized, placebo-controlled, double-blind crossover study design to compare the effects of MDMA and the effects of placebo. The study will enroll up to 20 participants. Participants can enroll in this protocol after meeting all inclusion criteria without meeting any exclusion criteria and after successfully completing a sponsor-developed MDMA therapist training program. The investigators will conduct two experimental sessions in their treatment facility using the same setting employed in their Phase 2 study of MDMA-assisted psychotherapy in subjects with treatment-resistant

PTSD. Participants will be randomly assigned to receive placebo during one day-long experimental session, and MDMA during the other session. Participants will undergo a 90-minute preparatory session with the investigators one day prior to undergoing the first experimental session. Each participant will then undergo a day-long experimental session within a psychotherapeutic context. In accordance with random assignment, participants will either receive an initial dose of placebo or MDMA followed by a supplemental dose of the same compound as the initial dose one and a half to two and a half hours later, if mutually agreed upon by investigators and participant. The initial dose of MDMA will be 125 mg, and the supplemental dose will be 62.5 mg. Following the session, the participant will stay overnight at the study site. Each participant will have a 90-minute, integrative psychotherapy session on the day after the first experimental session. On the following day they will undergo a second day-long experimental session, receiving MDMA if they received placebo during the first session, and placebo if they received MDMA during the first session. The second experimental session will include an overnight stay and be followed the next day by a second 90-minute integrative session. The preparatory session before experimental sessions, and the integrative sessions after each experimental session will serve to prepare subjects for the MDMA experience and subsequently to address any transient distress that may result from the experimental sessions. All sessions will be recorded to audio and video, and participants will receive copies of their sessions upon request. Starting the day after the second integrative session telephone calls will be made to participants each day for seven days, as well one and two months after the first experimental session. These will serve as additional opportunities to monitor safety and to help subjects understand and integrate the experience.

To assess current mood state at three time points during each experimental session, participants will complete the Profile of Mood States (POMS) on the day of the preparatory session, five to six hours after drug administration on the day of each experimental session and at the end of each integrative session the day following an experimental session. To assess feelings of interpersonal closeness, they will complete the interpersonal closeness measure at the same time points as the POMS on the day of the preparatory session, experimental sessions, and integrative sessions following each experimental session. To assess psychological symptoms and monitor for safety they will complete the Brief Symptoms Inventory (BSI) on the day of the preparatory session, twice on the day of each experimental session (one hour before drug administration and five to six hours afterwards), on the day of each integrative session and on days one and seven of telephone follow-up, as well as at the one month and two month telephone follow-up interviews. Participants will complete the Neuroticism-Extroversion-Openness Personality Scale (NEO) just prior to the preparatory session and two months after the first experimental session.

As a safety measure participants will complete the C-SSRS at baseline, after the preparatory session, twice during each experimental session (once just prior to drug administration and once five to six hours after drug administration, at each integrative session on the day following an experimental session, on the first and seventh days of telephone contact, and one and two months after the first experimental session. Additional administrations of the C-SSRS will be performed at other points following drug administration or during

follow-up telephone contact if a subject is experiencing psychological distress that does not respond readily to processing with the therapists according to the methods described in the MDMA-assisted psychotherapy treatment manual.

5.1 Planned Duration of Protocol

The duration of active participation in the protocol will be five days of study visits followed by integrative telephone calls occurring daily for a week after the second integrative session and then again 1 and 2 months following the MDMA session. The last telephone call occurring two months after the first experimental session will be considered the termination visit of the protocol. Assuming an enrollment of 20 participants, the expected time from enrolling the first participant until the final participant completes this protocol is 2 to 3 years. This estimate is based on enrollment of approximately one participant per month, but assumes delays relating to the scheduling and completion of the training program.

5.2 Randomization and Subject Numbering

A randomization monitor will generate a list of 35 random numbers between 50 and 100. Each number on this list will be randomly assigned to one of the two sequences of drug administration. Subjects will be assigned in a blinded fashion to the next available randomization number on the list at Visit 1. The randomization numbers will be pre-printed on the drug packaging labels. There will be one carton to hold all drug for a subject. The carton will hold four smaller containers. These smaller containers will hold one capsule each, and will be labeled:

- Experimental Session 1 dose 1 (125 mg)
- Experimental Session 1 dose 2 (62.5 mg)
- Experimental Session 2 dose 1 (125 mg)
- Experimental Session 2 dose 2 (62.5 mg)

The containers with the initial (dose 1) and supplemental (dose 2) doses for the first experimental session will be marked with a "1", and the containers holding the doses for the second experimental session will be marked with a "2". Initial and supplemental dose capsules will have shells of different colors to ensure identification as an initial or supplemental dose. Participants who replace any participant who has withdrawn from or been removed from the study will be assigned the next consecutive number in the series. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant. For this purpose, the randomization monitor will provide the investigators with a numbered sealed envelope corresponding to each container with an enclosed card indicating the condition order for that container. These sealed envelopes will be stored in the safe and opened only in the event that early unblinding is required. In all other cases, the blind will be maintained until all participants have completed the study. The investigators and participant will be blind to condition (sequence of administration) assignment.

5.3 Recruitment and Subject Population

The investigator will recruit men and women aged 21 or older who meet the inclusion criteria and do not meet any exclusion criteria, and who have successfully completed a sponsor-developed training program for MDMA-assisted psychotherapy. Participants will be individuals licensed to perform psychotherapy, physicians, nurses, or individuals enrolled in a graduate program that will lead to their becoming a licensed psychotherapist. After written informed consent, participants will undergo screening to confirm eligibility.

5.3.1 Inclusion Criteria

Individuals eligible to be enrolled into this protocol are participants who:

1. have successfully completed a sponsor-supported program for training therapists to perform MDMA-assisted psychotherapy research;
2. are at least 21 years old;
3. may have a history of a mood disorder (except bipolar affective disorder type I, see exclusions) and/or an anxiety disorder or other non-excluded psychiatric disorder.
4. are willing to commit to medication dosing\experimental session and integrative follow-up sessions, and to complete evaluation instruments;
5. are willing to refrain from taking any psychiatric medications from study enrollment until up to seven days after the second experimental session, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first experimental session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life). Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual);
6. agree that, for one week preceding the first experimental session will refrain from:
 - a. taking any herbal supplement (except with prior approval of the research team);
 - b. taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team);
 - c. taking any prescription medications with the permission of their physician (with the exception of birth control pills, thyroid hormones or other medications approved by the research team);
7. agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the experimental session;
8. refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session;
9. agree not to use caffeine or nicotine for 2 hours before and 6 hours after drug administration;
10. are willing to remain overnight at the study site;
11. agree to have transportation other than driving themselves after the integrative session on the day after each experimental session;

12. are willing to be contacted via telephone for all necessary telephone contacts;
13. if a woman of childbearing potential, must have a negative pregnancy test and agree to use an effective form of birth control;
14. are proficient in speaking and reading English;
15. agree to have all clinic visit sessions recorded to audio and video.

5.3.2 Exclusion Criteria

Individuals not eligible to be enrolled into this protocol are those who:

1. are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control;
2. have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 or, dissociative identity disorder (with history of affective disorder or anxiety disorder permitted if currently in remission)
3. have current psychiatric diagnosis other than adjustment disorder.
4. have evidence or history of coronary artery disease or cerebral or peripheral vascular disease, hepatic disease with abnormal liver enzymes, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration;
5. have hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions [47];
6. have a history of hyponatremia or hyperthermia;
7. weigh less than 48 kg;
8. have used "ecstasy" (material represented as containing MDMA) within 6 months of the MDMA session;
9. require ongoing concomitant therapy with a psychotropic drug;
10. meet Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
11. is not able to give adequate informed consent;
12. have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

6.0 Methods

Participants will receive consent materials describing the protocol.

After consenting to take part in the protocol, participants will be screened by a physician who will obtain medical and psychological history by interview and perform a general physical examination, brief neurological exam and clinical laboratory assessments (see 6.2.1 for details). Further examination will be medical-history-directed if the investigators have additional questions about participant eligibility. Additional tests or assessments may be requested. If, after reviewing all information, the investigators conclude that a participant is eligible they will schedule a five-day period during which the preparatory session, two experimental sessions and two integrative session will take

place. If tapering medication is necessary, the MDMA session will be scheduled to occur after washout is complete.

Eligible participants will travel to the offices of the investigators, where participant will have one 90 minute-long preparatory session with the investigators, followed by the first of two experimental sessions. Each participant will be assigned to one of two drug administration orders, either receiving MDMA during the first experimental session or placebo during this session. The participant will have a 90-minute integrative session with the investigators on the morning after the first experimental session. The second experimental session will occur 48 hours after the first experimental session. Participants who received MDMA first will now receive inactive placebo, and participants who received placebo first will receive MDMA. Participants will have a 90-minute integrative session with the investigators on the morning after the second experimental session. There will be a week of daily telephone contact beginning on the day after the second integrative session, as well as follow-up telephone calls one and two-months after the MDMA session will be made to participants.

6.1 Assessments and Measures

6.1.1 Assessment of Psychological Effects

The POMS is a 65-item self-report assessment of current mood state [48], containing six subscales Composed-Anxious, Elated-Depressed, Agreeable-Hostile, Energetic-Tired, Clear-headed-Confused, and Confident-Unsure. Participants will complete the POMS on the day of the preparatory session, on the day of the first experimental session approximately five to six hours after drug administration, on the day of the first integrative session, five to six hours after the drug administration in the second experimental session, and on the day after the second experimental session..

The measure of state interpersonal closeness is a five-item non-verbal self-report measure. Participants are asked to draw on a sheet of paper “how close you feel right now” to the self as observed, the investigators, a selected significant other and “the world.” Distance in mm between the self and each target will be considered an indirect measure of interpersonal closeness. The measure is expected to take between two and four minutes to complete. Participants will complete the measures of interpersonal closeness on the day of the preparatory session, five to six hours after drug administration during each experimental session, and on the day of each integrative session.

The NEO [49] will serve as a measurement of personality. The NEO is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It 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. Participants will complete the NEO after completing the preparatory session and again two months after the first experimental session.

During Visit 3, for both research and educational purposes, the investigators will require participants to produce a written narrative account of each experimental session. This is

expected to take between 10 and 30 minutes. Participants may also use other means of expression, such as visual art, to represent their experience.

6.1.2. Safety Measures

As safety measures, vital signs and a measurement of psychological distress will be assessed during both experimental sessions. Participants will repeatedly rate their current degree of subjective distress during both experimental sessions using a single-item, self-report scale, the Subjective Units of Distress (SUD) scale, with the degree of distress marked along seven points.

The BSI is the short form of the Symptoms Checklist 90-Revised and is designed to assess clinical and psychological symptoms [50, 51]. It contains 53 items and takes eight to 12 minutes to complete. It contains nine dimensions (Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism) and three global indices of distress (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total). The participants will complete the BSI on the day of the preparatory session, twice on the day of each experimental session, once just prior to drug administration and five to six hours after drug administration or when most drug effects are no longer present, and on the day of each integrative session that follows each experimental session.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [52]. It consists of a “Baseline” form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during face to face interview or over the telephone. The C-SSRS will be administered once during screening and ten times after enrollment; after the preparatory session, twice during each experimental session (once just prior to drug administration and once five to six hours after drug administration), after each integrative session, on the first and seventh days of daily telephone contact, one month and two months after the first experimental session.

Spontaneously reported side effects, Adverse Events (AEs) and Serious Adverse Events (SAEs) will be recorded during the first and the second experimental session and for a period of seven days after the second experimental session, for a total of eleven consecutive days. The investigators will also assess participant well-being via interview during the introductory session, on each integrative session and integrative telephone calls for seven days following the integrative session after the second experimental session, and the follow-up telephone calls one and two months after the first experimental session.

6.1.3 Measure of Strength of Double Blind

Participant and investigator beliefs concerning substance identity for a preceding experimental session (either MDMA or inactive placebo) will be assessed during the integrative session occurring on the day after each experimental session. On the second integrative session, participants and investigators will also be asked if they changed their minds

about their original guesses concerning drug administered during the first experimental session.

Table 1: Time and Events Table

Visit #	Pre-Study	V1	V2 and V4	V3 and V5	Contact	Phone Contact
Type of Visit	Screening may take place over more than one day	Preparatory Session	Experimental Session	Integrative Therapy	7 days of Contact post V5	Follow up
Approximate Study Day	Up to one month prior to Visit 1	1	2 and 4	3 and 5	6 to 12	32 and 62
Visit Timing and Windows		1 day Prior to V2	Day of Dosing	1 day Post V2 and V4	1 day Post Visit 5	30 and 60 days post V2 +/- 3 days
Provide Consent Materials/Informed Consent	X					
Medical and Psychiatric History (by interview)	X					
General Physical Exam (BP, Pulse, Temp, brief systems check)	X					
Brief Neurological Exam	X					
ECG	X					
Clinical Laboratory Tests, including HIV test	X					
Collect Concomitant Medication	X	X	X	X	X	X
Medication Taper (if applicable)	X	X				
Study Enrollment after meeting Inclusion/Exclusion		X				
Record to Audio/Video		X	X	X		
General Well-Being		X	X	X	X	X
Drug Screen			X ^E			
Pregnancy Screen (if applicable)	X		X			
Complete Randomization Procedure		X				
NEO Personality Inventory		X				Day 62 only
POMS		X	X ^A	X ^B		
BSI		X	X ^{A, B, C}	X ^B		
Interpersonal closeness measure		X	X ^A	X ^B		
C-SSRS	X	X	X ^{A, B, C}	X ^B	Day 6 and 12	X
Administer Dose (MDMA or Placebo)/Therapy			X			
Monitoring of Blood Pressure, Pulse and Temp.			X			
SUDS			X ^{B, D}			
Beliefs of Condition Assignment				X		
Overnight Stay			X			
Integrative Therapy Session				X		
Narrative Report (optional)				X		
Integrative Telephone Contact					X	X
Adverse Events Requiring Dr. Visit			X	X	X	
Spontaneously Reported Side Effects			X	X	X	
Adverse Events that are of Concern to the Participant			X	X	X	X
Serious Adverse Events		X	X	X	X	X
Study Termination						X

^A Approximately 6 hours post MDMA

^B at the beginning of the session

^C as needed

^D Approximately every 60 minutes

^E Given on first experimental session only

6.2 Visit Descriptions

6.2.1 Prescreening and Screening

After giving written informed consent, a screening number will be assigned to each participant. The screening number will be used on all subject records prior to enrollment. Participants will provide a medical and psychological history through interview, during which the C-SSRS will be administered to establish suicide risk. Participants will undergo blood draw and urine collection and a general physical examination performed by a physician who is not one of the investigators. The examination will involve the following procedures: blood pressure, pulse, height, weight, body temperature, examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities, brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function), electrocardiogram (ECG), clinical laboratory assessments to include: Alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide; chloride, serum; creatinine, serum; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum, Complete Blood Count (CBC), which includes: Hematocrit; hemoglobin; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW); percentage and absolute differential counts; platelet count (RBC); red cell count; white blood cell count (WBC), Urinalysis, which includes: Color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen and Thyroid functions: TSH (high sensitivity), Free T4 Free T3]. In addition, Human Immunodeficiency Virus (HIV) serology will be performed. Results of HIV serology will be kept confidential, and appropriate referral for counseling will be made if necessary. The clinical laboratory values will not be captured in the Case Report Form (CRF), but will be used to establish eligibility and will be kept with the subject's source record. Any abnormal results that are not exclusionary will be captured as medical history. A urine-dip pregnancy test for females of childbearing potential will be performed as well. If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated.

The investigators will review this information and will contact the participant if all inclusion criteria and no exclusion criteria are met and will schedule five clinical visits, including the preparatory session, the first experimental session, the first integrative session, the second experimental session and the second integrative session, within a five-day period. Any participant who must refrain from taking a medication will begin tapering off that medication, with the first experimental session scheduled to occur after complete washout. The entire visit should take between 1½ and 2½ hours. This screening may take place over more than one day and up to one month prior to visit 1.

Upon enrollment, each participant will be assigned a unique five-digit subject number. Participants will be enrolled to one of two conditions (order of drug administration). MDMA will be given on either the first or the second administration, with investigator and participant remaining blind to order of drug administration.

6.2.2 Preparatory Session (Visit 1)

Prior to beginning the preparatory session, participants will complete the NEO, POMS, interpersonal closeness measure, BSI and C-SSRS. The investigator will inquire about any possible changes in the participant's health to ensure that they continue to meet eligibility criteria and if applicable, will confirm that they have appropriately tapered off of medications. After eligibility is confirmed the participant will be considered enrolled and will be issued a subject number. The participant will undergo a 90-minute preparatory session with the investigators at their offices the day prior to the first experimental session, in part to reduce the likelihood of psychological distress during the experimental session and in part to model the sequence of events that an individual receiving the therapy in a clinical treatment trial would experience. The preparation session will follow the format used in current studies of MDMA-assisted psychotherapy. The investigators will also assess participant baseline general well-being and mental health via clinical interview. The preparatory session will be followed by approximately forty minutes of completing assessments and measures, including the BSI, NEO, POMS, interpersonal closeness measure and C-SSRS.

The participant and investigators will discuss goals for the MDMA session and will review what will happen during the MDMA session, following standard procedures and techniques discussed in the sponsor-developed treatment manual. However, these will be adapted for the present context in which the subject does not have a psychiatric disorder. The investigators and participant will discuss the fact that it is not possible to predict the content of an experimental session, and that specific psychological issues may arise in the course of self-exploration stimulated by MDMA. Participants will be reminded that difficult emotions, including grief, rage and fear or panic, may arise during MDMA-assisted psychotherapy sessions, and that sometimes the process can produce surprising and profound experiences even in people without any psychiatric conditions.

If a participant would like another individual present during one or both of the experimental sessions, a meeting between the investigators and that individual will be scheduled during the introductory session. Permission must be granted by the investigators for the presence of another individual during an experimental session. The introductory session will be recorded to audio and video. The investigators will supply the participant with a set of instructions and restrictions for conduct 24 hours prior to each experimental session, including restrictions on food and alcohol consumption. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before an experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session. Participants must not use caffeine or nicotine for 2 hours before and 6 hours after drug administration. All SAEs will be recorded from the time the participant is enrolled at Visit 1.

6.2.3 Experimental Sessions (Visits 2 and 4)

There will be two experimental sessions scheduled to occur 48 hours (two days) apart. Each experimental session will follow identical procedures and sequences of events. Each participant will receive 125 mg MDMA possibly followed by 62.5 mg during one ex-

perimental session, and an equivalent weight of placebo during the other experimental session, with investigators and participants blind to order of presentation.

On the day of each experimental session, the participant will arrive approximately one hour prior to the start of the session. Continuing eligibility will be confirmed and, if appropriate, a urine pregnancy test will be performed at the start of both experimental sessions. Urine drug screening will be performed at the beginning of the first, but not the second, experimental session, as MDMA may produce a positive reading for amphetamines, and such a reading on the second experimental session could risk unintentional breaking of the blind. If the subject continues to meet criteria and the participant reports that he/she followed appropriate rules and restrictions, the session will proceed; a positive pregnancy screen is cause for withdrawal from the protocol, a positive drug screen will be reviewed by the investigator and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study.

The participant will complete the C-SSRS and the BSI approximately one hour to a half hour prior to drug administration.

The investigators will review procedures for an experimental session as they would for an MDMA-assisted psychotherapy research session. The investigators will record both experimental sessions to video and audio. The session will last for eight hours or longer, followed by an overnight stay at the study site.

The investigators will follow standardized techniques and procedures for an MDMA-assisted psychotherapy research session as described in the treatment manual used for training, including familiarizing the participant with the space and equipment, and reviewing session goals and the logistics of the session. Participants will complete the SUD just prior to initial dose administration.

At approximately 10:00 A.M., participants will receive the initial dose of 125 mg MDMA or an equivalent weight of lactose placebo along with a glass of water. The participant will sit or recline on comfortable furnishings, and there will be eyeshades and a program of music available if the participant wishes to use them. The participant will be encouraged to spend much of the time focusing attention on their inner experience without talking, but may speak to the investigators whenever they wish, and will receive guidance and support as needed. If the subject has not spoken within an hour, the investigators will inquire briefly about their experience.

Blood pressure and pulse will be measured at the outset of the experimental session, once every 15 minutes for the first 6 hours of each experimental session and every 30 minutes for another 2 hours. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic or pulse 110 are exceeded. Participant body temperature will be measured via tympanic thermometer and participants will complete the SUD every 60 minutes, until the session is over, allowing a window of plus 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the investigators can

make a greater number of measurements as their clinical judgment dictates. If the investigators conclude that it is appropriate to do so, they will initiate the first question of the C-SSRS at any point in the session if the participant is experiencing significant psychological distress that does not respond readily to processing with the therapists according to the methods described in the MDMA-assisted psychotherapy treatment manual. The investigators will record any spontaneously reported side effects during each experimental session. Each effect will be rated mild, moderate or severe, with mild defined as no limitation in normal daily activity, moderate as some limitation in normal daily activity and severe being unable to perform normal daily activity.

A supplemental dose of 62.5 mg MDMA, which is half the initial dose, or an equal weight of lactose placebo, will be administered 1.5 to 2.5 hours after the initial dose upon mutual agreement between the investigators and participant.

The participant will complete the POMS, interpersonal closeness measure, C-SSRS and BSI approximately six hours after initial drug administration.

A support-individual who has previously agreed and been approved to remain with the participant during an experimental session may arrive during the session.

The investigators will remain with the participant until the physical and psychological effects of the session have substantially subsided and the subject is judged to be in a stable condition and appears to have returned to baseline mental status. The investigators will end recording to audio and video when they have established that the participant returned to baseline function or is very close to doing so.

The participant will remain at the study site overnight, in a comfortably furnished suite that allows for accompaniment by a significant other, friend or attendant. An attendant will remain with any participants who are unwilling or unable to locate another individual to stay with them at the study site during the overnight stay. The attendant will be of the same sex as the participant, and he or she will be trained for assisting in this protocol. Attendants will be selected for their ability to act as reliable and compassionate attendants to participants while allowing participants room for introspection or further self-exploration as needed. All participants will receive instructions for contacting one of the investigators if needed, via telephone or 24-hour pager.

Participants will be instructed not to use caffeine or nicotine for 6 hours after drug administration. Spontaneously reported side effects, AEs of concern to the participant, and AEs requiring a doctor's visit will be collected starting on the day of the experimental session through the seventh telephone daily telephone call. All SAEs will be recorded.

6.2.4 Integrative Sessions (Visits 3 and 5)

On the morning after the MDMA session, the participant will meet with both investigators during a 90-minute integrative therapy session to discuss their experience of the experimental session. The participant will complete the POMS, interpersonal closeness measure, BSI and C-SSRS just prior to beginning the integrative session. Prior to the in-

tegrative session, the participant and both investigators will indicate their beliefs concerning the identity of the drug the participant received during the experimental session preceding the integrative session. The discussion during each session may include processing any thoughts, feelings or memories that arose during an experimental session, addressing any goals set at the start of a previous session, considering goals or plans for an upcoming experimental session, and relating one or both experimental session to anything the participant learned about MDMA-assisted psychotherapy research prior to the session, including information gleaned from the training program. Whenever possible the investigators and participant will attempt to follow the procedures for integration sessions described in the treatment manual. Integrative sessions will be recorded to audio and video. If the participant has already generated a narrative report of their experience during an experimental session and wishes to share it with the investigators, they may do so at this time. The investigators will make a copy of the narrative report and return the original to the participant. This is expected to take between ten and 30 minutes. Likewise, participants may use other means of expression, as visual art, to represent their experience.

The therapist-investigators will assess participant mental health and the presence of any remaining side effects via clinical interview during the integrative follow-up session and telephone contacts.

The participant must have a pre-arranged ride from the study site to the place where she or he is residing, and if the participant has been unable to arrange transport, then the investigators will assist the participant in locating a ride to the location where the participant is staying.

If the participant confronted unexpectedly intense or disturbing material during an experimental session, the investigators will provide means of continued contact throughout this day as needed. The integrative telephone contact schedule will be reviewed and additional integrative sessions with the participant may be scheduled, if needed.

Spontaneously reported side effects, AEs of concern to the participant, AEs requiring a doctor's visit and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded.

6.2.5 Daily Integrative Telephone Contact for Seven days after 2nd Integrative Session

One or both of the investigator will contact the participant daily for 7 days after the second integrative session, starting the day after the second integrative session. The integrative telephone contact will be for a brief check-in lasting 5 to 15 minutes, or as long as necessary to address any participant's concerns and to assess participant well-being. Additional telephone contact or an additional integrative session can be scheduled at the request of the investigators or participant. If a participant has an additional integrative session during this interval, the same assessments will be made face to face instead of via telephone. On the first and seventh day of telephone contact, the participant will complete the C-SRRS over the telephone.

6.2.6 Integrative Telephone Contact 1- and 2-months post 1st Experimental Session

The investigator will contact the participant one and two months after the first experimental session. This telephone contact will be for a brief check-in lasting 5 to 15 minutes, but with duration permitted to last as long as necessary to address any participants concerns and to assess the participant's general well-being, whether undergoing the experimental sessions affected their conducting therapy and whether the experience matched their expectations.

The participant will complete the C-SSRS over the telephone during the one-month and two-month integrative telephone calls.

Approximately a week prior to the two-month telephone contact, the investigators will mail the subject a copy of the NEO. The participant will complete the measure and return it in an envelope that uses the offices of the investigators as both mailing and return address.

AEs of concern to the participant and concomitant medications for treatment of AEs will be collected. All SAEs will be recorded.

6.3 Removal of Participants from MDMA Administration

Participants can withdraw consent at any time without prejudice. The investigator can withdraw a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of experimental sessions and related visits that are critical for safety. If the investigator withdraws a participant from the session, the investigators will explain the reason for withdrawing the participant.

Participants will be clinically monitored after withdrawal, the cause of which will be recorded in the participant's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable.

6.4 Premature Discontinuation of Program

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue the protocol at any time. If the protocol is prematurely terminated, the investigator will promptly inform participants and will provide appropriate follow-up to participants, if necessary. If the protocol is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. Participants will still receive recordings of sessions if they request them.

7.0 Risks In Study Participation

7.1 Screening

Medical data will be collected via medical and psychiatric history interview, general physical examination, and additional tests, assessments or interviews, if applicable. Submitting to a full medical examination and psychiatric assessment may be time-consuming, distressing or uncomfortable for some. These procedures are intended to en-

sure that only those without any contraindicated conditions for receiving MDMA are enrolled. Because medical history, physical examination and the collection of laboratory specimens are all part of the screening procedure, they cannot be omitted from the protocol design.

7.2 Risks and Discomforts Associated with Drawing Blood

Prior to enrollment, blood will be drawn as part of screening to assessing eligibility. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood-draw site. There is also a remote possibility of inflammation or infection at the blood-draw site.

7.3 Risks and Discomforts of Completing Assessments and Measures

Some measures contain items that may provoke negative emotions. It is possible that completing these measures could be upsetting.

7.4 Risks of Receiving MDMA

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies in non-psychiatric populations. Common side effects include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, drowsiness, impaired gait or balance, dry mouth, headache, and thirst. Other slightly less common side effects include nausea, restlessness, parasthesias, perspiration, muscle tension, drowsiness, diarrhea and nystagmus, rumination, and sensitivity to cold. These effects are transient and wane as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, weakness, dry mouth, low mood or irritability. Sub-acute effects are reported less often than acute effects. More information on drug side-effects is contained in the Investigator's Brochure.

MDMA may produce mild alterations in sensory perception and altered perception of time [1, 6, 7]. Women may be more sensitive to these effects [2]. MDMA acutely affects attention, information processing and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of scene change [33].

Participants may discuss emotionally distressing or embarrassing issues during their MDMA session. This may cause psychological distress.

7.4.1 Cardiovascular Effects

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 1.5 to 2.5 hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. Approximately 5% of participants enrolled in controlled trials with MDMA have had elevations in blood pressure above 200/100 mmHg or above a cut-off of 140/90 mmHg [6, 53]. Table 2 shows the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. No subjects in the completed trial or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure, pulse or temperature, and all values returned to normal spontaneously. Maximum peak blood pressure during a given session in some cases rose

above the cut-off for making more frequent measures (150 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP). The degree of additional blood pressure and pulse elevation after a second dose of MDMA that is half the original dose and given 1.5 to 2.5 hours after the first dose is minimal. Preliminary data gathered by the principal investigator, who recently conducted a study of MDMA-assisted psychotherapy in 21 participants with PTSD, reports that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose. The investigators will be collecting baseline, mid-point and endpoint vital signs, and the peak blood pressure, pulse and temperature for each subject on the case report forms.

Table 2. Physiologic Data: Increases over Baseline and Range of values

All Experimental Sessions

Highest recorded increase over baseline per experimental session	MDMA	Placebo
	Mean increase (St. Dev.) [Range of values]	Mean increase (St. Dev.) [Range of values]
Systolic blood pressure, mmHg	28.21 (14.11) [96-179]	13.38 (10.40) [83-157]
Diastolic blood pressure, mmHg	15.38 (6.85) [56-113]	10.94 (6.93) [60-102]
Heart rate, beats/minute	28.13 (11.87) [60-141]	16.69 (12.35) [68-107]
Temperature, °C	0.72 (0.52) [36.6-37.83]	0.42 (0.32) [36.39-37.76]

Group comparisons of vital signs were tested for change pre-session (15 minutes prior) to highest recorded and pre-session to post-session (6 hours post) using *t*-tests. There was a significantly greater increase in all physiologic measures from pre-session to highest recorded value during experimental sessions for the MDMA group than for the placebo group ($p < .05$). There were no significant differences when comparing changes from pre-session to post session ($p > .05$). All values returned to pre-session norms by six hours after session completion.

7.4.2 Psychological Distress

Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from investigator, with occasional use of benzodiazepines for anxiety. In the proposed protocol, participants may confront emotionally intense or upsetting memories, thoughts and feelings. Signs of psychological distress, panic or other unpleasant psychological reactions may not be as strong as expected in people with psychiatric disorders, but may still be present. The investigators will be monitoring degree of psychological distress during the MDMA

session with the SUDS and via observation. The investigators will be collecting baseline, mid-point, peak and endpoint SUDS for each subject on the case report forms.

Less commonly, mild anxiety and depressed mood are reported 1–3 days after MDMA administration [2, 13], and see the IB. Some of these effects are likely to occur, but it is expected that proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects.

7.4.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [2], and ambient temperature does not enhance or attenuate this slight elevation in humans[28]. Maximum body temperature could rise above normal temperature, as with the maximum peak of 100° Fahrenheit (F) during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, including all 21 participants and two drop-outs enrolled in this session, MDMA and placebo conditions combined), but body temperature returned to normal without treatment other than simply lowering the ambient temperature, which may or may not have been necessary.

7.4.4 Immunological Changes

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA [54-56]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon- γ and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings [57-59]. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [56, 60]. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [61, 62], and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [62]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.4.5 Abuse Liability

MDMA is classified as a Schedule 1 compound, largely on the basis of its growing popularity at nightclubs and parties in the early to mid-1980s. The DEA placed MDMA in

Schedule 1, a category reserved for drugs with high abuse potential and no known medical use [63]. Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA [64-66]. However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA [67, 68]. Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence [69, 70], though studies of non-representative samples have reported higher rates of dependence [71]. Most regular ecstasy users report taking ecstasy no more often than once a week [72]. Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

There is no evidence that MDMA-naïve, healthy volunteers exposed to MDMA in previous Phase 1 or Phase 2 studies have been motivated to seek out and use MDMA in non-medical settings. When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that “none of the participants expressed any interest in taking MDMA as a recreational drug” after receiving MDMA in a controlled research setting, (p. 166) [2].

In the currently proposed protocol, diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.4.6 Toxicity

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 [73], and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Serious MDMA toxicity is rare even in uncontrolled settings, considering the millions of users taking ecstasy of unknown identity, potency, and purity [74-76], with many users consuming estimated MDMA doses that are several times higher than those used in the proposed program, without any apparent toxicity. Under unsupervised and nonmedical conditions, the most common SAE involves hyperthermia, described in Appendix A. In addition to hyperthermic syndromes, other rare AEs include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia, and these are described in more detail in the Investigator’s Brochure. The majority of ecstasy users visiting emergency departments do so because of anxiety or panic [77, 78]. In the proposed clinical protocol, volunteers will be excluded on the basis of any conditions that might increase risk of adverse events occurring and participants will be carefully monitored for signs and symptoms of these

unlikely events. Contingency plans for responding to these events are described in Appendix A.

7.4.7 Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nucleus, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density [79-81], with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin [82]. Similar changes can be induced by methamphetamine and other psychostimulants [83-85]. Previous studies in nonhuman primates overestimated human-equivalent doses [86], and previous studies in rodents may also have overestimated human-equivalent doses [87]. Studies in rodents and monkeys that employed lower or fewer doses of MDMA, or that involved self-administration, have failed to find some or all of the markers of serotonin neurotoxicity listed above [64, 88-90]. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [91]. However, they are basing their case on studies that employed inappropriately high doses of MDMA, and studies comparing the effects of repeated use of ecstasy, often along with other drugs, as discussed below.

There is controversy as to whether analogous changes in brain serotonin occur in humans, and a wealth of literature exists that compares ecstasy users to non-users [92]. Earlier studies were retrospective and possessed a number of methodological flaws, particularly in relation to appropriate matching of ecstasy users with controls. Later research employed longitudinal study designs, allowing for comparisons over time. Retrospective and longitudinal imaging studies have detected decreased estimated serotonin transporter (SERT) sites in current heavy ecstasy users when compared with controls [93-95], but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users [92, 96, 97]. A number of these studies reported impaired cognitive function only in heavy users, and not in moderate users, and some recent studies suggest that use of other drugs may contribute to impaired cognition [98-101], though other studies also reported that abstinence from ecstasy did not attenuate memory impairment in heavy users [95, 102]. There is also some evidence that ecstasy users are more likely to report symptoms of anxiety or depression, and to exhibit more behavioral impulsivity than non-ecstasy user controls [103-106]. Findings from prospective and longitudinal studies suggest that young people with existing psychological problems are more likely to try ecstasy than people without these problems [69, 70], and it appears that polydrug use may contribute to this association [103, 106-108]. Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands has examined samples of people before and after reporting their first uses of ecstasy. These researchers

have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task, and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets [109-112]. The team also performed studies expressly in heavy ecstasy users [113-116]. They failed to find reductions in SERT sites, signs of neuronal injury or changes in performance on or brain activity during a working memory task in samples reporting use of no more than six ecstasy tablets [109, 110]. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else [110]. Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory [109]. When comparing cognitive function in people before and after their first use an average of 3.2 tablets and non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users [112]. It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, that all participants in the study of cognitive function performed within the normal range, and that one individual had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other studies. Furthermore, there are some findings that at least women who decided to use ecstasy had higher impulsivity scores prior to use [117]. Taken together, their findings fail to confirm serotonergic neurotoxicity after low ecstasy use, yet found some possible indications of impaired memory.

The risks of neurotoxicity are minimal in the proposed protocol. This is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Nevertheless, the risks of neurotoxicity arising from MDMA administration will be described and noted in application materials prior to and during the completion of the application, and the investigators will informally monitor for any signs of changes in cognition after the MDMA-assisted session.

7.4.8 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [118, 119], as discussed below in the "Pharmacology" section and in the Investigator's Brochure. Pregnant and lactating women will be excluded from participation in the proposed protocol, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to using birth control during the period of the protocol.

7.5 Medical Emergencies

The preparatory session, and the experimental and integrative sessions will all be conducted in the psychiatric offices of the investigators. The offices are located 2.6 miles from the nearest emergency room. The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Benadryl, injectable epinephrine and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. Available emergency medications include antihypertensive agents (such as nitroprusside and labetalol), pressor agents, anxiolytics, and intravenous fluids. In ad-

dition to drugs, the crash cart will contain a defibrillator (with rhythm monitoring capability), an oxygen tank, a 12-lead electrocardiogram (EKG) device, a suction device, a pulse oximeter, an IVAC pump and intubation equipment (including laryngoscope, and endotracheal tubes). Equipment for placing an arterial line and monitoring arterial pressure will be present. For a recently completed Phase 2 trial, the researchers have established (in communication with the FDA) contingency plans for responding to those AEs that appear most likely, based on a comprehensive review of case reports of toxicity in illicit MDMA users reported by Baggott and colleagues in 2001 and in the current Investigator's Brochure. The same contingency plans and equipment will be used in this protocol. With these personnel and equipment, the researchers would be able to stabilize a participant in the office and then transport them by ambulance if hospital admission were required.

8.0 Adverse Events

8.1 Adverse Events

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

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

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

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

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

1. Not Related

The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or argu-

ments to suggest a causal relationship, or the AE is more likely related to the trainee/subject's pre-existing condition.

2. Possibly Related

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

3. Probably Related

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

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

8.2 Common Expected Side Effects

Commonly expected side effects that are spontaneously reported are collected on a separate CRF page and will be categorized as mild, moderate or severe. Common, expected side effects are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Impaired Gait/Balance, Increased Irritability, Rumination (increased private worries), Insomnia, Jaw Clenching, Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Nystagmus, Parasthesias, Perspiration, Restlessness, Sensitivity to Cold, Thirst and Weakness. Spontaneously reported side effects will be collected on days two through twelve.

8.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above

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

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

8.4 Adverse Event Collection

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitors:

Julie Holland, MD
NYU School of Medicine
200 East 33rd Street, Suite 16H
New York, NY 10016
Tel: (212) 358-5808
jholland@inch.com

Study Monitor:

Valerie Mojeiko
Email: valerie@maps.org

████████████████████
████████████████████

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

- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions occurring from the first experimental session through 7 days after the second experimental session
- Any event of concern to the participant throughout the protocol
- Any adverse event leading to withdrawal from the protocol
- Common expected side effects will be collected on the day of each experimental session and for seven days after the second experimental session

9.0 Collection of Concomitant Medications

Participant concomitant medications will be recorded during screening. If necessary, the investigators will make plans for tapering off and discontinuing any contraindicated medication at this time, in consultation with the prescribing physician. The investigators will request information about any changes in medication just prior to the first experimental session. Medications taken during the course of the protocol, including medications taken to treat AEs will be recorded on concomitant medications CRF. Participants must be willing to refrain from taking any psychiatric medications from study enrollment until seven days after the second experimental session, with the exception of gabapentin when prescribed for pain control. Any psychoactive drugs will be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first experimental session to avoid the possibility of interactions (the interval will be at least 5 times the particular drug's half-life). Participants may receive a designated rescue medication that may be administered in the event of symptoms that require it during or after an experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Participants must agree that, for one week preceding the first experimental session:

- a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
- b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
- c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).

10.0 Clinical Laboratory Assessments

The principal investigator will examine laboratory assessments gathered in screening for assessing participant eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol, and will indicate justification for admitting participants with abnormal values.

The following laboratory assessments will be performed as a part of screening:

Serum electrolytes and the metabolic profile, which includes:

ALT/SGPT;
albumin:globulin (A:G) ratio;
albumin, serum;
alkaline phosphatase, serum;
AST/SGOT;
bilirubin, total;
BUN;
BUN:creatinine ratio;

calcium, serum;
carbon dioxide;
chloride, serum;
creatinine, serum;
globulin, total;
glucose, serum;
potassium, serum;
protein, total, serum;
sodium, serum;

CBC, which includes:

Hematocrit;
hemoglobin;
MCV;
MCH;
MCHC;
RDW;
percentage and absolute differential counts;
RBC;
red cell count;
WBC;

Urinalysis, which includes:

Color;
appearance;
specific gravity;
pH;
protein;
glucose;
ketones;
occult blood;
leukocyte esterase;
nitrite;
bilirubin;
urobilinogen;

Thyroid function, which includes:

TSH high sensitivity;
Free T4;
Free T3.

In addition, HIV serology will be performed.

A urine-dip pregnancy test for females of childbearing potential will be performed as well.

The laboratory assessments other than the urine drug screen and pregnancy test will be performed at:

Laboratory Corporation of America
1280 Johnnie Dodds Blvd, Ste 108
Mount Pleasant, SC 29464

The urine drug screen and pregnancy test will be performed at the study site.

11.0 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained prior to the start of the protocol. The clinical study site will be monitored by site visits and telephone calls to the investigator by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate (CRA) to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each participant enrolled. Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor will review the study documentation used for planning, conducting and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

During or after the clinical protocol, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

12.0 Data Analysis

The investigators will compare NEO scores at baseline and two months after the second experimental session to detect changes in any one of the five scores by performing a paired-sample t-test upon the scores. The investigators will also compute descriptive statistics for each administration of POMS, and interpersonal closeness measure. They will compare scores made at different time points and across placebo and MDMA conditions by performing a two way repeated-measures analysis of variance (ANOVA), with time of administration as repeated measure and drug (placebo, MDMA) as a within-subjects factor. There will be no between-subject or group factors.

The investigators will maintain data for assessment of safety, including BSI and C-SSRS scores at each time point, blood pressure, pulse and temperature values, psychological distress, and AEs. They will collect data for blood pressure, pulse, body temperature and SUDS pre-drug administration baseline, approximately three hours after initial dose administration, seven hours after initial dose administration and peak values on case report forms. The investigators will compute descriptive statistics for these variables. The inves-

tigators will examine beliefs about condition assignment, computing descriptive statistics and comparisons between those who received MDMA versus placebo during the first session, to assess strength of blinding for participants and investigators.

12.1 Statistical power

The proposed study is a pilot investigation intended to gather data on the effects of MDMA on mood, personality, interpersonal closeness and psychological symptoms, when given in a therapeutic setting. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. As described in Section 2.3 (“Supporting Information”), several studies have employed the POMS, and a review of these studies described effects as robust. [1]. These findings suggest an estimated effect size of 0.7 to 0.8.

The sponsor used Java applications created by Lenth to calculate estimated statistical power for this study, assuming an effect size of 0.7 and employing a paired t-test as a means of examining estimated power in a crossover study with 20 participants [120], and estimated effect size was 0.84, indicating that the study possesses significant power to detect differences in mood for MDMA and placebo administration. As described earlier in 2.3 “Supporting Information,” narrative and anecdotal reports describe greater interpersonal closeness after use of ecstasy, but the effect is not so readily detected in the laboratory. Using an estimated effect size of 0.5 and a paired-sample t-test, statistical power of 0.56 was calculated. It is likely that the effect size for changes in personality score are lower, and so an estimated effect size of 0.4 was used for this calculation, obtaining estimated statistical power of 0.39. Hence the study may be underpowered for the detection of changes in personality score while possessing enough statistical power to the effects of MDMA on mood.

13.0 Informed Consent

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

Information about events during the MDMA session must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the study, including experimental sessions and of the subject’s legal rights, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator.

The investigator will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator’s study file.

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

The subject should be informed in a timely manner if new information becomes available that may affect the decision to take part in the MDMA session. The communication of this information should be documented.

Because this activity is an optional element open only to those completing a sponsor-developed training program for potential therapists conducting MDMA-assisted psychotherapy research, the sponsor may have access to the names of participants as enrollees in the training program. However, only the subject numbers and subject identification codes will be recorded in the CRF. Written consent to take part in the MDMA session includes giving the investigators permission to view the participant's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, MAPS will have full access to the subject's medical records, including termination visit information. If a participant revokes only the HIPAA authorization, MAPS will have full access to all of the participant's medical records prior to the date and time of revocation.

13.1 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research participants. Despite this, privacy cannot be guaranteed. All data will be identified only by the participant's initials on the source document and five-digit subject number numeric code. Copies of audio and video recordings intended for sharing with participants will only be marked with the participant's subject number. Any materials mailed to participants will be sent along with stamped return envelopes using the office address of the principal investigator both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Each participant may, upon request, receive audio or video recordings of any of the five sessions, including both experimental sessions. They may wish to review them as a means of observing and retaining information to support their own performance of MDMA-assisted psychotherapy research. The investigators will not mark these recordings with participant name or address. If session recordings are unavailable by the end of the integrative session, then the investigators will mail recordings in appropriate packages that list only investigator name and address and that maintain anonymity.

Participants will sign forms for the release of information, such as prior medical records, upon consent to permit screening for protocol enrollment.

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

13.2 Costs to Participants

Participants will not be charged for any research activities, including any tests or assessments performed for screening, MDMA, any psychotherapy or intervention administered to the participant, or any other activity or procedure related to the experimental sessions. If a participant undergoes a medical or laboratory test solely for the purpose of establishing eligibility for study participation, then the sponsor will reimburse the full cost of the test or assessment. The sponsor will be responsible for payment for treating any study-related injuries. Participants will pay for any care not related to the protocol. Participants who are not currently working on MAPS-sponsored MDMA/PTSD pilot studies will need to pay for travel-related expenses to and from the study location.

14.0 Record Retention

Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Record Retention Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records.

15.0 Signature Page

Study title: A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers

Protocol: MT-1

I have read the foregoing protocol and agree to conduct the protocol as outlined. I agree to conduct the protocol in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

Investigator Signature

Date

Print name: _____

On behalf of MAPS, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical protocol.

Sponsor Designee Signature

Date

Print name: _____

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Appendix A: Prevention and Response to Possible Serious Adverse Events

Risk Mitigation

Information from a considerable body of research indicates that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low [1], see also Section 6 of the “Investigator’s Brochure.” Psychiatrists in the U.S. and Europe reported administering MDMA to at least a thousand patients before the drug was made illegal without any drug-related SAEs occurring during sessions [40, 121-124]. There have been no drug-related SAEs during the course of a study of MDMA-assisted psychotherapy in people with PTSD under the direction of the principal investigator for the proposed protocol. Procedures for monitoring for toxicity and risks for the training program will be similar to those employed in the study of MDMA-assisted psychotherapy in people with PTSD.

Although serious untoward reactions are unlikely, the researchers will closely and continuously monitor participants during an experimental session. Throughout all sessions, participants will be attended by the investigators, a psychiatrist who is board-certified in emergency medicine and internal medicine as well as psychiatry and who maintains Advanced Cardiac Life Support (ACLS) certification, and a psychiatric nurse who will maintain Basic Life Support (BLS) certification. The principal investigator and assisting investigator will thus provide a team of an experienced emergency physician and a registered nurse to respond in the unlikely event of a medical emergency. In the unlikely event of cardiac arrest, they will follow the American Heart Association guidelines for 2-person BLS for Healthcare Providers (including defibrillation with an automated external defibrillator (AED) until the arrival of EMS, at which time ACLS procedures will be instituted.

The listed means of minimizing the likelihood of any of the SAEs that are reported to occur in ecstasy users will be similar to the procedures and strategies employed in the current study of MDMA-assisted psychotherapy in people with PTSD.

Psychological Distress

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. Psychological distress may arise at any time after the onset of the effects of MDMA until the last effects have dissipated (approximately 3 to 5 hours after drug administration), with anxiety or distress potentially lasting for as little as 15 minutes to as long as 5 hours. It is also possible that anxiety or other psychological distress may arise after the acute effects of the MDMA have subsided. Participants will be individuals without current psychiatric disorders who have completed a sponsor-developed training program on MDMA-assisted psychotherapy research. The likelihood of their experiencing clinically significant anxiety during an experimental session is lower than for people with current psychiatric problems. It is still possible, though

unlikely, that MDMA may spark a panic response or other forms of psychological distress.

The potential for destabilizing psychological distress will be minimized by excluding people who might be more vulnerable to psychological distress as stated in the exclusion criteria, by creating an atmosphere of trust before and during the experimental session, and by close monitoring and daily contact for a week (or more if necessary) after the experimental session.

At the end of the 6–8 hour experimental session, if the participant is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

- If the participant is anxious, agitated, in danger of any self-harm or is suicidal at the end of the experimental session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques, will talk with the participant to help him or her gain cognitive perspective of their experiences, and will help them implement the self-soothing and stress inoculation techniques presented during the preparatory session. If this situation should occur during an integrative therapy session, at least one of the investigators will be available to stay with the participant for at least two additional hours.

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

- A. The attendant will stay with the subject until the investigators arrive to stay with the participant if requested or until the time of his or her appointment with investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed. At any time during this process, the principal investigator may make the clinical judgment to proceed to option

- B. Hospitalization for stabilization.

Participants hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the investigator will carefully evaluate the participant's emotional status. The investigators will submit an SAE report to the IRB and the FDA in cases of drug-related hospitalization.

For those subjects engaged in an on-going therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapists will be involved in the management of any psychiatric complications.

If a participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety or insomnia following an experimental session, the investigator may prescribe a benzodiazepine or zolpidem as a “rescue medication.” This medication will be captured on a psychotropic concomitant medications CRF page. Means of monitoring for and preventing possible risks of MDMA other than the cardiovascular risks and psychological distress are described in detail below.

Angina or Myocardial infarction

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored for cardiac rhythm, vital signs and oxygen saturation (by pulse oximetry). He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in individuals who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI [125].

Stroke

If any participant has neurologic deficits, whether or not they are associated with hypertensive crisis, he or she will receive oxygen and an IV and will be monitored as described above. He or she will be transported to the 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 [126, 127].

Hyponatremia

History of hyponatremia or detection of hyponatremia on initial physical examination will be cause for exclusion from the proposed protocol. Participants will be given primarily electrolyte solutions such as Gatorade instead of water in order to decrease the likelihood of dilutional hyponatremia. They will not be allowed to drink more than 3 L of fluids, and fluid intake will be appropriately spread out across the session. If there are any signs or symptoms of hyponatremia, a stat serum sodium will be drawn and fluids will be withheld until the results are obtained. If the serum sodium is less than 25mEq/L, serum and urine osmolality and sodium will be measured, and the subject will be transported to the East Cooper Medical Center, where further intervention can be provided.

Hyperthermia

Body temperature will be taken every 60 to 90 minutes throughout each experimental session. If temperature rises more than 1° Celsius (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 subject. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, ice packs will be used, blood will be drawn for stat CBC, electrolytes, BUN, creatinine, glucose, creatine phosphokinase (CPK), prothrombin time (PT), partial thromboplastin time (PTT), platelets and liver enzymes, and urine will be collected for urinalysis. If there are significant abnormalities in these tests, if the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity the participant will be transferred to the intensive care unit at the East Cooper Medical Center.