

individuals with mild to moderate psychological difficulties reported obtaining some lasting benefits after MDMA-assisted therapy (Greer and Tolbert 1986).

As described in the Introductory Statement, a sponsor-supported pilot study of MDMA-assisted psychotherapy in 21 people with PTSD is almost completed in Charleston, South Carolina. This study employs the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded, independent assessor at baseline, a week after each experimental (MDMA or placebo) session, and two months after the final experimental session. To date, all participants in this study have tolerated MDMA, and preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo. A recent analysis conducted by the independent rater detected a significant decline in CAPS score in the MDMA condition when compared with placebo (see attached report).

The ongoing study in Switzerland comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA and a supplemental dose of 12.5 mg in people with PTSD has enrolled six of 12 subjects. The design of the study permits the investigator to provide up to two additional open-label sessions to individuals who do not respond to three experimental dose MDMA-assisted psychotherapy sessions. In these additional sessions, the investigator is permitted to administer either 125 mg followed by a supplemental dose of 62.5 mg or a higher dose of 150 mg followed by 75 mg supplemental dose. To date, one participant has received two additional experimental sessions with 150 mg MDMA and supplemental dose without incident. This study is estimated to conclude before the end of 2009.

The ongoing study in Israel comparing the effects of 125 mg MDMA followed by a supplemental dose of 62.5 mg with 25 mg MDMA followed by a supplemental dose of 12.5 mg in people with PTSD is currently designed to have two experimental sessions. One subject out of 12 has completed the study. This study is estimated to conclude before the end of 2009.

The potentially therapeutic effects of MDMA were initially investigated starting in 2000 in a MAPS-sponsored dose-response pilot study in Spain in women survivors of sexual assault with treatment-resistant PTSD. Unfortunately, the study in Spain was halted in 2002 due to political pressure from the Madrid Anti-Drug Authority. Prior to its suspension, six women were enrolled in this study without any adverse events or signs of deteriorating mental health, and with some mild signs of improvement, with single doses ranging from 50 to 75 mg. MAPS is currently exploring the possibility of starting a new pilot study in Barcelona, Spain, under the direction of the PI from our initial study.

Summary

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive two MDMA-assisted sessions with either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of

62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later.

After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions scheduled three to five weeks apart, during which they will randomly receive either the experimental or active placebo dose of MDMA. Participants will undergo one non-drug-psychotherapy session 24 h after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. PTSD symptoms will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session.

Baseline assessments of symptoms of PTSD and depression conducted by an independent rater will be compared with assessments made six weeks after the third double-blind (experimental) session. Baseline assessment of neurocognitive function will be compared with assessments made six weeks after the third double-blind (experimental) session. The blind will be broken after completing this assessment. Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD symptoms and depression six weeks after the third open-label session.

Principal Investigator

Ingrid Pacey MBBS FRCP[C] is a practicing psychiatrist in Vancouver, BC. She has worked as a psychiatrist for 36 years. She has a private practice in Vancouver, BC. She has performed Holotropic Breathwork, a therapeutic breathing practice capable of producing alterations in consciousness, in people with PTSD. She has also written papers on Holotropic Breathwork and has taught others the technique. She worked as a clinical supervisor in the UBC Student Women's Office from 1992 to 1996.

Co-Investigators

Andrew Feldmár, M.A., has practiced psychotherapy as a psychologist for almost 40 years in Vancouver, Canada. He has given workshops, lectures and seminars on psychotherapy and topics of psychotherapeutic interest. See his work in Hungary as presented on the website of the Feldmár Institute: <http://www.feldmarinstitute.hu/>. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. The independent rater will be Karen Tallman Ph.D, a clinical psychologist who has worked as a clinical psychologist for 15 years and has conducted psychiatric diagnostic and competency assessments. She has a private practice and has worked at the Short Term Assessment and Treatment Centre at Vancouver General Hospital.

Ethics

The trial will not be initiated until appropriate Health Canada and 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, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. The protocol will also be submitted to FDA under MAPS' IND 63,384.

This trial 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 Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

Informed Consent of Subject

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.

The information about the trial 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 trial and of 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 trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

The principal investigator or the co-investigator therapist will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator's study file.

The written informed consent form 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 ethics board before use.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g. pathologist report), it will be obscured before the copy of the document is supplied to the sponsor.

Written consent to take part in this study includes giving the investigators permission to view the participant's recent medical records to assess study eligibility. Information necessary for study participation includes physical examination, tests of metabolic and liver function, thyroid panel and psychiatric diagnostic interview.

Recruitment and Screening

Candidates for study participation will be Canadian residents recruited by letters of referral sent to psychiatrists and psychotherapists and through word of mouth. One of the investigators will interview prospective participants by telephone to learn if they meet basic eligibility criteria. If the prospective participant is interested in taking part in the study, the investigators will provide the prospective participant with consent materials through postal mail or situated on a website, for review and consideration. If, after review, an applicant remains interested in taking part in the study, then he or she will meet with the investigators to complete the consent process. Applicants will complete a quiz addressing questions relating to information contained in the consent forms, with the investigators going over quiz responses with the prospective participant to ensure that he or she correctly understands study procedures, risks and benefits.

Study Objectives

The study seeks to examine whether a fully active (experimental) versus active placebo dose of MDMA-assisted psychotherapy will reduce or attenuate PTSD symptoms and whether there is sufficient safety for this innovative treatment.

Primary Efficacy and Safety Objectives: The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators will analyze changes in PTSD symptoms during the start of the study, six weeks after the third experimental session. Scores on the PDS will also be compared at the start of the study, six weeks after the third experimental session.

The investigators will administer the CAPS to participants who received active placebo and opted to enroll in the open-label study segment six weeks after their final experimental open-label session. They will compare CAPS scores six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare scores at the start of the randomized session with scores six weeks after the third open-label session.

The investigators will also gather information on physiological effects and side effects after MDMA.

Secondary Objectives: The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will examine changes in BDI scores at baseline, six weeks after the third experimental session.

The investigators will administer the BDI to participants who received active placebo and enrolled in the open-label study segment, comparing scores at the start of the open-label segment and scores six weeks after the third open-label session. They will compare depression symptoms six weeks after the third experimental session and six weeks after the third open-label session, and they will also compare study baseline scores and scores six weeks after the third open-label session.

The investigators will also compare scores at the open-label study segment baseline with scores six weeks after a participant's final open-label session.

General Investigational Plan

Study Population and Characteristics

The study will enroll twelve (12) participants aged 21 years or older. The study will enroll both men and women. Eight of 12 participants will be randomly assigned to receive the experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hrs later and four will be randomly assigned to receive the active placebo dose of 25 mg followed by a supplemental dose of 12.5 mg 1.5 to 2.5 hrs later. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Inclusion Criteria

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

1. Participants must meet DSM IV criteria for current PTSD. They must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must either:
 - a. have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI) and one unsuccessful treatment with any form of psychotherapy for which there exist a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy, and eye movement desensitization (EMDR) [5, 29-31]. Treatment with an SSRI must have lasted for at least three months, or the participant must have refused to

take SSRIs. Psychotherapy must have lasted for six months and included at least twelve sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

- b. Be a veteran who meets all criteria listed above in 2a and with PTSD symptoms that have persisted for no longer than ten years.
3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because there is marked frequency of co-existence of other psychiatric disorders among people with PTSD (Brady et al. 1994; Faustman and White 1989).
4. Participants must be willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.
5. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If they are being treated with psychoactive drugs at the time they are recruited into the study, the prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, and will be required to give Dr. Pacey permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). No new medications may be started until after the evaluation session, which will occur six weeks after the third experimental session. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.
6. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. They must sign a release if they want to permit the investigators to communicate directly with their therapist. They may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session six weeks after the third experimental session.
7. Participants must agree that, for one week preceding each MDMA/placebo session:
 - a. They will refrain from taking any herbal supplement (except with prior approval of the research team)
 - b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
 - c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each 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 active placebo dose/experimental

- dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.
9. Participants must be willing to remain overnight at Dr. Pace's clinic after each experimental session until the non-drug session occurring the next morning. An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. Pace at the request of the participant or if there are signs that the participant is under physical or psychological distress. At the participant's request and with Dr. Pace's approval, a significant other can remain with the participant for support between the end of the experimental session and the non-drug session the next morning.
 10. Participants will be asked to locate an individual willing to drive them home the morning after the experimental sessions, after the non-drug therapy session. If a participant is unable to locate someone to transport them home, the investigators will assist the participant in obtaining transport from the clinic to the participant's home or any other location where he or she is staying temporarily.
 11. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
 12. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
 13. Participants must be literate. They must be proficient in reading documents written in English.

Exclusion Criteria

Prospective participants will be excluded from the study if they have the following conditions or characteristics:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. People with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. People with hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions

- (Rosendorff et al. 2007), peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. People weighing less than 48 kg
 7. People with prior use of "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
 8. People who would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, with suicide risk ascertained via face to face interview and through the use of the Adult Suicidal Ideation Questionnaire (ASIQ).
 9. People requiring ongoing concomitant therapy with a psychotropic drug.
 10. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 6 months.
 11. Any person who is not able to give adequate informed consent.

Planned Duration of Study

The randomized, double-blind, active-placebo controlled study segment will last approximately four months from screening and baseline evaluation up until the evaluation six weeks after the third experimental session..

The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation two months after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Drug Description and Dosage

Upon enrollment in the study, the participant will be randomly assigned to the active placebo or experimental dose condition. The two therapist-investigators and the independent assessor will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of the participant's condition assignment, the blind may be broken for an individual participant.

Participants in the active placebo condition will be assigned to receive three experimental sessions with an initial dose of 25 mg MDMA followed 1.5 to 2.5 hours later by a supplemental dose of 12.5 mg MDMA. Participants assigned to the experimental dose condition will receive three experimental sessions with an initial dose of 125 mg followed 1.5 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. Eight of 12 subjects, or 66.6%, will be assigned to the experimental dose condition, and four of 12, or 33.3%, will be assigned to the active placebo condition.

Participants in the active placebo condition will be offered the option of undergoing a study segment using nearly identical procedures to those in the randomized study segment but with participants receiving experimental dose MDMA within an open-label context.

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in the studies of MDMA-assisted psychotherapy currently underway in the US, Switzerland and Israel. Previous researchers have also used doses within this range (Cami et al. 2000a; Freedman et al. 2005; Grob et al. 1996; Harris et al. 2002; Kuypers et al. 2006; Liechti et al. 2001). Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA (Cami et al. 2000b; de la Torre et al. 2000a; Freedman et al. 2005; Grob 2001; Mas et al. 1999; Tancer and Johanson 2003). Prior to the time MDMA was placed in schedule 1 identical or similar doses and regimens were used in psychotherapy (Greer and Tolbert 1986; Metzner and Adamson 2001; Stolaroff 2004). The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects (Grob 2001; Harris et al. 2002) and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dose may produce slight alterations in consciousness, such as increased relaxation or tension (Harris et al. 2002).

Table 1
Drug Doses for proposed study

	Initial Dose	Supplemental Dose	Cumulative Dose
<i>Active Placebo</i>	25 mg	12.5 mg	37.5 mg
<i>Experimental Dose</i>	125 mg	62.5 mg	187.5 mg

Method

The researchers will employ a randomized, double-blind, active-placebo controlled design to compare symptoms of PTSD and depression before and after receiving MDMA-assisted psychotherapy with an experimental or active placebo dose of MDMA. The double-blind study will consist of twelve 60 to 90 minute “conventional” or non-drug augmented psychotherapy sessions and three experimental sessions of MDMA-assisted psychotherapy, and two assessments of symptoms of PTSD and depression. An independent rater not involved with performing psychotherapy will assess symptoms of PTSD with CAPS and PDS, and depression with the BDI at study baseline and six weeks after the third experimental session.

The investigators will break the blind individually for each participant after the assessments six weeks after the third experimental session.

Participants who learn they are assigned to active placebo can enroll in the open-label study segment. Active placebo condition participants enrolled in Stage 2 will have three sessions with experimental-dose MDMA.

Time and Events for Randomized Study segment

Time and Events M-P4	Baseline and Screening			Therapy and Evaluation 1						Therapy and Evaluation 2				Therapy and Evaluation 3						
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Type of Visit	Prestudy	Consent	Screening Baseline	Intro Psychotherapy ¹	Intro psychotherapy ²	Intro psychotherapy ³	Experimental 1	Integrative Therapy ¹	Integrative Therapy ²	Experimental 2	Integrative therapy ⁴	Integrative therapy ⁵	Experimental 3	Integrative Therapy ⁶	Integrative Therapy ⁷	6 wk post V11	End Randomized Segment			
Approximate Study Day			0	1	14	21	28	29	35	42	49	56	63	70	77	84	91	112	119	
Visit Timing and Windows	Post telephone	[Post consent, may be same day]	(4/4/3 d)	Post V4	Post V5	post V6	24 h post-experimental session 1	Between V8 and V11	Post V9	>3-5 wks post V8	24 h post V11	Post V11	Post V13	>3-5 wks post V11	24 h post V15	Post V15	Post V17	6 wk post V15	May be same day as V19	
Study Staff	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew, Karen	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew, Karen	Ingrid+Andrew	
Telephone Screening	X																			
Provide consent materials		X																		
Study informed consent		X																		
Medical Examination			X																	
ECG			X																	
Liver FCT			X																	
Drug Screen			X					X			X					X				
Pregnancy Screen			X					X			X					X				
Psychiatric examination			X																	
SCID			X																	
ASIQ			X						X			X					X			
Baseline evaluation			X																	
CAPS			X															X		
PDS			X															X		
BDI			X															X		
RBANS			X															X		
PASAT			X															X		
Study Enrollment			X																	
Record to audio & video				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychotherapy-No Drug				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
General Well-Being				X	X	X		X	X	X		X				X			X	
Administer MDMA							X				X									
Psychotherapy + MDMA							X				X									
Administer higher dose MDMA																				
Blood Pressure								X			X	X						X		
Pulse								X			X	X						X		
Body Temperature								X			X							X		
SUD								X			X						X			
Common Side Effects								X	X		X						X			
Oversleep stay								X			X	X					X			
Serious Adverse Events				X	X	X	x	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events Requiring Dr Visit				X	X	x	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unblinding																			X	
Consent for Stage 2(open-label)																			X	
RRPQ																		x		
End Randomized phase																		x		
IA=Independent Assessor																				

Time and Events for Open-Label Study Segment after Randomized Study for Active Placebo Participants

Visit #	20	V21	V22	V23	V24	V25	V26	V28	V29	V30	V31	V32	V33	V34	V35	V36	V37
Type of Visit	Consent	"Baseline"	Review/Intro Therapy	Open-Label 1	Integrative Therapy8	Integrative Therapy9	Integrative Therapy10	Open-Label 2	Integrative therapy11	Integrative Therapy12	Integrative Therapy13	Open Label 3	Integrative Therapy14	Integrative Therapy15	Integrative Therapy16	6 wk post Open-Label 3	End Stage 2
Approximate Study Day	112	113	120	127	128	135	142	149	150	157	164	171	172	179	186	213	
Visit Timing and Windows	On/Post V15	On/Post V19	Post V16	Post V17	24 h post Open Label 1	Between V24 and V28	Post V25	"=>3-5 wks post V23"	24 h post Open Label 2	Between V29 and V32	Post V30	"=>3-5 wks post V28"	24 hours post Open Label 3	Between V33 and V36	Post V34	6 wk post V32	
Study Staff	Ingrid/Andrew	Karen Andrew/Ingrid	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew Karen	Ingrid/Andrew	
Telephone Screening																	
Provide consent materials	X																
Study informed consent	X																
Medical Examination																	
Liver FCT																	
Drug Screen	X			X					X				X				
Pregnancy Screen	X			X					X				X				
Psychiatric examination	X																
SCID																	
Baseline evaluation	X																X
CAPS	X																
PDS	X																X
BDI	X																X
RBANS	X																
PASAT	X																
Study segment enrollment	X																
Psychotherapy-No Drug			X		X	X	X		X	X	X		X	X	X		
General Well-Being			X		X	X	X		X	X	X		X	X	X	X	x
Administer MDMA				X					X				X				
Psychotherapy + MDMA				X					X				X				
Administer higher dose MDMA													X*				
Blood Pressure				X					X				X				
Pulse				X					X				X				
Body Temperature				X*					X*				X*				
SUD				X					X				X				
Common Side Effects				X	X				X	X			X	X			
ASIQ					X					X			X				
Overnight stay					X				X				X				
Serious Adverse Events		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Requiring Dr Visit				X	X	X	X	X	X	X	X	X	X	X	X	X	X
RRPQ																	X
End Stage 2																	
*=if appropriate																	

Assessments and Measures

Screening and outcome measures were chosen to be well-recognized in the literature and because of prior use in other sponsor-supported studies of MDMA-assisted psychotherapy in people with PTSD.

Psychiatric diagnoses will be made through the Structured Clinical Interview for Diagnoses (SCID), and suicide risk by clinical judgment and via Adult Suicide Ideation Questionnaire (ASIQ). PTSD symptoms will be measured by the Clinician Administered PTSD Scale (CAPS) during screening to determine whether an individual may participate in the study. The CAPS will serve as the primary outcome measure in this study. The BDI will be a secondary outcome measure to assess symptoms of depression before and after undergoing MDMA-assisted psychotherapy.

The primary outcome measure will be the Clinician-Administered PTSD Scale (CAPS), a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. The CAPS provides a means to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the patient's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability (Blake et al. 1990; Nagy et al. 1993). An independent rater will assess all participants at study baseline and six weeks after the third experimental session. The same independent rater will assess all participants enrolled in stage 2 six weeks after their third open-label session.

The Posttraumatic Diagnostic Scale will serve as an additional measure of PTSD symptoms. The measure was designed to assess PTSD following DSM criteria (Foa et al. 1997; Foa et al. 1993). This 49-item self-report scale assesses degree of distress, and presence of intrusive thoughts, avoidance of situations that trigger intrusive thoughts, and hypervigilance. The PDS assesses duration of symptoms and degree of impairment. The independent rater will administer the PDS, collect completed measures and score them at baseline and six weeks after the third experimental session. The independent rater will also administer, collect and score the PDS six weeks after the third open-label session for participants enrolled in Stage 2.

The Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms (Beck and Steer 1984; Beck and Ward 1961) that will serve as a measure of depression. It takes five to ten minutes to complete. Participants will complete the BDI at the same times when the CAPS is administered.

The ASIQ is 25-item self-report measure of suicidal ideation and behavior (Reynolds 1991) will be employed along with a face to face interview to assess suicide risk at screening and after completing integrative psychotherapy on the day after an experimental or open-label MDMA-assisted psychotherapy session. The scale produces a

single unitary score and has been used to predict nonfatal suicide attempts (Osman et al. 1999).

Two measures of cognitive function will be administered at baseline and again six weeks after the third experimental session. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (Randolph 1998) and the Paced Auditory Serial Addition Task (PASAT), a measure of information processing speed and efficiency (Roman et al. 1991) will all be administered at these two time points.

All participants will complete measures of PTSD symptoms twice during the study, while participants enrolled in Stage 2.

1. *Baseline assessment, either at Screening visit or after an appropriate washout period in people taking psychiatric medicines*
2. *Six weeks after Experimental Session 3*

Participants enrolled in Stage 2 complete measures six weeks after open label session 3. Participants who do not enroll in Stage 2 will not have any additional assessment of PTSD symptoms.

All outcome measures will be administered by an independent assessor. The independent assessor will remain blind to subject condition and will not be present during non-drug or MDMA-assisted psychotherapy sessions.

During the course of each MDMA-assisted psychotherapy session, the Subjective Units of Distress (SUD), a simple, one-item visual analog scale, will be used to assess degree of psychological distress experienced at various points during the session. Participant and investigator beliefs concerning participant condition assignment (either experimental or active placebo MDMA) will be assessed during the non-drug psychotherapy session occurring on the day after each experimental session. Neither the SUD nor condition assignment beliefs measures are outcome measures.

Response to study participation and perceived degree of choice in taking part in the study will be assessed with the Reactions to Research Participation Questionnaire (RRPQ) (Newman et al. 2001). Participants will complete this measure during their final study visit, with exact time of completion varying in accordance with participant enrollment in the open-label study segment. The RRPQ is intended to assess the participant's experience as a research subject, perceived reasons for consenting to be a research participant and perceived freedom to take part in the study, and is not an outcome measure.

All sessions from introductory psychotherapy through weekly integrative psychotherapy and including MDMA-assisted sessions, will be recorded to audio and video in their entirety. These recordings will be used for further analysis of patient behaviour, defense mechanisms, therapist interventions and for development of a manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

Visit Descriptions

Initial Screening and Diagnostic Evaluation

Participants will undergo medical and psychiatric screening after giving written informed consent take part in the study. Screening will include medical history and physical examination, psychiatric interview, including administration of the SCID, for diagnosis of included and excluded psychiatric disorders, assessment of suicide risk via face to face interview and assessment with the ASIQ, urinary drug and pregnancy screening, and baseline CAPS administration by the independent rater. Medical screening will also include a blood draw for performance of standard laboratory measures of liver function, thyroid function and metabolism, and an electrocardiogram to assess heart function. The independent rater will administer the CAPS after undergoing medical and psychiatric examinations. Participants must have a global CAPS score equal to or higher than 50 to be enrolled in the study. Only participants who continue to meet all study criteria without meeting any exclusionary criteria will be enrolled in the study.

Subject Numbering

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 4-digit subject number. The first two digits identify the study site. The next two digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 0401, second 0402, etc.

Enrollment and Baseline Evaluation

Participants will be enrolled in the study if they meet all study inclusion criteria without meeting any exclusion criteria. CAPS, PDS and BDI scores from screening evaluation will serve as baseline measures of symptoms of PTSD and depression in all cases except those of participants who underwent screening while still taking psychiatric medication. Any participant taking psychiatric medications at the time of the screening evaluation will be re-assessed after an appropriate washout period of at least five times drug half-life, with the second assessment treated as baseline CAPS values. This is to ensure that an appropriate comparison will be made between baseline symptoms of PTSD and symptoms two months after the second experimental session, when individuals will be medication-free.

Randomization

Upon enrollment into the study, each participant will be randomly assigned to one of two conditions, active placebo or experimental dose. Each participant has a 66.6% chance of assignment to the experimental dose condition and a 33.3% of assignation to the active placebo condition. This study will employ a blinded adaptive randomization procedure in order to maintain the 66%/33% ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. A randomization monitor will generate and maintain a list of random numbers between one and 100. A randomization list will be run to assign either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles randomly assigned a number between 1 and 100. The randomization monitor will

also create replacement doses that retain the same ratio of experimental dose to active placebo dose condition. The randomization monitor will supervise the procedure of filling bottles with either MDMA or placebo. The investigators will contact the randomization monitor after enrolling a participant, and the randomization monitor will select a number from amongst the set of 12 numbers, represented as cards or other indicators, thus providing the investigators with the bottle number to be used for the participant. 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. In all other cases, the blind will be maintained up through the assessment occurring six weeks after the third experimental session. The independent rater and both investigator-therapists will be blind to condition assignment.

Psychotherapy

Participants will undergo a course of psychotherapy consisting of sessions of non-drug, assisted "conventional" psychotherapy and MDMA-assisted psychotherapy.

Conventional psychotherapy sessions prior to the first experimental session will prepare participants for MDMA-assisted psychotherapy and help develop a therapeutic alliance with the investigators, and psychotherapy subsequent to MDMA-assisted psychotherapy is intended to integrate and develop experiences participants had during MDMA-assisted psychotherapy. All psychotherapy sessions will be recorded to audio and video. This includes introductory sessions, each experimental or open-label MDMA session and integrative psychotherapy. Participants may upon request receive copies of the audio and/or video recording of their experimental and/or open-label sessions for their own review, and they may also request copies of the audio and/or video recording of their non-drug assisted psychotherapy session recordings.

Introductory Sessions

The participant will undergo two sixty to ninety minute introductory sessions with the therapist-investigators, who will consist of a male and a female therapist. The investigators will work with the participant to prepare him or her for MDMA-assisted psychotherapy. The investigators and participant will seek to form a strong working relationship with each other, and they will help the participant prepare for upcoming experimental sessions. Introductory sessions will promote a safe space for confronting trauma-related memories, emotions and thoughts. During the third and last introductory session, the investigators will provide participants with instructions listing specific rules and guidelines for food, beverage and drug or medication consumption prior to MDMA-assisted psychotherapy.

MDMA-assisted Psychotherapy

All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Each experimental session will last approximately eight hours. Experimental sessions will be conducted by the male and female therapist. Procedures for MDMA-assisted psychotherapy will remain the same across each of the two sessions, and all procedures except drug dose will be the same for participants assigned to the full dose and active placebo condition.

Experimental sessions will begin at approximately 10:00 AM and [REDACTED]. The participant will have had nothing by mouth except alcohol-free liquids since approximately 12 AM on the evening before each experimental session. Participants will arrive at approximately 9:00 AM for collection of a urine specimen that will be used in drug and pregnancy screening. If drug screening results are negative and pregnancy test is negative or not applicable and the participant reports that he/she followed appropriate rules and restrictions, then the session will proceed; a positive pregnancy screen is cause for withdrawal from the study. A positive drug screen or failure to follow one or more instruction related to pre-session food or beverage consumption may lead to delaying the session start time, rescheduling the session or withdrawing the participant from the study. The investigators will assess blood pressure and pulse upon arrival and at least twice prior to administering MDMA.

Before administering MDMA, the therapists and participant will discuss and review the participant's goals, intentions and concerns and some of the commonly experienced effects of MDMA. Participants will complete the SUD just prior to initial dose administration. At approximately 10:00 AM, participants will receive the initial dose of MDMA along with a glass of water. The initial dose will either be 25 or 125 mg MDMA in accordance with condition assignment, and the dose will be administered in a double-blind manner. The supplemental dose will always be one half (1/2) the initial dose and will be administered between 1.5 and 2.5 hours after the initial dose.

After the session begins, participants will lie or recline in a comfortable position with eyes closed or wearing eyeshades if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material (Bonny and Savary 1990; Grof 2000: 1980; Unkefer 1990). After the first hour, if the participant has not spoken spontaneously, the therapist-investigators will check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapist-investigators will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging. The therapist-investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused inward in order to allow for the further unfolding of their inner experience. Water and electrolyte containing fluids will be available ad lib throughout the session within the limits described under "Monitoring for Toxicity." Food will be available during the latter part of the session. All experimental sessions will be recorded to audio and video in their entirety.

The therapeutic approach during an MDMA-assisted session is non-directive, following and encouraging the MDMA-supported process. Discussions between therapist and participant are only intermittent. The therapists may employ other techniques, including focused body work and anxiety management techniques. Focused body work employs nurturing touch (hand-holding or hugging) and touch aimed at intensifying and thereby releasing body tension and pain by giving resistance for the participant to push against. Focused body work is always performed with explicit consent from the participant and

respecting boundaries and vulnerabilities of the patients. Transference is not a main focus and is addressed openly in early stages if necessary. Subsequent MDMA-assisted sessions are expected to lead to deeper emotional experiences, building on the experiences and results from the previous sessions. MDMA is expected to induce or facilitate the following therapeutic effects and processes: prolonged spontaneous reliving of and confrontation with traumatic memories and emotions; cognitive restructuring, processing of difficult emotions, release of tension and somatic symptoms, increased awareness of past and present positive experiences, new perspectives and changes of meaning.

Blood pressure and pulse will be measured at the outset of each experimental session and once every thirty minutes (0.5 hour) for the duration of the experimental session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure participant body temperature via tympanic thermometer every 60 to 90 minutes. Subjective units of distress (SUDs) will be measured at least once prior to drug administration and every 60 to 90 minutes until the session is over. The exact timing will be at the discretion of the therapists so that testing will not interfere unnecessarily with the therapeutic process, and if necessary, the investigators can make a greater number of measurements. If at any time blood pressure exceeds 160 systolic or 110 diastolic, or pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. The research site will contain equipment for assessing blood pressure, pulse and body temperature, and for dealing with potential adverse events, such as hypertension, and a means to transport individuals to the nearest hospital in case of a medical emergency. Ambient temperature will be kept comfortably cool to decrease the likelihood of hyperthermia. For more details, see Table 3.

Table 3. Schedule of procedures and measures for experimental sessions

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

Approximately 1.5 to 2.5 hours after the initial dose, the therapist-investigators will offer the participant the supplemental dose of MDMA. They will only do so if, in their judgment, the participant does not show any signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event. If the participant agrees to take the supplemental dose, then it will be administered with 250 to 300 mL water or electrolyte-containing beverage. Sessions will last up to eight hours, depending on when the participant feels that he or she has arrived at a point of completion and dependent on the therapists' determination of the mental and physical state of the participant.

With the permission of the therapists, a significant other, such as a spouse, relative or close friend, may join the participant during the experimental session or at some point after it has ended. The investigator will discuss with the participant the advantages and pitfalls of a significant other present during the experimental session and will meet and approve the significant other prior to their stay at the study site.

If all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will end. The investigators will depart the site when they have concluded that the participant is emotionally and medically stable.

Both therapist-investigators [REDACTED], and both can quickly return to the site if necessary. Throughout the study, at least one of the therapist-investigators will remain available to participants via 24-hour cellular phone.

Participants will remain overnight in an [REDACTED]

With the approval of the therapists, a significant other may accompany the participant during the overnight stay. A same-sex attendant will remain with the participant during the overnight stay, even if a significant other is present. The attendant will monitor participant health and will help participants relax during the overnight stay. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The investigators will seek where possible to select attendants who have worked with Holotropic Breathwork, a technique that produces an altered state of consciousness through hyperventilation, or who have worked at Iboga Therapy House, a Vancouver clinic that administered the psychedelic and anti-addictive compound ibogaine to people with substance abuse issues, or who have other experience working with people in psychological distress as a consequence of psychedelic drugs. In addition, the investigators will offer specialized training for all attendants, including any individuals who lack any prior experience working with people experiencing alterations in consciousness. If there is an emergency or the participant needs additional support, the attendant can contact the investigators. The participant and if applicable, his or her significant other, will receive information that will allow them to contact the investigators during the overnight stay in the case of an emergency or request or additional support. Participants will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

Integrative Psychotherapy

Participants will undergo non-drug psychotherapy on the day after each MDMA-assisted session and on a weekly basis during intervals after each MDMA-assisted session. During these sessions, the therapist-investigators will support the participant as he or she seeks to reach a new perspective and understanding after the experimental session. Expressive techniques such as writing or drawing are encouraged. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness and reduced fear experienced in MDMA sessions to emotionally threatening everyday situations. The therapist-investigator attitude will be supportive, validating the MDMA experience and facilitating understanding and emotional clearing. Therapists are accessible any time the participant needs support outside the scheduled integration sessions.

Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy

A ninety-minute therapy session with the male and female therapist will take place in the morning of the day after each MDMA-assisted session. The participant and investigator will discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the therapist-investigators will help the participant to reduce any residual psychological distress he or she is experiencing. The therapist-investigators will assess participant mental health and the presence of any remaining side effects during integrative psychotherapy immediately after each experimental session. The non-drug psychotherapy session can also serve as an opportunity for the therapist-investigators to gather information about the effects of MDMA on the participant in an

unstructured manner. After this psychotherapy session, a person previously selected by the subject will provide a ride home. If the participant is unable to locate an individual willing or able to take him or her home, or if the designated person is unable to assist the participant due to unforeseen events, the investigators will assist the participant in finding an alternative means of returning home.

Prior to integrative psychotherapy, the participant and both therapist-investigators will indicate their beliefs concerning participant condition assignment. After completing the integrative psychotherapy session, participants will complete the ASIQ to assess suicide risk after the experimental session.

Weekly Integrative Sessions

The participant will have weekly non-drug psychotherapy sessions with both therapist-investigators during the interval between the first and second experimental session, between the second and third experimental sessions and after the third experimental session. Participants will have at least nine 60 to 90 minute integrative psychotherapy sessions prior to the evaluation six weeks after the third experimental session that will signal the end of the randomized study segment. The investigators may conduct more sessions if they and the participant deem it necessary. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during one or both experimental sessions. The investigators will use clinical judgment to assess the participant's psychological well-being during this period of time. If there are any indications of continuing anxiety or distress, the investigators may arrange to work on reducing the distress at a specially scheduled non-drug therapy session, through continuing contact, or at the next regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study.

Daily Telephone Contact

Starting on the day of the non-drug psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone on a daily basis for one week.

Evaluation Six weeks after the Third experimental session

The final evaluation in the double-blind portion of the study will occur six weeks after the third experimental session. Participants will meet the independent rater for 90 to 120 minutes. The independent rater will administer the CAPS and participants will complete the BDI and PDS. The independent rater will administer the RBANS and PASAT. The measures are described earlier in "Assessments and Measures."

Unblinding and Opportunity for Participants in Active Placebo Condition Enroll in Open-Label Study Segment ("Stage 2")

After undergoing assessment of symptoms of PTSD and depression with the independent rater, the participant will meet with the therapist-investigators for approximately a half hour to an hour and the blind will be broken for the individual participant. The independent rater will remain blind to condition assignment at this time. The

investigators will provide consent materials for the open-label study segment to participants assigned to the active placebo condition. These participants who elect to enroll in stage 2 will undergo a course of therapy and evaluation nearly identical to the randomized study, but with experimental dose MDMA given in an open-label context. They must give written, informed consent before enrolling in the open-label study segment.

Assessment of PTSD symptoms and depression six weeks after the third experimental session will serve as baseline assessments for comparison with assessments made after final open-label sessions except in the case of people who begin open-label sessions more than thirty days afterwards. In that case, the independent rater will re-administer the CAPS, PDS and BDI, and these scores will serve instead as baseline for comparison to assessment after final open-label session.

Participants who are not continuing on to the open-label study segment will complete the Reactions to Research Participation Questionnaire (RRPQ) after their final assessment when they have completed the study.

Open-Label Study Segment for Active Placebo Participants (“Stage 2”)

Participants assigned to active placebo during the randomized study segment will undergo three open-label MDMA-assisted therapy sessions that follow a course and schedule similar to the randomized study except that participants undergo one instead of three introductory sessions. After giving written informed consent, participants enrolled in Stage 2 will meet with both therapist-investigators for a single review and re-introductory psychotherapy session, followed by an open-label MDMA-assisted therapy session. Participants will have the same sequence of integrative therapy and open-label sessions scheduled three to five weeks apart.

Assessment Six weeks after Third Open-Label Session

All participants in Stage 2 will be assessed by the independent rater six weeks after their final open-label session. The independent rater will assess all participants on the CAPS and participants will complete the PDS and BDI, and the RRPQ.

Removal of Subjects from Therapy or Assessment

The participant, or where applicable, the participant's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

The subject will be clinically monitored after withdrawal, the cause of which will be recorded on the “Study Termination” CRF. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section.

Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out.

Premature Discontinuation of the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and will assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, will be treated in accordance with federal and local regulations.

Data Analysis

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of PTSD as assessed via CAPS global scores by conducting between subjects / within-subjects analyses of variance (ANOVAs) with condition (active placebo versus experimental) as a between-subjects variable and time of administration (baseline versus six weeks after third experimental session) as a repeated measure. The investigators will perform post-hoc tests on any interaction and probability of rejecting the null hypothesis will be set at 0.05. If there is a significant interaction between condition and time of administration, the investigators will perform separate between-subjects / within-subjects ANOVAs on CAPS sub-scale scores to examine whether any facet of PTSD symptoms is particularly affected by MDMA-assisted psychotherapy. The investigators will perform the same analyses upon PDS scores.

The investigators will perform a correlational analysis that will examine possible relationships between symptoms of PTSD and depression by correlating CAPS global scores and BDI scores at each time of administration, with the probability of rejecting the null hypothesis set at 0.05. They will perform a correlational analysis examining the relationship between PDS score and BDI scores at each time of administration.

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of depression, measured by BDI scores, by performing a between-subjects / within subjects ANOVA with condition (active placebo versus experimental dose) as a between-subjects factor and time of administration (baseline versus six weeks after the third experimental session) as a repeated measure.

The investigators will further examine the effects of MDMA-assisted psychotherapy on symptoms of PTSD and depression by comparing symptoms after experimental and open-label sessions. The investigators will perform repeated-measures ANOVAs comparing CAPS, PDS and BDI scores at randomized study baseline and six weeks after the third experimental session, with time of administration as a within-subjects factor and with p. set at 0.05. They will perform one analysis comparing CAPS, PDS and BDI scores after experimental and open-label sessions for participants in the experimental condition and another analysis for participants enrolled in "Stage 2."

The investigators will examine the effects of MDMA on neurocognitive function by performing a between-subjects / within-subjects ANOVA with condition as a between-subjects factor (active placebo versus experimental dose MDMA) and with time of administration (baseline, six weeks after the third double-blind session) as a within-subjects factor and with p. set at 0.05. Participant scores on the RBANS and PASAT will be compared at both times.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The investigators will informally or formally compare peak blood pressure, heart rate and body temperature for participants after sessions using 125 and 150 mg MDMA, depending upon the number of times, if any, ,the investigators administer 150 mg during the study.

Statistical power

The proposed study is a pilot investigation intended to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with PTSD. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Because it is a pilot study in a small sample, statistical power is difficult to assess but it is likely to be low. However, preliminary analyses of MAPS' almost completed US study of MDMA-assisted psychotherapy in 21 people with PTSD has produced promising results and suggests a medium effect size with respect to treatment efficacy. Hence estimated effect size may follow between 0.5 and 0.7. The sponsor intends to use preliminary data gathered from this and other studies in part to guide future estimates of effect size and statistical power in future studies. The sponsor intends to conduct meta-analyses of CAPS scores gathered across all pilot-studies in addition to analyses of individual study data. Meta-analyses will be able to increase overall statistical power.

The sponsor used Java applications created by Lenth and posted on the website listed below to calculate estimated statistical power for this study, assuming an effect size of 0.6 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms of PTSD and depression (Lenth 2006). We initially conducted a two-sample independent t-test comparing one group of eight and another of four with effect size set at 0.6 and with equal sigma (estimated standard deviation) assumed and set at 1. The software calculated an estimated power of 0.144, indicating an underpowered study. After taking into account preliminary analyses of CAPS scores occurring in the randomized, placebo-controlled study of MDMA-assisted psychotherapy taking place in South Carolina, we conducted a second estimate assuming a larger effect size of 0.8, reaching estimated statistical power of 0.22.

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low (Baggott et al. 2001; Dumont and Verkes 2006; Jerome 2004; 2005; 2007).

Approximately 390 people have received MDMA during controlled trials without the occurrence of any drug-related serious adverse event, and psychiatrists in the US and

Europe reported administering MDMA to at least a thousand patients before the drug was made illegal without any drug-related serious adverse events occurring during sessions (Adamson 1985; Gasser 1994; Greer and Tolbert 1986; Metzner and Adamson 2001; Widmer 1998). There have been no drug-related serious adverse events during the course of a study of MDMA-assisted psychotherapy in 21 people with PTSD under the direction of Dr. Mithoefer, nor in MAPS' Swiss MDMA/PTSD study with six subjects or in MAPS' Israeli MDMA/PTSD study with one subject having completed the study.

Recent findings in humans and nonhuman primates have failed to find any significant interactions between ambient temperature and body temperature in humans receiving 2 mg/kg MDMA (Freedman et al. 2005; Von Huben et al. 2006), a finding in line with inconsistent results concerning elevation of body temperature after MDMA (de la Torre et al. 2000c; Fantegrossi et al. 2004; Farre et al. 2004; Johanson et al. 2006; Liechti et al. 2000a). These findings suggest that unlike rodents, extreme elevation in body temperature after MDMA is rare in humans, likely due to differences in rodent and primate thermoregulation.

Although the safety data is reassuring,, we intend to monitor closely for the unlikely possibility of an untoward reaction. The sessions will be conducted in a psychiatric office where basic emergency equipment will be immediately available. The site is approximately five to fifteen minutes from two nearby hospitals with emergency departments, University of British Columbia Hospital and St. Paul's. Both hospitals are accessible during the day, while only St. Paul's remains accessible for 24 hours. Participants will be sent to whichever emergency department is accessible in case of a medical emergency.

Hypertension and related cardiovascular Effects

Blood pressure and pulse will be measured at regular 30-minute intervals (see table 3). If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. During this time the principal investigator will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. The principal investigator will make a clinical judgment about whether additional monitoring or treatment is required. Reasons for moving a patient to an emergency department would include, but not be limited to, severe headache in the setting of hypertension, angina or neurological deficits regardless of blood pressure. The investigator may, at any time, make a clinical judgment to transfer the participant to the emergency department for closer monitoring and additional treatment. If such transfer is required a team of paramedics would be summoned to transfer the subject to the nearest hospital by ambulance.

Angina or Myocardial Infarction:

The investigators will observe the participant and note any complaints of chest pain. If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, paramedics will be summoned to stabilize the subject by

administering oxygen and any other appropriate drugs or resuscitative measures within their scope of practice. The paramedics will start an IV and cardiac monitoring and transport the subject to a nearby hospital where appropriate further evaluation and care can be given. If further evaluation at the hospital reveals that the participant has had an acute myocardial infarction (AMI), he or she will be well within the time frame required for definitive therapy.

Stroke:

The investigators will attend to any signs or symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress. If any participant has neurological deficits, whether or not they are associated with hypertensive crisis, he or she will receive further care by paramedics and transport to a nearby hospital as described in the above section on Angina or Myocardial Infarction.

Psychological Distress:

During preparatory sessions, participants will be made aware of the fact that difficult emotions, including fear, panic, grief or rage, may arise during experimental sessions. They will be told that such symptoms will not be treated pharmacologically during the sessions because they present an opportunity to therapeutically address the symptoms and underlying causes of PTSD. Every effort will be made to help participants move through difficult emotions and arrive at a more comfortable and relaxed state by the conclusion of the session. In the event that a participant is experiencing severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an experimental session, then the principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem.

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

If, by the end of an MDMA-assisted psychotherapy session, the participant is still severely agitated or experiencing great psychological distress, the following measures will be taken:

- If a participant is anxious, agitated, in danger of any self harm or is suicidal at the end of the experimental session, the investigators will remain with the participant for at least two more hours. During this time, the investigators will employ affect management techniques described in the treatment manual draft under development for MDMA-assisted psychotherapy in people with PTSD (Ruse et al. 2005), will talk with the

participant to help him or her gain cognitive perspective of their experiences, and will help them implement the self soothing and stress inoculation techniques they were taught in the introductory sessions. If this situation should occur at the end of one of the ninety-minute follow-up sessions at least one of the investigators will be available to stay with the participant for at least two additional hours.

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

A. The attendant will stay with the participant until the time of his or her appointment with the investigators the next day. The investigators will then meet with the participant daily until the period of destabilization has passed. At any time during this process, Dr. Pacey may make the clinical judgment to proceed to option B.

B. Hospitalization for stabilization

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

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

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

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

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

Hyperthermia:

The investigators will assess body temperature every 60 to 90 minutes with a tympanic thermometer. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more

than 1.5° C above baseline despite these efforts, the investigators will consult by telephone with a physician at the nearest emergency room to discuss whether the subject should be transported for further evaluation. If the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity paramedics will be summoned to stabilize and transport the subject as described above under Angina or Myocardial Infarction.

Dehydration:

Study participants will not be engaged in strenuous exercise and are not expected to be sweating profusely during experimental or open-label sessions. However, participants will have access to water and electrolyte-containing beverages throughout these sessions and the investigators will encourage participants to drink fluids if they observe very little fluid consumption within three to six hours, and noting participant activity, degree of water loss through sweat and body temperature.

Hyponatremia:

Electrolyte solutions such as Gatorade will be available throughout each experimental or open-label session. Participants will not be allowed to drink more than 3 L. of fluids over the course of the experimental session, and fluid intake will be spread out appropriately during the session. The investigators will ensure adequate fluid intake by encouraging the subject to drink electrolyte solution or water at least hourly if subjects are not doing so spontaneously. If there are any signs or symptoms of hyponatremia such as confusion, vomiting, myoclonus or ataxia, beyond mild, transient symptoms that may be associated with MDMA effect the subject will be transported to the nearest emergency department for evaluation as described in the above section on Angina or Myocardial Infarction.

If a participant exhibiting signs of clinically significant hyponatremia is sent to a hospital and testing finds that he or she has low serum sodium during an experimental session, then the principal investigator will not enroll the participant in any subsequent experimental or open-label sessions.

Liver toxicity:

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

Neuropsychological toxicity:

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

Abuse and dependence:

On the basis of findings from research in humans and nonhuman animals and considering the setting of use, the likelihood for abuse or dependence on MDMA triggered by participation in this study is very low (see “Abuse Potential” below). The investigators will exclude all participants meeting the criteria for substance abuse or dependence 60 days prior to screening. Urine drug testing will occur before each experimental or open-label MDMA session. The researchers will be alert to the question of MDMA abuse during the treatment phase and will explicitly address this point at the closing visit.

Medical Emergencies

The study site will contain equipment for assessing blood pressure, pulse and body temperature and there will be an automatic external defibrillator (AED) on site. Dr. Pacey will maintain basic life support (BLS) certification or its equivalent in Canada in cardiopulmonary resuscitation (CPR) including training in using an AED. The site is 5 minutes from the University of British Columbia emergency department and eight to 15 minutes away from St. Paul’s Hospital emergency department. In the event of a medical emergency paramedics will be summoned and study subjects will be transported by ambulance to either hospital as appropriate. We consider this to be an adequate level of emergency back-up based on experience with previous phase II studies in the US and Switzerland during which there have been no adverse events during experimental sessions requiring emergency care or any other medical intervention.

The first US phase II trial with MDMA to be completed in September, 2008, was conducted in an outpatient setting with a “crash cart” of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately ten minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study MDMA was administered on 51 different occasions at a dose of either 125 mg. by mouth or 125 mg. followed in 2 – 2.5 hours by an additional 62.5 mg. Blood pressure, pulse and temperature were closely monitored, but never reached levels that required intervention, nor were there any other medical problems requiring treatment during the MDMA sessions. Subsequently a similar study has been approved in Switzerland and is being conducted in an outpatient psychiatry office approximately 5 minutes from the nearest hospital without a crash cart or emergency personnel on site. As of this writing the Swiss investigators have administered 125 mg followed by 62.5 mg MDMA on 20 occasions and administered 150 mg MDMA on two occasions without medical incident.

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

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

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

Mild: no limitation in normal daily activity.

Moderate: some limitation in normal daily activity.

Severe: unable to perform normal daily activity.

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

1. Not Related

The AE is not related if exposure to the investigational product has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

2. Possibly Related

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

3. Probably Related

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

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

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

Results in death

Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.

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.

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

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

Adverse Event Collection

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

Medical Monitor: [REDACTED]

Study Monitor: [REDACTED]

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

- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions.
- Any adverse event leading to withdrawal from the study.

Additional adverse events collected for seven days after each experimental session are:

- Common side effects.
- Exacerbation of anxiety.

Collection of Concomitant Medications

All prescription concomitant medications will be recorded at baseline. The investigators will keep track of any newly initiated medications taken during the course of the study, including herbal or nutritional supplements. Only newly initiated medications will be recorded after baseline.

Laboratory Assessments

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance.

After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained during the initiation visit. During each monitoring visit, source data verification will be performed by qualified staff representing the sponsor [REDACTED] Monitoring visits will occur every six to 12 months (26 to 52 weeks). A CRF collation supplied by the sponsor will be completed for each subject. The entries will be checked by trained delegates of the sponsor.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

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

Risks and Discomforts

Risks and Discomforts Associated with Drawing Blood

Blood specimens will be obtained from the subjects during baseline evaluation. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood drawing site. There is also a remote possibility of inflammation or infection at the blood drawing site. Blood samples will be used for the most part to determine whether the participant is healthy and can safely take part in the study. Hence the temporary discomfort is outweighed by the need to ensure that participants are healthy, meet all inclusion criteria at screening, or are not experiencing any changes in condition prior to entering open-label study segments.

Risks and Discomforts Associated with Screening Procedure

Medical data will be collected via history and physical examination and measurement of vital signs. Submitting to a full medical examination may be time consuming, and may be distressing or uncomfortable for some. Because medical examinations are part of the screening procedure, they cannot be omitted from the study design.

Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

During non-drug and MDMA-assisted psychotherapy sessions, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy, experimental and open-label sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (MDMA-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

All psychotherapy sessions will be recorded to audio and video. Participants may feel uncomfortable with having their sessions recorded. The recordings will be used for developing a manualized form of MDMA-assisted psychotherapy, and participants may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment. Participants will receive information on who will have access to recordings and will have control over any presentation of this material beyond viewing by investigators or regulatory agencies.

Risks and Discomforts of Receiving the Study Drug (MDMA)

Side effects of MDMA are modest and have generally not been associated with serious discomfort by volunteers in previous studies (Baggott et al. 2001). Decreased appetite, jaw clenching, dry mouth, impaired gait or balance and impaired concentration are commonly reported during peak MDMA effects, while fatigue may be felt up to several days afterward. Less commonly, mild anxiety and depressed mood are reported one and three days after MDMA administration (Harris et al. 2002; Liechti et al. 2001; Liechti et al. 2005; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998). Commonly reported side effects reported by Mithoefer in participants who received the experimental drug while undergoing MDMA-assisted psychotherapy also included neck and back pain

and diarrhea. Some of these effects are very likely to occur, but proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them. Other common side effects are listed in the Investigator's brochure.

Cardiovascular and Sympathomimetic Effects

In doses similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants (Cami et al. 2000b; Grob 2001; Grob et al. 1996; Harris et al. 2002; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2003). The amount of MDMA used in all experimental conditions in this study is not likely to produce changes in blood pressure or heart rate greater than 40% of resting values. These changes should last no more than six hours. These changes have been well-tolerated by volunteers in previous studies and should not pose large risks to participants who have been carefully screened for cardiovascular and related problems. In less than 5% of volunteers in phase 1 studies, increases in blood pressure were higher. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of participants and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity.

Perceptual Alteration

MDMA may produce mild alterations in perception and altered perception of time (see for example Cami et al. 2000b; Dumont and Verkes 2006; Vollenweider et al. 1998). Women may be more sensitive to these effects of MDMA (Liechti et al. 2001).

Psychological Distress

Some participants receiving MDMA report experiencing periods of increased anxiety (Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003). It is possible for psychological distress after MDMA to arise from the first indications of drug effects up until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress may last for as little as 15 minutes or for as long as 5 hours. In previous Phase I studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from investigators. In the proposed study, participants will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. Investigator responses to psychological distress is discussed in detail in "Monitoring for Toxicity."

Less commonly, people report experiencing mild anxiety and depressed mood one and three days after MDMA administration (Baggott et al. 2001; Harris et al. 2002; Huxster et al. 2006). At least some of the physiological or psychological side effects listed above are very likely to occur. Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute side effects, so that they will not be unduly troubled by them.

Immunological Changes

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA (Pacifici et al. 2004; Pacifici et al. 2000; Pacifici et al. 2001a; Pacifici et al. 1999b). They reported a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon- γ and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunsuppressive and anti-inflammatory) cytokines measured in blood. Research in rodents confirms these findings (Connor 2000; Connor II). Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine (Pacifici et al. 2000; Pacifici et al. 2001). Because of their limited duration, these changes are not likely to have clinical significance beyond an increased risk of the common cold or similar illness for several days. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose (Pacifici et al. 2001a; Pacifici et al. 2002), and a second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose (Pacifici et al. 2002). Given this data, it is possible that administering a smaller supplemental dose 2.5 h after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase I studies have not reported any indication of increased risk of illness occurring after MDMA administration. The investigators will use clinical judgment when considering enrolling participants who are otherwise immunocompromised. It is notable that at least some anti-retrovirals produce dangerous interactions with MDMA.

Toxicity

Serious MDMA toxicity is rare even in uncontrolled settings, considering that millions of users taking ecstasy of unknown identity, potency, and purity with many users consuming estimated MDMA doses that are several times higher than those used in the proposed study without any apparent toxicity (Baggott et al. 2001). Under unsupervised and non-medical conditions, the most common serious adverse event involves hyperthermia, described above in "Monitoring for Toxicity" (Liechti et al. 2005; Williams et al. 1998). This event has not occurred during controlled studies of MDMA. A comparison of findings in humans with those in rodents suggests that rodents are more sensitive to elevation in body temperature after MDMA (Gordon 2007). In addition to hyperthermic syndromes, other rare adverse events include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia. In the proposed clinical study, volunteers will be excluded on the basis of any conditions that might increase risk of their occurring and/or will be carefully monitored for signs and symptoms of these unlikely events.

Potential Neurotoxicity Associated with Ecstasy Use

Extensive studies in animals indicate that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nucleus, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site density (Cole and Sumnall 2003b; Green et al. 2003; O'Callaghan and Miller 1994), with a study in squirrel monkeys suggesting long-lasting effects on brain serotonin (Hatzidimitriou et al. 1999). Similar changes can be induced by methamphetamine and other psychostimulants (Miller and O'Callaghan 1996; Molliver et al. 1990; Sabol et al. 1995; Seiden and Sabol 1996). Previous studies in nonhuman primates overestimated human-equivalent doses (Mechan et al. 2006), and previous studies in rodents may also have overestimated human-equivalent doses (Baumann et al. 2007). Studies in rodents and monkeys that employed lower or fewer doses of MDMA, or that involved self-administration, have failed to find some or all of the markers of serotonin neurotoxicity listed above (Banks et al. 2008; Fantegrossi et al. 2004; Wang et al. 2005; Wang et al. 2004). Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials (McCann and Ricaurte 2001). However, they are basing their case on studies that employed inappropriately high doses of MDMA, and studies comparing the effects of repeated use of ecstasy, often along with other drugs, as discussed below.

There is controversy as to whether analogous changes in brain serotonin occur in humans, and a wealth of literature exists that compares ecstasy users to non-users (Cole and Sumnall 2003a). Earlier studies were retrospective and possessed a number of methodological flaws, particularly in relation to appropriate matching of ecstasy users with controls. Later research employed longitudinal study designs, allowing for comparisons over time. Retrospective and longitudinal imaging studies have detected decreased estimated serotonin transporter (SERT) sites in current heavy ecstasy users when compared with controls (McCann et al. 2005; Reneman et al. 2006a; Thomasius et al. 2006), but with estimated SERT sites returning to normal or numbers inversely related to period of abstinence. Likewise, studies have detected impaired memory and executive function in ecstasy users (Cole and Sumnall 2003a; Laws and Kokkalis 2007; Zakzanis et al. 2007). A number of these studies reported impaired cognitive function only in heavy users, and not in moderate users, and some recent studies suggest that use of other drugs may contribute to impaired cognition (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Hoshi et al. 2007; Roiser et al. 2007), though other studies also reported that abstinence from ecstasy did not attenuated memory impairment in heavy users (Gouzoulis-Mayfrank et al. 2005; Thomasius et al. 2006). There is also some evidence that ecstasy users are more likely to report symptoms of anxiety or depression, and to exhibit more behavioral impulsivity than non-ecstasy user controls (Daumann et al. 2004; Morgan et al. 2006; Sumnall and Cole 2005; Sumnall et al. 2004). Findings from prospective and longitudinal studies suggest that young people with existing psychological problems are more likely to try ecstasy than people without these problems (Huizink et al. 2006; Lieb et al. 2002), and it appears that polydrug use may contribute to this association (Daumann et al. 2004; Medina and Shear 2006; Scholey et al. 2004; Sumnall et al. 2004). Findings from retrospective studies are of limited value in estimating the potential risk of neurotoxicity from two doses of MDMA, as average

cumulative dose and frequency of use in most of these studies is considerably higher than doses in human trials of MDMA. A better estimate of the potential risk of neurotoxicity can be found in findings from prospective studies comparing people before and after their first use of ecstasy.

Starting in the early 2000s, a team of researchers in the Netherlands examined samples of people before and after reporting their first uses of ecstasy. These researchers have assessed estimated SERT sites, chemical markers of neuronal injury, changes in cerebral blood flow, performance and brain activity related to a working memory task, and cognitive function in samples of ecstasy users reporting an average use of 1 to 3 tablets (De Win 2006; de Win et al. 2007; Jager et al. 2007b; Schilt et al. 2007). The team also performed studies expressly in heavy ecstasy users (de Win et al. 2004; Jager et al. 2007a; Reneman et al. 2006b). They failed to find reductions in SERT sites, signs of neuronal injury, changes in working memory task performance or brain activity when performing this task in samples reporting use of no more than six ecstasy tablets (de Win et al. 2007; Jager et al. 2007b). They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else, and they failed to find any markers of neuronal injury (de Win et al. 2007). Low use of ecstasy also failed to alter brain activity or performance on a measure of working memory (Jager et al. 2007b). When comparing cognitive function in people before and after their first use an average of 3.2 tablets and non-user controls at similar points in time, ecstasy users showed less improvement on a memory task than non-users (Schilt et al. 2007). It is notable that the study examining SERT sites and cerebral blood flow did not employ non-user controls, and that all participants in the study of cognitive function performed within the normal range, and that one individual had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other studies. Taken together, their findings fail to confirm serotonergic neurotoxicity after low ecstasy use, yet found some possible indications of impaired memory.

We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. Nevertheless, the risks of neurotoxicity arising from MDMA administration will be described and noted in application materials prior to and during the completion of the application. Cognitive function will be assessed at baseline and again six weeks after the third double-blind session, and the investigators will informally monitor for any signs of changes in cognition after each MDMA-assisted session.

Abuse Liability

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at night clubs and parties in the early to mid-1980s. MDMA possesses abuse liability, and this is discussed in “Additional information.” Whether or not MDMA’s abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. Mithoefer and colleagues are in the process of conducting a long-term follow-up of

participants who took part in the study of MDMA-assisted psychotherapy that will address this question. Mithoefer reported that anecdotally it appeared that people did not develop problems with MDMA/ecstasy abuse and that a number of participants volunteered that they would never seek out ecstasy outside a legal, controlled therapeutic setting. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted. More information on the abuse liability of MDMA can be found in "Additional Information."

Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the "Pharmacology" section and in pp. 29-30 in the Investigator's brochure (Bateman et al. 2004; McElhatton et al. 1999). Pregnant women will be excluded from participation in the proposed study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each client-role session and must agree to using birth control during the period of the study.

Risks and Discomforts of Receiving the Active Placebo Dose of Study Drug

Receiving the active placebo doses of 25 mg MDMA followed 1.5 to 2.5 hours later by 12.5 mg MDMA may be associated with some of the risks above but to a far lesser degree. People receiving low doses of MDMA report only a few subjective effects and do not exhibit significant cardiovascular changes (Grob et al. 1996). It is possible that the addition of the supplemental dose will produce slight increases in positive and negative mood and slightly elevate blood pressure, as reported after administering approximately 35 to 40 mg (Harris et al. 2002). The active placebo dose of MDMA is not expected to produce most or all of the potentially therapeutic effects of the drug, such as increased positive mood, facilitated recall and changed perception of meaning, and increased feelings of closeness to others. Hence people receiving active placebo may experience a lesser reduction in PTSD symptoms from MDMA-assisted sessions.

Alternative Treatments and Procedures

The alternative to participating in the research study is to decide not to take part in the study. The decision not to participate in this research study will not in any way alter or compromise the care offered to individuals receiving therapy from the investigator or any physician involved in this research study.

The investigators will discuss alternatives to study participation, including other available treatments, with all potential participants. There are a number of recognized treatments for PTSD. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments for PTSD include anxiety management (stress inoculation training), cognitive therapy, exposure therapy and psychoeducation. Psychodynamic psychotherapy and Eye Movement Desensitization and Reprocessing are also used to treat PTSD.

Drugs available in Canada for treating PTSD include paroxetine, and in the US only Sertraline and paroxetine are approved for use in treatment of PTSD. Sertraline has been shown to decrease the hyperarousal and avoidance symptoms, but not the re-experiencing symptoms, of PTSD. Paroxetine has been shown to have an effect on all three categories of symptoms in approximately 62 % of patients. Other medications commonly used are other SSRIs, nefazodone, venlafaxine, tricyclic antidepressants, benzodiazepines, buspirone, zolpidem and mood stabilizers.

Confidentiality

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a randomly generated numeric code on all secondary documents and databases. The investigators will retain a key associating these new numbers with those assigned to participants upon study enrollment. All measures, records, audio and video recordings will be kept in a locked file drawer in a locked office. Access to measures will be limited to regulatory agencies, researchers assessing the participant for changes in symptoms, and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Participants will sign forms for the release of information to any of the individuals who will need to obtain this information. Interested parties might include the prescribing physician or psychiatrist.

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

Costs to Participants

There will be no costs to participants for any study-related procedures. The sponsor (MAPS) will pay for all assessments, laboratory work or physical examinations needed to determine study eligibility. The sponsor will also cover costs of the study drug and remaining at the study site on the night after each MDMA-assisted psychotherapy session. The sponsor will pay for all study drugs and study procedures. The sponsor will

cover all costs for travel, food and lodging. Travel cost will include air fare for an economy class ticket to the study site if necessary and will include train or parking costs. Participants will not be paid for their participation in this study.

Risk/Benefits Analysis

Developing an array of potential treatment options for PTSD will increase the likelihood of symptom reduction and recovery in people with this debilitating psychiatric disorder. MAPS intends to develop MDMA-assisted psychotherapy as one such treatment. If efficacious, this treatment could require fewer visits with psychotherapists and less use of daily medication. MDMA-assisted therapy may help people whose PTSD symptoms persist despite treatment with established psychotherapies and pharmacotherapies. The sponsor has supported one investigation that is almost complete in the US, and investigations that are now underway in Switzerland and Israel. If results from these Phase II studies, including the proposed study, are promising, then MAPS will embark upon Phase III investigations at multiple sites.

Administering the study drug exposes study participants to a number of potential risks and discomforts that would not otherwise occur. The experimental dose of MDMA is liable to produce common physiological and psychological side effects during each experimental dose MDMA-assisted session, such as increased blood pressure or elevated anxiety. People with PTSD receiving MDMA within a therapeutic setting may very well experience strong negative emotions during the session, as fear, rage or grief. There are reports of a number of serious adverse events in people in uncontrolled, non-medical settings after taking ecstasy. However, there is good evidence that conducting three separate experimental sessions administering initial doses of 125 mg followed by 62.5 mg MDMA in a clinical setting poses a low risk to participants. Conference presentations of data from a controlled study and prospective studies of people before and after ecstasy use have found little to no differences in brain activity and serotonin system function (de Win et al. 2007; Ludewig S et al. 2003; Vollenweider and Scherpenhuyzen 2000). A preliminary data analysis of cognitive function at baseline and two months after the second experimental session in the study of MDMA-assisted psychotherapy in 21 participants failed to find any significant differences between participants who received two doses of MDMA and participants who received placebo (Wagner 2008). However, one prospective study comparing cognitive function before and after ecstasy use found differences between ecstasy users and non-users (Schilt et al. 2007). When tested a second time an average of eleven months later, people who had not used ecstasy improved their performance on a verbal memory task, while people who used ecstasy did not improve performance on this task. However, it is notable that at least one participant reported use of 30 tablets and all participants performed within the normal range. As well, other studies have failed to find impaired memory or decision-making in moderate ecstasy users, with moderate use often defined as below 50 tablets or occasions of use (Back-Madruga et al. 2003; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Medina et al. 2005). Hence it is very unlikely that the dosing and schedule of sessions proposed in this study will result in impaired verbal memory.

A third of the study participants will receive an active placebo dose of MDMA. The initial and supplemental doses to be used in the active placebo condition were chosen to produce only a few of the subjective effects of MDMA. While the active placebo dose is hypothesized to have little to no therapeutic benefit, it will also produce fewer and less strong side effects and is associated with lesser cardiovascular effects. Study participants in the active placebo condition will receive a course of non-drug therapy along with the MDMA-assisted sessions. All participants in this study will have the opportunity to undergo three sessions with fully active doses of MDMA. Active placebo participants can enroll in Stage 2, which will be identical in structure and scheduling to sessions received during the randomized study segment. An active placebo group is required in order to properly assess the efficacy of study drugs, and an active placebo is required when dealing with psychoactives such as MDMA. Because MDMA produces a unique array of effects, the investigators will use a lower dose of the study drug that may produce enough of these effects to be a credible active placebo.

After taking into consideration the costs and benefits associated with the current study versus alternative treatments available for people diagnosed with PTSD, we conclude that the benefits of conducting the proposed study outweigh the risks, as the risks are minimal and the investigators will further reduce these risks through careful screening and monitoring of study participants. If MDMA-assisted psychotherapy is found to be efficacious, it has the potential to improve the lives of people with PTSD.

Chemistry, Manufacturing and Control Information

The drug product is (+/-)-(3,4)-methylenedioxymethamphetamine HCl, also referred to as N-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅NO₂. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by

On January 30, 2006, a quality control analysis was performed by [REDACTED] This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. [REDACTED] with no decomposition products detectable and a HPLC purity >98%.

The encapsulation will be performed by an individual possessing the appropriate skills, as a pharmacist. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, mannitol or a similar inactive compound used to ensure that all capsules have similar weights. The lowest dose contained in one capsule will be 12.5 mg, which is the supplemental dose offered to participants in the Active Placebo condition, and the highest dose contained in one capsule will be 150 mg, which is the higher initial dose that can be used during two open-label sessions. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent investigators and participants from distinguishing contents of Active Placebo and Experimental Dose capsules. Dosage for open-label sessions will be

clearly indicated in the packaging as either being 125 and 62.5 or 150 and 75 mg. Bottles will contain both initial and supplemental doses.

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

Pharmacokinetics and Pharmacodynamics

Primary Pharmacology

The compound to be used in this study is racemic 3,4-methylenedioxymethamphetamine (MDMA). This ring-substituted phenylisopropylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and uptake inhibitor (Battaglia et al. 1988; Setola et al. 2003; Verrico et al. 2007). Its direct actions on serotonergic, adrenergic and other receptors is considerably lower.

MDMA interacts with plasma monoamine transporters and storage vesicles to increase extracellular levels of serotonin (5-HT), dopamine, and norepinephrine (Cozzi et al. 1999; Fitzgerald and Reid 1990; Hiramatsu and Cho 1990; Kankaanpaa et al. 1998; Nash and Brodkin 1991; Rudnick and Wall 1992; Schuldiner et al. 1993). Direct MDMA stimulation of postsynaptic 5-HT_{2A} receptors and α2 adrenoceptors also contributes to MDMA's effects (Gudelsky 1996; Koch and Galloway 1997; Palfreyman et al. 1993; Schmidt et al. 1992; Yamamoto et al. 1995). For example, dopamine release is also indirectly increased by MDMA stimulation of 5-HT_{2A} receptors on GABAergic striatonigral neurons (Yamamoto et al. 1995).

Although the specific mechanisms of MDMA's therapeutic effects are not fully understood, several observations and hypotheses can be made. The direct and indirect effects of serotonin release may make a large contribution to producing the subjective effects of MDMA, as pre-treatment with SSRIs reduces most or all the drug's subjective and physiological effects (Farre et al. 2007; Liechti et al. 2000a; Liechti and Vollenweider 2000b; Tancer and Johanson 2007), with one study reporting reductions in sociability (Farre et al. 2007). Indirect effects of serotonin release of potential significance include indirect activation of 5HT_{1A} receptors and elevating the neurohormone oxytocin (Thompson et al. 2007). Studies in rats reported that stimulating 5HT_{1A} receptors attenuated aggression, and administering a 5HT_{1A} receptor antagonist to rats given MDMA reduced adjacent lying, a prosocial behavior (Morley et al. 2005). This occurs likely through an increase in oxytocin associated with stimulating 5HT_{1A} receptors (Thompson et al. 2007). Pre-administration of the 5HT_{1A} and β adrenergic antagonist pindolol had few effects in a sample of men, but the researchers did not assess interpersonal closeness or social interactions (Hasler et al. 2008). A naturalistic study comparing blood oxytocin in people with and without detectable blood MDMA found that MDMA was associated with elevated oxytocin (Wolff et al. 2006), a hormone that

may increase trust and accuracy of emotion perception as well as regulating water/sodium balance (Domes et al. 2007; Zak et al. 2005). Other indirect effects of serotonin release include elevation in cortisol (Grob et al. 1996; Harris et al. 2002; Mas et al. 1999), a hormone with a complex and sometimes paradoxical relationship to stress and challenge (Het and Wolf 2007; Putman et al. 2007; Wirth and Schultheiss 2006). Dopamine release likely plays a role in elevating positive mood and euphoria, which may partially contribute to an enhanced sense of confidence when facing emotionally intense feelings or memories. Administering the D₂ antagonist haloperidol decreased positive mood and increased anxiety after MDMA, suggesting that indirect stimulation of D₂ receptors may play a role in some MDMA effects on mood (Liechti and Vollenweider 2000a). There are no studies to date investigating the role played by norepinephrine release on the cardinal effects of MDMA.

Though they differ in some respects, early and later pharmacological profiles of MDMA reported an affinity for specific serotonergic, noradrenergic, cholinergic and histaminergic receptors (see Table 3 below). It is possible but not yet demonstrated that 5HT_{2B} and α₂ receptors may contribute to at least some of the subjective effects of MDMA, while little is known as to whether there are any potential contributions from M₃ or H₁ receptors. 5HT_{2B} receptors in the medial amygdala may contribute to the anxiolytic effects of MDMA, as may also be true for the serotonin releaser and 5HT_{2B} agonist fenfluramine. Direct MDMA stimulation of postsynaptic α₂ adrenoceptors may also help individuals remain emotionally calm despite noradrenergic activation, as with related α₂ agonists clonidine and guanfacine, possibly through altering the balance between α₁ to α₂ stimulation (Franowicz and Arnsten 1998).

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

Receptor	Ki (mM)	Hot Ligand	Species	Source	Reference
Serotonin transporter	0.072 or 0.102	Functional (1), 3H-citalopram (2)	Rat, Human	Brain, Cloned	(Jones et al. 2004; Setola et al. 2003)
Norepinephrine Transporter	0.110	Functional	Rat	Brain	(Setola et al. 2003)
Dopamine transporter	0.278	Functional	Rat	Caudate	(Setola et al. 2003)
5HT _{2B}	0.5 or 0.7	3H-LSD	Human	Cloned	(Setola et al. 2003), (PDSP 2007)
α _{2C}	1.12	3H-Clonidine	Human	Cloned	(PDSP 2007)
Calcium Channel	1.2	3H-Nitrendipine	Rat	Heart	(PDSP 2007)
α _{2B}	1.8	3H-Clonidine	Human	Cloned	(PDSP 2007)
M ₃	1.8	3H-QNB	Human	Cloned	(PDSP 2007)
H ₁	2.1	3H-Pyrilamine	Human	Cloned	(PDSP 2007)
α _{2A}	2.5	3H-Clonidine	Human	Cloned	(PDSP 2007)
M ₅	6.3	3H-QNB	Human	Cloned	(PDSP 2007)
M ₄	8.2	3H-QNB	Human	Cloned	(PDSP 2007)
5HT _{2A}	8.3	3H-ketanserin	Rat	Cortex	(Lyon et al. 1986)

Primary Pharmacodynamics

Drug Activity Related to Proposed Action

MDMA has a unique profile of psychopharmacological effects making it well suited to intensive psychotherapy. In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection (Greer and Tolbert 1986; Grinspoon and Bakalar 1986). Placebo-controlled clinical trials have confirmed that MDMA produces an easily-controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Cami et al. 2000b; Harris et al. 2002; Hernandez-Lopez et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003; Tancer and Johanson 2001; Vollenweider et al. 1998). Findings in samples of largely drug-naïve individuals are similar to those reported by people with previous experience with ecstasy (see for example Cami et al. 2000 versus Vollenweider et al. 1998). An increase in positive mood, increased access to emotionally intense material, increased interpersonal trust and compassion for the self and others, and anxiolysis likely all contribute to the therapeutic effects of MDMA. It is significant that anxiety is reduced without the physiological effects of a depressant, and that people can still experience and reflect upon intense emotions. Increased interpersonal closeness may permit people to explore usually upsetting thoughts, memories or feelings, and facilitated recall and changes in the meaning of perception may contribute to generating new perspectives about past or current thoughts, feelings and experiences.

To date, no work has specifically addressed the relationship between the pharmacological effects of MDMA and one or more of its proposed therapeutic effects within a psychotherapeutic context. Since pre-treatment with an SSRI significantly attenuates most subjective and physiological effects of MDMA, it is likely that serotonin release contributes to therapeutic effects, such as reduced anxiety and increased positive mood. However, none of the studies employing SSRI pre-treatment occurred in a therapeutic setting, and none of these studies assessed interpersonal closeness or social interaction. Serotonin release could contribute to proposed therapeutic effects via indirect activation of serotonin receptors, or its therapeutic effects may arise because serotonin influences levels of neuroendocrine hormones, such as oxytocin or arginine vasopressin. Since pre-treatment with the dopamine D₂ receptor antagonist haloperidol reduced positive mood and increased anxiety after MDMA (Liechti and Vollenweider 2000a), indirect effects of dopamine release also appear to play a role in one potentially therapeutic effect. However, preventing action at D₂ receptors had less impact on either subjective or physiological effects of MDMA when compared with serotonin release (Liechti et al. 2000a). While research reported that pre-treatment with the 5HT_{2A} antagonist ketanserin attenuated perceptual alterations after MDMA (Liechti et al. 2000b), researchers did not employ a measure that would have allowed them to determine whether 5HT_{2A} receptor activation played a role in potentially therapeutic effects, as facilitated recall or changed meaning of perception.

Secondary Pharmacology

Safety Pharmacology

The psychotherapeutic effects of MDMA are accompanied by dose-dependent physiological effects including vasoconstriction and increased heart rate and blood pressure (see pp. 44-48 Baggott et al. 2001; Lester et al. 2000; Liechti et al. 2001; Mas et al. 1999; Tancer and Johanson 2003). Physiological effects of MDMA reach their maximum within 1 and 2 hrs after oral MDMA administration and subside within 6 hrs of drug administration (Harris et al. 2002; Vollenweider et al. 1998; Liechti et al. 2001; see also Baggott et al. 2001). Data on maximum changes in heart rate and blood pressure collected from human studies published or in preparation in mid-2001 are summarized in Table 3.1 in Baggott et al. 2001. Data from more recent reports (Farre et al. 2004; Lamers et al. 2003; Tancer and Johanson 2003) are similar to data from previous reports. Two of three studies found reported that pre-treatment with a selective serotonin uptake inhibitor (SSRI) attenuated elevation in blood pressure and heart rate (Farre et al. 2007; Liechti and Vollenweider 2000b), while the third reported that SSRI pre-administration only attenuated increased heart rate after MDMA (Tancer and Johanson 2007). The 5HT_{2A} receptor antagonist ketanserin reduced elevated diastolic pressure (Liechti et al. 2000b), while the D₂ antagonist haloperidol failed to attenuate any of the cardiovascular effects of MDMA (Liechti and Vollenweider 2000a). These findings suggest that cardiovascular effects are at least partially due to serotonergic activity. When given in controlled settings, MDMA produced only slight increases in body temperature (Harris et al. 2002; Liechti et al. 2000b; Tancer and Johanson 2003), with the increase undetected in a number of studies (de la Torre et al. 2000c; Fantegrossi et al. 2004; Farre et al. 2004; Johanson et al. 2006; Liechti et al. 2000a). Humans, unlike rodents, exhibit the same slight elevation in body temperature whether in a warm or a cool environment (Freedman et al. 2005).

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 2.5 h is expected to produce significant increases in blood pressure and heart rate, but is not expected to produce sustained increases in heart rate or blood pressure above 170/100 mm Hg. The physiological effects of a second dose of MDMA that is half the original dose and given one and a half to two and a half hours after the first dose are not yet known, but personal communication from Michael Mithoefer, the principal investigator conducting the study of MDMA-assisted psychotherapy in people with PTSD, reports that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose (Mithoefer 2007; email sent to L. Jerome on July 7, 2007). A dose of 150 mg may produce peak elevations greater than 170/100, as reported in one participant in the study of Peter Oehen, but these effects were transient (Oehen 2008b).

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotropic hormone, and dehydroepiandrosterone (DHEA) concentrations (Grob 2001; Grob et al. 1996; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. A second dose of 100 mg MDMA given four hours after an initial dose of 100 mg produced a second increase in cortisol during an interval when cortisol levels were declining (Pacifici et al. 2001b). Harris and colleagues failed to

detect any changes in luteinizing hormone (LH), estradiol, progesterone or follicle stimulating hormone (FSH) in women participants. 40 mg MDMA acutely increased circulating levels of antidiuretic hormone (arginine vasopressin) in eight male volunteers, with maximum levels reached between one and two hours after drug administration (Henry et al. 1998). A naturalistic study reported an association between detectable blood MDMA and elevation in oxytocin (Wolff et al. 2006). Increased retention of fluid is unlikely to be of any consequences in a clinical setting.

Studies conducted in Spain suggest that MDMA acutely affects the immune system (Pacifici et al. 2000; Pacifici et al. 2001a; Pacifici et al. 1999a). These acute changes in immunologic function include reduced CD4 T-cell count, increased NK cell count, and decreased phytohaemoagglutin A-induced lymphocyte proliferation. These effects are transient and unlikely to last any longer than 24 to 48 hours after drug administration. MDMA decreased levels of the immune system stimulating and proinflammatory cytokine interleukin 2 (IL-2) and increased levels of the immunosuppressive and anti-inflammatory cytokine interleukin 10 (IL-10) (Pacifici et al. 2004; Pacifici et al. 2001). Generally, MDMA appears to decrease the concentration of Th1 cytokines and increase Th2 cytokines measured in blood. For example, the CD4 T-cell count decrease was similar in magnitude to that produced by 0.8 g/kg oral ethanol (the equivalent of 4-5 drinks) in the same report (Pacifici et al. 2001b). The mechanism of immunomodulation is unclear but may be at least partly due to increased glucocorticoid levels or sympathomimetic activity, and activity at α adrenergic receptors (Connor et al. 2005). Serotonin release probably plays a role in these changes, since paroxetine pretreatment attenuated and in some cases eliminated immunological effects of MDMA (Pacifici et al. 2004) while only partially reducing elevated cortisol. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998).

MDMA acutely affects attention, information processing and memory. MDMA enhances pre-pulse inhibition, the ability of a less intense stimulus (as noise) to reduce startle response to an intense stimulus. MDMA acutely impaired verbal memory and recall for object location without affecting recall of scene change (Kuypers and Ramaekers 2005). MDMA did not affect Stroop task performance, but impaired performance on the Digit Substitution task (Cami et al. 2000a; Gamma et al. 2000). When examined in the context of skills related to driving motor vehicles, MDMA reduced weaving and produced overly cautious response to the actions of another driver (Kuypers et al. 2006; Ramaekers et al. 2006). The mechanism or mechanisms behind these acute changes remains unknown. However, since the noradrenergic and dopaminergic agonist methylphenidate failed to alter verbal memory or driving skills in the same way as MDMA, it is likely that serotonin release contributes directly or indirectly to these effects. Acute effects of MDMA upon verbal and visual memory were no longer apparent 24 hours later.

Published animal and *in vitro* studies have specifically investigated the possibility of hyperthermia, hepatotoxicity and neurotoxicity after MDMA exposure. These types of toxicity appear to be dose-dependent and all available evidence indicates that the risks in

these areas are minimal in the currently proposed study. These areas of toxicity are discussed below.

MDMA may cause modest changes in cerebral blood flow lasting several weeks after drug exposure. These changes have been hypothesized to be the result of short-term down-regulation of serotonergic receptors controlling cerebral vasodilatation (Reneman et al. 2002; Reneman et al. 2000). MDMA induced decreased regional and global cerebral blood flow (CBF) 10 to 21 days after administration (Chang et al. 2000), as reported in a study of 10 ecstasy users given two separate ascending doses of MDMA at a two-week interval, with comparisons made at baseline and after the administration of both doses. Doses per administration in this study ranged from approximately 17 mg (0.25 mg/kg) to approximately 175 mg (2.5 mg/kg). The authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported 211 ± 340 exposures) were compared to 21 nonusers, suggesting that effects on CBF do not last indefinitely, a prospective study in people before and after using ecstasy found changes in rCBF only in one brain area, the dorsolateral prefrontal cortex. There are no known consequences of these changes and neurocognitive performance was not altered in these volunteers.

Hyperthermia

As discussed above, MDMA administered in a controlled setting produces only a slight increase in body temperature, and ambient temperature does not enhance or attenuate this slight elevation in humans. However, hyperthermia is one of the most commonly reported serious adverse events in ecstasy users (Baggott et al. 2001; Henry and Rella 2001). Researchers working with rodent models have suggested several potential causes, including nonshivering heat production or the action at norepinephrine receptors, and they have reported that hyperthermia is more likely in group-housed rodents (Fantegrossi et al. 2003; Mills et al. 2004; Sprague et al. 2004a; Sprague et al. 2004b). However, given that rodents face different thermoregulatory challenges when compared to humans (Gordon 2007) and given that human body temperature after MDMA is unaffected by ambient temperature, it is not clear whether and to what degree these models are relevant to humans. Hyperthermia may be dose dependent, as suggested by case series of people who took ecstasy in the same London area nightclub on the same evening (Greene et al. 2003). Hence it is possible that a dose of 150 mg may produce a greater elevation in body temperature than a dose of 125 mg. A case report and at least some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans (Martin et al. 2007; Sprague et al. 2007). However, even when given in a warm environment, 2 mg/kg MDMA did not produce a clinically significant increase in body temperature (BT) (Freedman et al. 2005). In addition, the investigator in Switzerland who has administered 150 mg to one participant on two occasions reported variations in BT in the same subject across sessions involving 125 and 150 mg (Oehen 2008a, personal communication). To date, there have been no cases of clinically significant hyperthermia in any human MDMA trial, and it is unlikely to occur in this study.

Psychiatric Problems

Psychiatric problems occurred in 22.1% of 199 case reports examined in 2001. Psychiatric symptoms included affective responses, as dysphoria, anxiety or panic, and psychotic response, as well as cases with mixed psychotic and affective features (Baggott et al. 2001). The most common problem reported as psychotic response (see for example McGuire et al. 1994). There was a family history of psychiatric disorders in a large minority of cases of psychosis after MDMA. These psychiatric problems generally occurred in experienced rather than novice ecstasy users. Some panic responses resolved without further assistance (Whitaker-Azmitia and Aronson 1989). The mechanisms behind ecstasy-associated psychiatric problems remain unclear but are likely the result of an interaction between pharmacology and individuals susceptibility. The difficulty of assessing the frequency of these events is increased given that pre-existing psychiatric problems occur in people who go on to use ecstasy (Huizink et al. 2006) and findings of an association between use of ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after ecstasy use resolved after supportive care ((Liechti et al. 2005; Williams et al. 1998). Anxiety responses reported in controlled trials has never required clinical intervention and abated with the waning of drug effects.

Hepatotoxicity

Liver damage was reported in approximately 16% of 199 case reports examined in an initial review of the literature (Baggott et al. 2001), making hepatotoxicity the third most common serious adverse event occurring in ecstasy users. There is more than one pattern of ecstasy-related hepatotoxicity. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet (Dykhuijen et al. 1995; Ellis et al. 1996; Ellis 1992). In other cases, hepatotoxicity has occurred after regular ecstasy use for months (Andreu et al. 1998). Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure (Frith et al. 1987), nor have any cases of liver disease arisen during controlled studies. Examining case reports and a number of in vitro studies suggests an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, with it appearing after continued use and resolving after abstinence, suggesting a potential immunological response.

Because hepatotoxicity has been noted in ecstasy users, in vitro and in vivo studies have examined the hepatotoxicity of MDMA. These studies show that high doses of MDMA can impair liver cell viability. In vitro studies found that high to very high concentrations of MDMA increased ALT, AST and LDH activity (Beitia et al. 2000), increased profibrogenic activity in cultured stellate cells (Varela-Rey et al. 1999) and slightly reduced cell viability without producing lipid peroxidation (Carvalho et al. 2001). Incubating cells with slightly smaller concentrations of MDMA at high temperatures further reduced cell viability (Carvalho et al. 2001; Montiel-Duarte et al. 2002), with apoptosis (cell death) seen when concentrations of MDMA approximately eleven times those seen in humans were incubated at high temperatures (Montiel-Duarte et al. 2002). Hepatotoxicity is probably the result of oxidative stress (Carvalho et al. 2004; Montiel-Duarte et al. 2004). Peak liver exposure to MDMA in the proposed clinical study should be approximately

one-eleventh the concentration shown to impair cell viability in these in vitro studies. No cases of liver disease or hepatotoxicity has occurred in a controlled trial of MDMA.

Hyponatremia

A number of case reports describe hyponatremia after ecstasy use (Baggott et al. 2001; Henry and Rella 2001), with case reports of hyponatremia appearing subsequent to review (see for example Brvar et al. 2004; Rosenson et al. 2006). Behavioral factors, including vigorous exercise and consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressin and oxytocin likely all contribute to these very rare but serious adverse events in ecstasy users. Hyponatremia has not occurred during a controlled study.

Neurotoxicity

Extensive studies in animals indicate that high or repeated dose MDMA exposure can damage serotonergic axons originating in the dorsal raphe nucleus of the brainstem (Molliver et al. 1990). This is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter. Although some regrowth occurs, seemingly permanent redistribution of axons was noted in a study with squirrel monkeys (Hatzidimitriou et al. 1999). These serotonergic changes have not been associated with lasting behavioral impairment in the vast majority of animal studies, despite dramatic serotonin depletions. The great volume of research addressing MDMA neurotoxicity has been extensively reviewed and discussed in past and current revisions of the Investigator's Brochure (Baggott et al. 2001; Cole and Sumnall 2003b; Green et al. 2003; Jerome 2004; 2005). Several studies in nonhuman primates suggest that previous research employed doses or regimens exceed doses normally used by humans (Bowyer et al. 2003; Fantegrossi et al. 2004; Mecham et al. 2006). Two studies performed by the same team of researchers comparing MDMA administration in rats (three 7.5 mg/kg doses given i.p.) found changes in some but not other markers of damage to the serotonin system (Wang et al. 2005; Wang et al. 2004), specifically finding a dissociation between changes in serotonin levels and proteins that mark neuronal injury. Considering these findings, it appears that the nature and extent of MDMA neurotoxicity remains contentious.

Findings from nonhuman animal research led researchers to compare ecstasy users with non-user controls. There are several reviews of this literature and discussion of it in the Investigator's Brochure (Baggott et al. 2001; Cole and Sumnall 2003a; Kish 2002; Laws and Kokkalis 2007; Zakzanis et al. 2007). To date, most retrospective studies have detected lower estimated serotonin transporter (SERT) sites in current ecstasy users, elevated numbers of anxiety or depression in current and former ecstasy users, and impaired verbal memory and executive function (decision-making and planning) in ecstasy users. These findings suggest that regular and especially heavy ecstasy use may pose risks of transient changes in SERT site number (Reneman et al. 2001; Reneman et al. 2006b) and long-term effects (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004). These retrospective studies contain a number of methodological flaws, particularly with respect to finding appropriately matched controls (Gouzoulis-Mayfrank and Daumann 2006).

Vollenweider and colleagues recently measured serotonin transporter density using positron emission tomography (PET) with [¹¹C]McN5652 before and after a single dose of MDMA (Vollenweider et al. 2000, data presented at the 2000 conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine). Vollenweider and colleagues were unable to detect any lasting effect of 1.5 or 1.7 mg/kg MDMA in a pilot study with six MDMA-naïve healthy volunteers and in a second study with two additional volunteers. This measurement technique was validated in a study using a baboon exposed to a neurotoxic MDMA regimen (Scheffel et al. 1998), and this validation study found that PET tended to overestimate serotonin transporter changes in most cases. The same team also presented data from a prospective study of MDMA on cognitive function, reporting failure to find impaired cognitive function after MDMA administration (Ludewig S et al. 2003).

More recently, a series of prospective studies examined brain serotonin transporter sites, signs of neuronal injury, brain activity and cognitive function in people before and after their first few uses of ecstasy, ranging from 0.5 to 6 tablets (de Win et al. 2007; Jager et al. 2007b; Schilt et al. 2007). The researchers conducting these studies recruited people who reported an interest in taking ecstasy in the future and assessed them when first contacted and again shortly after they reported their first few uses of ecstasy. These findings, described in more detail above in “Risks” and in pp. 3-4 of the current revision of the Investigator’s Brochure suggest that low ecstasy use has little impact on brain structure or function. Taken together, MDMA may be neurotoxic in high or repeated doses, but lower or less frequent doses are not neurotoxic, with little to no indications of long-term effects after moderate use.

Developmental Toxicity

There remains a paucity of findings concerning developmental or reproductive toxicity in humans. An early investigation reported detecting increased developmental problems in births from ecstasy-using mothers (McElhatton et al. 1999) while a later investigation examining a specific defect failed to detect an association between ecstasy use and this defect, due in large part to low levels of ecstasy use in the sample (Bateman et al. 2004). Studies in rats have consistently found developmental effects of repeated doses of MDMA, including impairment on learning and memory (Meyer et al. 2004; Vorhees et al. 2004; Williams et al. 2005). It is possible that exposure to MDMA during the third trimester in humans could have similar effects. To date, pregnant women have not been enrolled in any controlled study of MDMA, and there is no plan to include them in the proposed study.

Common side effects

Common side effects are described in “Risks of MDMA” above and include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Other slightly less common side effects include restlessness, parasthesias (odd somatic feelings, as reporting tingling, feeling hot or cold), changes in thought, perspiration, drowsiness, and nystagmus (eye-wiggle). These effects are transient and wane as drug effects are waning. Sub-acute effects that either continue for the next 24 hours or appear later include insomnia, fatigue, weakness,

heavy legs, dry mouth, low mood or irritability. Fewer people report sub-acute effects when compared with people reporting acute effects. More information on drug side effects is contained on pp. 20-22 of the investigator's brochure.

Acute Adverse Effects

Approximately 5% of participants enrolled in controlled trials with MDMA have had clinically significant elevations in blood pressure, as described above in "Risks of MDMA," though none have required any clinical interventions and blood pressure returned to normal. While maximum peak blood pressure during a given session in some cases rose above the cut-off of 150 SBP or 110 DBP for making more frequent measures, as with the maximum SBP peak seen in the first stage 2 open-label session (179, n = 6) or the average peak for the second stage 2 open-label session (151, n = 6), or peak DBP during second experimental session of 113 (from amongst both MDMA and placebo sessions, n = 21). None of the maximum peaks in blood pressure ever rose to the point wherein any further treatment was necessary. Likewise, maximum body temperature could rise above normal temperature, as with the maximum peak of 100 F during the first experimental session (n = 23, MDMA and placebo conditions combined), but simply lowering the ambient temperature was sufficient to lower body temperature. As also noted in "Risks of MDMA" above, no drug-related serious adverse effects have occurred, and the majority of ecstasy users visiting emergency departments do so because of anxiety or panic (Liechti et al. 2005; Williams et al. 1998). However, there are case reports of a number of serious adverse events occurring in ecstasy users, including hyperthermia, psychological distress and hepatotoxicity. More information on these events is described above in "Safety Pharmacology" above.

Abuse Liability

MDMA possesses moderate abuse liability, as discussed above in "Risks to Participants" and below in "Additional Information."

Pharmacokinetics/Toxicokinetics

The pharmacokinetics of MDMA, summarized in Table 4, have been primarily characterized by a group of Spanish researchers in samples of male subjects, with the exception of one publication from a team of researchers in the Netherlands that was not primarily concerned with pharmacokinetics. Additional pharmacokinetic parameters for MDMA and metabolites are given in the papers cited in Table 4. For example, after 125 mg MDMA, total clearance for MDMA was 51.1 ± 14.1 per hr, while renal clearance was 13.0 ± 5.4 per hr (de la Torre et al. 2000a). The findings of the Spanish researchers are consistent with other investigations using limited doses (Fallon et al. 1999; Hensley and Cody 1999) or illicit users (Crifasi and Long 1996; Moore et al. 1996; Ramcharan et al. 1998). More recently, a team of researchers in Maryland replicated this work in an ethnically varied sample of men and women using doses of 1 and 1.6 mg/kg MDMA (Kolbrich et al. 2008). They report findings similar to those of de la Torre and colleagues, but also report finding inter-subject variability and gender differences in MDMA metabolism, with women having higher peak values for MDMA and the minor metabolite MDA and lower values for major metabolite HMMA than men. The