Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. MDMA will be obtained from Lipomed AG. Active placebo doses of MDMA will also contain the inactive substance lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

Dosing Regimen

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 other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the US [14, 27, 35]. The supplemental dose is also identical to the one used in the US study. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective 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 [36, 37] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [37].

As described above, capsules containing the initial dose of MDMA will be administered [redacted] at approximately 10:00 AM. Supplemental doses will be administered upon mutual agreement by the investigators and participant one and a half to two and a half hours after the initial dose. There will be no take-home doses. The investigators may decide not to administer the supplemental dose of MDMA if they believe that the participant exhibits signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event.

There will not be any changes in dose regimen across the three MDMA-assisted sessions. If the participant experienced hypertension that required clinical intervention or had a serious adverse event during an experimental session, then no further doses of MDMA will be administered.

Washout Period

Participants taking psychiatric medications will undergo a medication-appropriate washout period beginning upon study entry and lasting for at least five times the medication half-life before an experimental session. Participants who undergo medication washout will have PTSD and depression symptoms assessed again after completing the

washout. This is to ensure that an appropriate comparison will be made between baseline symptoms of PTSD and symptoms six weeks after the third experimental session, when individuals will be medication-free. The first experimental session cannot occur until after a participant has completed medication washout.

Pre-study Screening and Baseline 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. If participants continue to meet all study criteria without meeting any exclusionary criteria, they will be enrolled in the study.

Upon enrollment, participants will undergo baseline evaluation. 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, as described above.

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, and this individual will have charge of maintaining randomization procedures. A randomization list will be run to assign random numbers from one to 100 and either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles. 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.

Treatment Visits

After baseline assessment, the 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. 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. The sequence of events and procedures in Stage 2 is nearly identical to that of Stage 1 except that participants undergo one and not three introductory psychotherapy sessions and all three MDMA-assisted psychotherapy sessions are open-label.

Psychotherapy: Study participants will receive conventional "talk therapy" before and after undergoing each experimental therapy session. They will receive three experimental psychotherapy sessions scheduled at three to five week intervals. Each experimental session will be followed by conventional psychotherapy, including psychotherapy on the morning of the day after the experimental session and two more sessions afterwards.

Introductory Psychotherapy: All psychotherapy will take place Prior to undergoing MDMA-assisted psychotherapy, participants will have three 60 to 90 minute long introductory psychotherapy sessions, during which they will meet with the male and female co-therapist team. Participants receive introductory psychotherapy to build a working alliance with the therapists and to prepare them for the experimental psychotherapy sessions.

Experimental Sessions: 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 co-therapist team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for participants assigned to the full dose and active placebo condition.

Participants will approximately one hour before drug administration for collection of a urine specimen for 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. 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 Subjective Units of Distress (SUD), a single-item measure of degree of psychological distress, 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.

Time and Events for Randomized Study segment

Table 1: Schedule of 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					
Visit #	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	Intro psychotherapy2	Intro psychotherapy3	Experimental 1	Integrative Therapy1	Integrative Therapy2	Integrative Therapy 3	Experimental 2	Integrative therapy4	Integrative Therapy5	Integrative Therapy6	Experimental 3	Integrative Therapy 5	Integrative Therapy6	Integrative Therapy7	6 wk post V11	End Randomized Segment
Approximate Study Day			0	7	14	21	28	29	35	42	49	56	56	63	70	71	76	85	112	119
Visit Timing and Windows		Post telephone	(Post-consent, may be same day	(-4/+3 d)	Post V4	Post V5	post V6	24 h post-experim. session 1	Between V6 and V11	Post V9	>3<5 wks post V8	24 h post V11	Post V11	Post V13	>3<5 w 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	Physician, Ingrid/Andrew, IA	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	Ingrid/Andrew, IA	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																	
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		
Psychotherapy-No Drug				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				X					
Psychotherapy + MDMA							X				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					
Overnight stay							X			X	X				X					
Serious Adverse Events			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	
Unblinding																				X
Consent for Stage 2/open-label																				X
RRPQ																				x
End Randomized phase																				x
IA=Independent Assessor																				
*=Optional & for nonresponders only																				

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	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															
CAPS		X														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																	

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 [38-40]. Throughout the duration of this session, the therapists will support and encourage the participant in emotional processing and resolution of emerging memories, thoughts or feelings. The therapist-investigators will also encourage periods of time in which the participant remains silent, focusing attention inward, in order to allow for the further unfolding of their inner experience. Water and electrolyte-containing beverages will be available for participant consumption, and food will be offered later on in the session.

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. SUDs will be 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.

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.

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 therapist-investigators and participant will discuss the issue of having a significant other present prior to permitting a significant other to accompany the participant.

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 and 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 appropriately furnished room With prior approval, 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 anyone with training or background in health care, particularly psychiatric health care with previous training in managing psychological distress, including distress

occurring after use of psychedelic drugs. If there is an emergency or the participant needs additional support, the attendant can contact the investigators.

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.

Integrative Psychotherapy: Participants will undergo non-drug psychotherapy on the day after each MDMA-assisted session and on a weekly basis during intervals after and between each MDMA-assisted session. During these 60 to 90 minute psychotherapy sessions, the participant and therapists will work to integrate material from experimental sessions into the participant's everyday life.

An integrative psychotherapy session will take place on the morning of the day after each experimental psychotherapy 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. Participant and investigator beliefs about participant condition assignment will be assessed on the morning of the day after each experimental session. After this psychotherapy session, a person previously selected by the subject will provide a ride home. The investigators will help secure a ride home for participants who are unable to locate a ride.

The participant will meet with the therapist for at least two more integrative psychotherapy sessions to be scheduled between experimental sessions or after the third and final experimental session. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during experimental sessions. 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. There will be no more visits for approximately one month between integrative psychotherapy after the third experimental session and assessment six weeks after the third experimental session.

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 a 90 to 120 minute evaluation wherein the independent rater will administer the CAPS and participants will complete the BDI and PDS. The independent rater will also administer the RBANS and PASAT.

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 blind will be broken for the therapist-investigators and the participant, with the independent rater remaining blind to condition assignment. During this 30 to 60 minute meeting, 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), a measure of experience as a research participant.

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.

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

Audio and Video Recording: All sessions from introductory psychotherapy through weekly integrative psychotherapy and including experimental and open-label 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, and therapist interventions and for development of a manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

Premature Withdrawal/Discontinuation Criteria

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. Cause for withdrawal from the study include, but is not limited to, positive urinary pregnancy screen, positive urinary drug screen, drug-related adverse event requiring hospitalization or immediate clinical intervention (as high, sustained elevation in blood pressure,

elevated body temperature, psychotic reaction), signs of liver disease, and signs of sustained impaired cognitive function, resumption of psychiatric medication for another condition, or failure to follow investigator instructions. Failure to follow one or more instruction related to pre-session food or beverage consumption may lead to delaying experimental or open-label session start time, rescheduling the session or withdrawing the participant from the study.

Rescue Medication and Risk Management

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 occurrence of drug-related serious adverse events [9, 11, 14, 41]. MDMA side effects include loss of appetite, dry mouth, impaired concentration, impaired gait or balance and tight jaw muscles, and fatigue lasting for up to two days afterwards [37, 42-46]. Increased anxiety, mild perceptual alterations (as colors seeming brighter) and increased anxiety are reported in clinical trials [35, 37, 46-48]. Approximately 5% of study participants exhibit clinically significant elevation in blood pressure, none requiring clinical intervention [46, 49].

Currently there is no known antidote to MDMA. There are pharmacological or psychotherapeutic treatments for specific effects of MDMA. Anti-hypertensives can be used to reduce elevated blood pressure. Supportive care can be used in response to anxiety or panic reactions. Benzodiazepines could also be used in response to panic reactions or psychotic responses. Human drug co-administration studies suggest that conventional (first generation) anti-psychotics will not reduce, and may even increase, anxiety after MDMA [44]. It is possible but currently uncertain, that serotonergic antipsychotics, such as olanzapine, could be used to treat psychotic response to MDMA. The investigators will not administer a subsequent dose of MDMA if an individual exhibits a severe panic response or signs of liver disease, and they may decide not to administer a subsequent dose of MDMA after elevation in blood pressure that required clinical intervention.

Serious adverse effects of ecstasy (material represented as MDMA) are rare even outside controlled settings [50]. In uncontrolled settings, hyperthermia is the most common of these events [42, 51]. In addition to hyperthermic syndromes, other rare adverse events include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia.

Hypertension and Cardiovascular Effects: Participants with hypertension, cardiovascular, coronary, pulmonary or cerebrovascular disease will be excluded from study participation. The investigators will address the cardiovascular effects of MDMA through periodically monitoring blood pressure and pulse at regular 30-minute intervals. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the

investigator to be safe. The investigators may send the participant to an emergency department if they judge it necessary to do so.

Psychological Distress: Preparation for each experimental or open-label session and supportive care during each session will be used to address and potentially reduce psychological distress. Participants with psychiatric conditions that place them at increased risk of psychosis, such as past or current psychotic disorders or dissociative identity disorder, will be excluded from study participation. Preparation will include discussing what might occur during an MDMA-assisted therapy session and teaching techniques such as diaphragmatic breathing. The investigators will explain to participants that anxiety will not be treated pharmacologically during the sessions because anxiety presents 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, the principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem. The investigators may remain with the participant until they believe that he or she is stable, and they have the option to hospitalize any participant who may be in danger of harming him or herself or others.

Hyperthermia: The investigators will address risk of hyperthermia by assessing 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 to a nearby emergency department.

Hypnatremia: 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.

Liver Toxicity: People with liver disease will be excluded from study participation. Participants will be monitored for signs of liver toxicity. 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: The investigators will exclude all participants meeting the criteria for substance abuse or dependence within six months prior to screening and all participants who report using ecstasy on five or more occasions or at any time in the past six months. 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.

Receipt of Active Placebo: As part of the active-placebo controlled study design, four of twelve participants will receive active placebo doses of MDMA during MDMA-assisted psychotherapy instead of experimental doses. Participants who receive active placebo dose MDMA during the randomized study segment will have the opportunity to undergo three open-label MDMA-assisted sessions in Stage 2.

Concomitant Medication

Participants are not allowed to take any psychiatric medications throughout the course of the study, with the exception of gabapentin for pain management. This includes antidepressants, anti-anxiety medication and antipsychotics.

For one week preceding each experimental or open-label MDMA-assisted psychotherapy session and by extension including the entire day of the experimental or open-label session, participants may not take any herbal supplement, nonprescription or prescription medication except any supplement or medication that the investigator has reviewed and given prior approval for use. However, participants may take these medications at all other times during the study.

Medications allowed throughout the study include birth control pills, non-steroidal anti-inflammatory medication (as aspirin, ibuprofen), acetaminophen and thyroid hormones. Specific anxiolytics, as benzodiazepines, may be administered to treat insomnia or anxiety more than 24 hours after an experimental or open-label session.

Efficacy Variables & Analysis

Global CAPS scores assessed six weeks after the third experimental (blinded) session will serve as the primary endpoint for assessing treatment efficacy. An independent rater who will not be present during any experimental or non-drug assisted sessions will administer the CAPS at baseline and again six weeks after the third experimental session. 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. CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [52, 53].

The primary endpoint of six weeks after the third experimental session was chosen to take place after all three experimental sessions of active placebo or experimental dose MDMA and after the participant had completed the course of psychotherapy for the study. The endpoint was also selected to make it comparable with the primary endpoint employed in earlier and ongoing sponsor-supported studies of two months after two experimental sessions. The endpoint is intended to examine the stability of response and to avoid any immediate effects of the experimental sessions.

Secondary endpoints for assessing efficacy will also occur six weeks after the third experimental (blinded active placebo or experimental dose MDMA) sessions, and will include scores on the PTSD Diagnostic Scale (PDS) and assessing symptoms of depression with the Beck Depression Inventory (BDI). The PDS was designed to assess PTSD following DSM criteria [54, 55]. 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 Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms [56, 57] that will serve as a measure of depression. It takes five to ten minutes to complete.

PTSD and depression symptoms will be assessed in people enrolled in the open-label Stage 2 study segment six weeks after the third open-label session in order to compare PTSD symptoms at the start of the study, after receiving active-placebo dose MDMA and after experimental-dose MDMA.

The final endpoint for assessing neurocognitive function after active-placebo or experimental dose MDMA-assisted psychotherapy will also occur six weeks after the third experimental session, with scores at this time compared with baseline performance. The RBANS, a battery of neurocognitive tests [58] and the PASAT, a measure of information processing speed and efficiency [59] will all be administered at these two time points. The RBANS is used to support the broad-based assessment of multiple cognitive domains with index scores for immediate memory, visuospatial/constructional, language, attention, and delayed memory. The PASAT is a sensitive measure of information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction.

Laboratory Assessments: Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. Urinary screens for drugs of abuse and pregnancy will be performed just prior to each experimental or open-label session; all other laboratory tests will be performed as part of screening for study

enrollment. Tests will include assessment of thyroid and liver function. 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.

Side Effects and Adverse Events: The investigators will record spontaneously reported side effects during and for one week after each experimental or open-label session.

Adverse events that will be collected for the duration of the study include any events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions and any adverse event leading to withdrawal from the study.

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 the medical monitor or the sponsor study monitor.

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.

Statistical 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 dose) 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 examining 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, and by correlating PDS and BDI scores at each time of administration.

The investigators will examine the effects of psychotherapy combined active placebo versus experimental dose MDMA 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 open label 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.

Safety of MDMA-administered psychotherapy will be assessed by performing descriptive statistics of 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.

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A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

(To be submitted to Ethics Board Health Canada and, if approved, to FDA under IND#63,384)
[November 17, 2008]

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Study Period	2008-2009

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Introductory Statement

This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). This study has been designed as part of an international, multi-site program of research sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org), a USA-based non-profit research and educational organization. MAPS' long-term goal is to develop MDMA into a prescription medication approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA) and Health Canada. MAPS is currently the only organization in the world of which we are aware sponsoring research into the therapeutic potential of MDMA.

MAPS is currently sponsoring under FDA IND #63,384 a nearly completed pilot study of MDMA-assisted psychotherapy in 21 patients with treatment-resistant posttraumatic stress disorder (PTSD), taking place in Charleston, South Carolina under the direction of Dr. Michael Mithoefer. Twenty out of 21 subjects have already completed the protocol. The final experimental session for the 21st subject occurred on July 18, 2008 and the final two-month follow-up evaluation will take place around September 18, concluding the study. Preliminary results are remarkably promising with no drug-related Serious Adverse Events (SAEs) and statistically significant results supporting the efficacy of MDMA-assisted psychotherapy (Wagner 2008, personal communication). A separate longer-term follow-up of participants a year or more after study participation has been approved by our IRB and will be initiated soon.

MAPS is sponsoring two additional ongoing pilot studies of MDMA-assisted psychotherapy in patients with PTSD, one in Switzerland under the direction of Dr. Peter Oehen, and one in Israel, under the direction of Dr. Moshe Kotler, Chair, Department of Psychiatry, Tel Aviv University, Sackler School of Medicine, and former Chief Psychiatrist of the Israeli Defense Forces. Both of these studies are designed for twelve subjects and are scheduled to be completed before the end of 2009. All studies are using the same primary outcome variable, the Clinician Administered PTSD Scale (CAPS), enabling examination of results across all studies, and meta-analyses of data pooled across each pilot study. All of MAPS' studies conducted outside of the US have been approved by regulatory authorities in those countries and have been submitted to FDA and are also being conducted under FDA IND 63,384.

MAPS has also helped initiate and fund an FDA-approved study investigating MDMA-assisted psychotherapy in people with anxiety related to advanced-stage cancer. This study is taking place at Harvard Medical School's McLean Hospital, under the direction of Dr. John Halpern MD, the Sponsor/Investigator. The second of twelve subjects has been enrolled. The first subject has completed the study safely with reports of reduced anxiety and pain (Halpern 2008).

This proposed Canadian pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, eight of 12 people will receive a dose of MDMA expected to be fully therapeutic (experimental dose) and four of 12 will

receive threshold "active placebo" dose of MDMA during three sessions scheduled three to five weeks apart. PTSD symptoms will be assessed at baseline on entry to the study and six weeks after the third double-blind MDMA-assisted psychotherapy session. Cognitive function will also be assessed at baseline and again six weeks after the third experimental session. Study participants will also receive psychotherapy before and after each day-long experimental MDMA-assisted psychotherapy session.

Participants who received active placebo during the course of the randomized study segment have the opportunity to take part in a second study segment that follows nearly identical procedures, but with participants receiving experimental dose MDMA in an open-label context.

MDMA is a ring-substituted phenylisopropylamine derivative invented by the Merck pharmaceutical company in 1912 that bears structural and pharmacological similarities to both the stimulant amphetamine and the psychedelic drug mescaline. It was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s (Freudenmann et al. 2006; Shulgin 1986). In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of extensive non-medical use (Greer and Tolbert 1986; Saunders 1993; Stolaroff 2004). Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

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

MDMA became illegal in the US and then internationally shortly after a rise in use of MDMA outside the confines of psychotherapy. Ecstasy (material represented as MDMA) continues to be used throughout the world. Serious adverse events such as hyperthermia,

hyponatremia or liver damage have occurred in association with ecstasy use, though these are relatively rare given the widespread use of ecstasy. It is notable that the purity and potency of illicit ecstasy is often unknown. Recent surveys of ecstasy tablets indicate that up to 40% are adulterated or contain no MDMA (Baggott et al. 2000; Cole et al. 2002). There is evidence that the use of frequent, high doses of Ecstasy in uncontrolled settings exacerbates its risks. The majority of serious adverse events after Ecstasy consumption have occurred in conditions of high ambient temperature, long periods of strenuous activity (dancing) and insufficient or uncontrolled fluid intake. All of these environmental circumstances may enhance or exacerbate problematic effects of Ecstasy. By contrast, people taking part in MDMA-assisted psychotherapy do not experience these behavioral or environmental factors.

Initial Phase 1 human trials of MDMA in approximately 390 subjects have demonstrated that the drug can be administered safely under controlled conditions. No drug-related Serious Adverse Events (SAEs) have been reported during the course of the ongoing MDMA/PTSD Phase II studies in the US, Switzerland and Israel. Preliminary examination of neuropsychological data from the US study has found no deterioration in condition after MDMA-assisted psychotherapy.

If data from MAPS' pilot studies continue to produce promising results, then MAPS will use the information gathered from these studies to formulate two large (N = approximately 280) multi-site Phase III studies of MDMA-assisted psychotherapy, one to be conducted throughout the United States and Canada and one to be conducted throughout Europe and Israel. MAPS' Clinical Plan (Doblin 2002) estimates that this process will require at least five years and will involve at least 560 subjects.

Background

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

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

PTSD affects an estimated 8% of the general population at some point during their lifetime (Kessler et al. 1995), as reported in a national survey of mental disorders in the general population of the US. There are still questions concerning what are the best treatments for this debilitating psychiatric disorder (Montgomery and Bech 2000). People

with PTSD face challenges in relationships and with work productivity (Brady et al. 2000). An array of psychotherapeutic options exists for treating PTSD, and two SSRIs (Zoloft and Paxil) are approved as PTSD treatments in the US. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies (Foa et al. 1999; Resick and Schnicke 1992), and at least one study of Paxil indicated that men with PTSD did not respond to this drug (Brady et al. 2000). These findings suggest that there is still substantial need for innovative treatments for PTSD.

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including subthreshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased to 10.3%. (Perkonigg et al. 2000). A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate (Frise et al. 2002). A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers who were deployed more than once (Richardson et al. 2007). These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD is clearly a public health problem that causes a great deal of suffering and accounts for a significant portion of health care costs. Acting Inspector General Jon A. Wooditch testified to the US Congressional Committee On Veterans' Affairs Subcommittee On Disability Assistance And Memorial Affairs that in 2004, the US Veterans Administration spent over $4.3 billion on disability payments to over 215,000 veterans with PTSD (2005). The search for novel and more effective treatments is therefore of major public health and economic significance. In the US National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In either subgroup, more than one-third of the patients still had symptoms several times per week after 10 years (Kessler et al. 1995). Generally, the number of people who do not improve after treatment can be high, between 40% and 60%. In a 2002 comparison of two types of psychotherapy for women with PTSD after sexual assault, 47% of each treatment group still were diagnosed with PTSD with high enough CAPS scores (Resick et al. 2002) and another study reported similar figures (Foa et al. 1999).

PTSD and MDMA-assisted psychotherapy

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

undergo more than one treatment to reduce or resolve PTSD symptoms (Hamner et al. 2004). However, a recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD (Benish et al. 2008).

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients (Greer and Tolbert 1998; Metzner and Adamson 2001; Stolaroff 2004; Widmer 1998). Treatment consists of several administrations of MDMA-assisted psychotherapy within the context of a brief to moderate course of non-drug psychotherapy. MDMA-assisted psychotherapy is hypothesized to reduce or ameliorate the hypervigilance and emotional numbing and withdrawal experienced by individuals diagnosed with PTSD.

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

Treatment goals for posttraumatic stress disorder include alleviating symptoms and interrupting the stress-induced neurochemical abnormalities produced by the condition. One approach is to discover drugs that directly counteract these neurobiological changes. Paxil and Zoloft are the only two drugs approved by the FDA in the US for treating PTSD, and are known to affect the serotonergic components of PTSD. They may also block the down-regulation of brain-derived neurotrophic factor, but it is not known whether it can arrest and reverse the hippocampal atrophy found in PTSD (Nibuya et al. 1996). Another approach to treatment of PTSD is to develop drugs and/or psychotherapeutic treatments that will indirectly interrupt the destructive neurobiological changes by decreasing or eliminating the stress reactions to triggers and the chronic hyperarousal of PTSD. Reports of past experience with MDMA-assisted psychotherapy suggest that it may also counteract the effects of PTSD. In fact, the biologic and psychotherapeutic approaches overlap and re-enforce each other. Knowledge about the connections between the neurobiological and the therapeutic effects of MDMA is far from complete, but it has been observed that MDMA acutely decreases activity in the left amygdala (Gamma et al. 2000). This action is compatible with its reported reduction in fear or defensiveness, and is in contrast to the stimulation of the amygdala observed in animal models of conditioned fear, a state similar to PTSD (Davis and Shi 1999; Rasmusson and Charney 1997).

To date, Phase I trials have been conducted by eight research teams in the United States, England, Spain, Switzerland, and the Netherlands, with MDMA administered to approximately 390 subjects overall without the occurrence of any serious adverse events (see for example Cami et al. 2000b; Chang et al. 2000; Dumont and Verkes 2006, review;

Kolbrich et al. 2008; Kuypers et al. 2008; Tancer and Johanson 2003; Vollenweider et al. 1998), When MDMA is used in doses similar to those proposed for this study, and in a controlled setting, the risk/benefit ratio is favorable. By and large, MDMA appears to have risks that are similar to those of other structurally-related sympathomimetic compounds (Mas et al. 1999; Tancer and Johanson 2003), such as amphetamine (Adderall), that have been used clinically for many years.

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

There has been no evidence of significant or lasting toxicity in subjects participating in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens (e. g.Hatzidimitriou et al. 1999; Lew et al. 1996; Sabol et al. 1996) and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Reneman et al. 2001; Thomasius et al. 2003). In contrast, all available Phase I data indicate that it is unlikely that the MDMA exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. As described in more detail below, more recent retrospective and prospective studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity. Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.

Previous Clinical Experience with MDMA

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

individuals with mild to moderate psychological difficulties reported obtaining 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 [redacted] 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. Pacey 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. Pacey'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**
Active Placebo	25 mg	12.5 mg	37.5 mg
Experimental Dose	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					
Visit #	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	Intro psychotherapy2	Intro psychotherapy3	Experimental 1	Integrative Therapy1	Integrative Therapy2	Integrative Therapy3	Experimental 2	Integrative therapy4	Integrative Therapy5	Integrative Therapy6	Experimental 3	Integrative Therapy 5	Integrative Therapy6	Integrative Therapy7	6 wk post V11	End Randomized Segment
Approximate Study Day			0	7	14	21	28	29	35	42	49	50	56	63	70	71	78	88	112	113
Visit Timing and Windows		Post telephone	[Post-consent, may be same day	(-4/+3 d)	Post V4	Post V5	post V6	24 h post-experim. session 1	Between V8 and V11	Post-V9	>3<5 wks post V8	24 h post V11	Post V11	Post V13	>3<5 w 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	Physician, 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	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		
Psychotherapy-No Drug				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				X					
Psychotherapy + MDMA							X				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					
Overnight stay							X			X	X				X					
Serious Adverse Events			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	
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	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															
CAPS		X														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	2nd 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 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 [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 0f 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