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Therapeutic Products Directorate

Direction des produits thérapeutiques

To/A:	Dr. Carole Legare Acting Director Office of Clinical Trials
From/De:	Dr. Beata Wiatrowska Clinical Group II Office of Clinical Trials

Security – Classification – de sécurité:
HC Protected
Date: 05/09/13

**Subject/
Objet:**

**Pharmaceutical Safety and Efficacy Assessment –
Clinical Trial Application Amendment**

PSEAT-CTA(A) GRP(PSE)-01-2(v1): Draft Date 2006/11/06

Brand (Proprietary) Name of Drug Product	MDMA	
TPD Target Date	07/09/13	
Control No. / File No.	167090	9427-M2544-21C
Parent Application Control No.	127822	

Reviewer Recommendation	It is recommended that a No Objection Letter be issued.
Reviewer Signature	

Clinical Trials Group II Manager Decision / Date	Agree with above recommendation.	<i>Sept. 6/13</i>
Manager Name	Dr. L. Bouthillier	
Manager Signature		

1. AMENDMENT SUMMARY

Trial Title and Number:

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada

PROTOCOL MP-4

Product:

3,4-methylenedioxymethamphetamine (MDMA)

Brief Summary of Change(s) and Rationale:

This amendment is being submitted prior to study start and is necessary due to the amount of time that passed between the original protocol approval to the time MAPS was allowed to import study drug. During the four years since the original approval the overall MDMA/PTSD development plan has progressed as studies have been completed, this amendment brings the protocol inline with the current Phase 2 program. This amendment reflects the most up to date study design, timing of treatment and selection of doses that MAPS is now investigating as part of the overall dose response investigation across multiple Phase 2 studies. The primary changes in Amendment 1 Version 2 effect the study design, cross over time point, timing of the primary endpoint, Stage 2 dosing and the addition of obfuscation to the informed consent. The primary changes are discussed below as well as in section 2.0. There are additional changes throughout the protocol that do not effect design but provide additional detail to procedures, provide clarifications or are administrative changes based on our new protocol template. A protocol in track changes is being provided as well as the summary of changes to document all changes in detail.

Summary of Design Changes

The protocol design has been amended to move the primary endpoint assessment of PTSD symptoms and unblinding from after the third experimental session to one-month after the second blinded experimental session. This change and the alignment of all study visit time points brings the study design into accordance with the timing of the primary endpoint and visits of other MDMA/PTSD Phase 2 studies in the clinical development plan.

Full dose subjects will still have three full dose experimental sessions as in the original approved protocol. The first two experimental sessions will be blinded. After unblinding, only full dose subjects will continue onto the 3rd experimental session and associated

integrative sessions in Stage 1. Upon unblinding at the primary endpoint, subjects in the comparator dose group will cross over from Stage 1 to Stage 2 after two instead of three experimental sessions. Previously, unblinding was after the third experimental session at the two-month follow-up. Subjects who received the comparator dose during the blinded portion of the study will continue to have the opportunity to cross over to Stage 2 and receive three experimental sessions. Stage 2 procedures and schedule will be similar to Stage 1 but will be open label. The doses in Stage 2 have been amended from full dose MDMA to explore the optimal therapeutic dose of MDMA. Subjects in Stage 2 will receive an initial dose of 100 mg at the first experimental session, either an initial dose of 100 mg or 125 mg MDMA at the second and third experimental sessions based on the opinion of the therapist team. The supplemental doses for each session will be half of the initial dose, respectively.

The crossover is three months earlier than the previous protocol version that required three experimental sessions for all subjects in Stage 1. This was done to decrease the amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether the treatment method will involve two rather than three experimental sessions. Based on our experience in previous studies, in those who have received a low or active placebo dose, we believe it is safe to administer three low dose sessions, but it may create an unnecessary hardship for subjects by extending their treatment at low and medium doses. We believe that only two sessions prior to unblinding are likely to demonstrate significant separation between the comparator dose group and the full dose group based on completed MDMA/PTSD studies sponsored by MAPS.

As a part of MAPS' ongoing efforts to optimize the double-blind of MDMA-assisted psychotherapy studies, subjects will be informed of the two groups that they may be randomly assigned to, but a level of obfuscation will be added to the informed consent process during the blinded portion of the study. The sponsor is currently exploring two approaches to successful maintenance of the double blind. One of these approaches is a dose-response design, which is already being tested in an ongoing MAPS-sponsored Phase 2 study in veterans and first responders in the USA. One complication of this approach is that confusion about the condition assignment is based on the subjective effects of the drug, which are likely to be proportional to the dose the subjects receive. If the subjective effects of the lower dose are large enough to confuse a subject about the dose they receive, the dose may also have some level of efficacy. One potential approach to this issue is to add obfuscation to the informed consent process in which subjects would be told they would receive either an inactive placebo or one of several doses of MDMA. Then subjects would be asked to guess if they received active MDMA or placebo to enable assessment of the double blind. In order for the lower dose to be confused with a full dose of MDMA, the informed consent form states that the comparator may or may not have MDMA. The obfuscation is for a limited period during treatment until subjects are fully debriefed upon unblinding after only two blinded drug-assisted sessions. The research cannot be practically conducted without this alteration to the protocol because obfuscation will make it possible for subjects to be less certain of the identity of the comparator.

A long-term follow up assessment has been added to the study, with symptoms assessed 1 year after a participant has had a final MDMA-assisted psychotherapy session. A number of secondary changes occurred in this amendment as a result of the addition of the long-term follow-up, including changes in wording and instructions concerning collection of adverse events and the use of a memory aid card for use between the final study visit and the long-term follow up assessment.

Finally, the protocol has been restructured. Some sections appear earlier in the Amendment than in the original protocol, and the section containing Pharmacology included in the original study protocol is omitted from the Amendment. Most of the information within the omitted section can be found in the 6th edition of the Investigator's Brochure. Changes were made to sections that are associated with the major changes discussed above these include updates to the protocol objectives, visit descriptions, time and events and analysis sections.

Grammatical changes were made throughout in order to accommodate the changes to the protocol. In addition, corrections to spelling and sentence structure have been updated for readability. These types of changes are not included in the change list below.

Due to the amount of changes in this protocol, a red-line version of the protocol will be provided to view exact changes (SEE THE HARD COPY)

Systematic Changes Effecting Multiple Sections

1. The PI has established Research Affiliate status with the Center for Addiction Research in British Columbia (CARBC) as a part of the University of Victoria in order to support qualifications for the study.
2. The study synopsis has been revised to match the Sponsor's new synopsis template, which no longer includes the inclusion/exclusion criteria and now includes protocol objectives, measures, procedures for recruitment and statistical analysis as well as an abbreviated study flowchart.
3. The Time and Events Table has been revised to match updated study procedures, and a new Summary of Events flowchart has been added to graphically depict study procedures.
4. Updated language throughout to match new template wording. Section numbers have been added to each section with numbers alongside headers, with the List of Abbreviations given the first number of 1.0, to provide a clear way to reference portions of the protocol. Rationale: This was done to make it easier to read and follow the protocol and to locate and reference specific sections of the protocol.
5. The protocol title has changed to reflect the study design. It is now titled "A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12

Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada”

6. A list of abbreviations now appears prior to the text of the protocol to provide clarity while reading the protocol.
7. “Principal investigator” and PI have been replaced by the terms “clinical investigator” and “CI” throughout the document.
8. Updated all sub-sections in 3.0 Background information with most recent scientific literature and results of clinical trials with MDMA-assisted psychotherapy for PTSD. Updated the purpose to be consistent with the new design.
9. A level of obfuscation was added to the informed consent process to better mask the blind. The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of 50 mg of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive full dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint assessments when unblinding occurs. Section 5.0 on Informed Consent has been revised to include this information as well as procedures for withdrawal of consent. The informed consent quiz has been removed in line with current procedures in MAPS-sponsored studies. Subjects will complete the informed consent process with the PI to ensure that accurate and thorough information is provided about the study in verbal and written form.
10. The plan for subject recruitment has been updated to reflect how this will be conducted for the subject population. Recruitment will now include the use of advertisements and announcements on internet sites, including the sponsor site.
11. Clarity was added to the overall study objective in light of completed studies of MDMA-assisted psychotherapy and the development of a Treatment Manual. Study Objectives have been rewritten so that there is a single primary study objective and so that secondary objectives address newly added measures.
12. The Primary Objective has been updated to reflect the unblinding at the primary endpoint after the second experimental session.
Previously: “Assess changes in PTSD symptoms as measured via Clinician-Administered PTSD Scale (CAPS) scores in Stage 1 in participants receiving the active placebo vs. full dose of MDMA-assisted psychotherapy.”

Now: "Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session. This update was to reflect the unblinding at the primary endpoint after the second experimental session."

13. The Secondary Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session. Additional secondary objectives describing process measures were added regarding adherence to the Treatment manual, belief of condition assignment, testing the two vs. three session treatment model, and exploration of the role of non-ordinary states of consciousness immediately after experimental sessions.

14. The Safety Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session and the proper assessment timeline to support the updated primary endpoint, but also added the Visual Analog Scale to collect changes to pre-existing tinnitus and/or chronic pain symptoms, specifically in subjects with a medical history of tinnitus and/or chronic pain. Objectives related to the RBANS and PASAT were moved from outcome measures to safety measures to appropriately reflect the goal of assessing neurocognitive function after MDMA-assisted psychotherapy. The safety objective concerning measures of cognitive function has been revised with the study design.

15. The RBANS and PASAT will be administered at a third visit two months after the third Stage 1 or Stage 2 session to assess the safety effects of MDMA in people who have all received full dose MDMA during the course of the study. The measures of cognitive function will be assessed via RBANS and PASAT again two months after the third Stage 1/Stage 2 experimental sessions in addition to baseline and primary endpoint assessments. The administration of a repeatable test battery will confirm and extend data concerning any potential effects of MDMA on cognitive function. At the secondary endpoint, most participants will have had received the maximum cumulative exposure of MDMA for the study.

16. The addition of the following assessments:

DES-II: Dissociation Experiences Scale II- The DES-II is a 28-item selfreport measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory. It is an established measure of dissociative symptoms. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms. Subjects will complete the DES-II at the same time as the CAPS is administered according to the Time and Events Table. Dissociation and

depersonalization are likely to be added to symptoms of PTSD with the upcoming revision of the DSM, DSM-V. In order to compare the prevalence of these symptoms to future studies that may use the DSM-V, this secondary measure will be used.

□ The NEO-PI (Neuroticism-Extroversion-Openness Personality Inventory-Revised) will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.

□ PSQI: Pittsburgh Sleep Quality Index- The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers.

□ SOCQ: States of Consciousness Questionnaire- The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues. It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day, and results will inform comparison of MDMA to the subjective effects other psychoactive drugs that have been studied with this measure.

□ Changes in Tinnitus or Pain using the Visual Analog Scale: A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain. The changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from “None” to “Worst Case Imaginable”. This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response. Changes will be collected in subjects presenting with a history of either. PTSD, chronic pain, and tinnitus are frequently co-morbid. In order to track the prevalence and variation in symptom severity of chronic pain and tinnitus symptoms for accurate collection of any exacerbations as Adverse Events, or any improvements in the symptoms as a result of study participation, this new measure has been added.

□ Perceptions of experimental sessions: Perceptions of the experimental sessions will be collected from each full dose subject during the primary endpoint visit after unblinding and from Stage 2 subjects during the secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage 2. Perceptions will be collected again at the end of Stage 1/Stage 2. These perceptions are collected as a part of the sponsor's

ongoing initiative to assess the therapeutic value of the third experimental session and information on the optimal therapeutic dose of MDMA.

□ The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [133, 134]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions.

□ Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

□ The revised Beck Depression Inventory, or BDI-II, will be used in place of the BDI.

□ The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the self or others.

□ The NEO-PI will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.

□ The suicidality assessment Adult Suicide Ideation Questionnaire (ASIQ) will be replaced with the Columbia Suicide Severity Rating Scale (CSSRS), and it will be administered more frequently than in the original study design, according to U.S. FDA requirements for psychiatric clinical trials. The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial. The C-SSRS will be performed by the PI at baseline, and repeated throughout the protocol to assess suicidality.

□ The long-term follow-up assessment will include a questionnaire concerning perceived benefits and harms of study participation and views concerning study participation.

17. Changed the comparator dose from 25 mg with an optional 12.5mg supplemental dose to 50 mg with an optional 25mg supplemental dose. Changed wording describing the lower dose from "Active Placebo" to "Comparator Dose" for consistency amongst protocols in describing the slightly higher 50mg dose. This change was made in line with the sponsor's progression through the clinical

development plan and completion of a study with the 25mg active placebo dose in the interim of the approval process for this study. Section 12.1 Statistical Power was updated to reflect the estimated effect size based on completed studies.

18. Defined and clarified treatment resistant subjects as those who “were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to either:

- a. Inability to tolerate psychotherapy for PTSD (e.g. persistent “overengagement” when attempting Prolonged Exposure Therapy).
- b. Inability to tolerate psychopharmacology for PTSD due to treatment emergent side effects;”

19. Addition of five new inclusion criteria of subjects who “Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by Clinical Investigators in the event of a subject becoming suicidal; those who “Agree to inform the Clinical Investigators within 48 hours of any planned medical interventions;” those who “Agree to have all clinic visit sessions recorded to audio and video;” those who “Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.” and those who “Are at least 21 years old.” These criteria were added to ensure that the results of the study are clearly attributed to the investigational treatment, that the recruitment population is clearly captured in the criteria, and that subjects are willing to share personal and medical information with the investigators.

20. Revision of the inclusion criterion for subjects who “Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control” to also allow for subjects “on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.” Instructions for medication tapering were added to Section 14.4 in the form of a table and additional wording describing the timing of preparatory sessions with medication tapering was added to Section 7.3 Study Duration and Visit Windows.

21. Addition of one exclusion criterion #12, those who “Have any current problem, which in the opinion of the Principal Clinical Investigator or Medical Monitor, might interfere with participation in the study.” The sponsor is continuing to refine exclusion criteria for the treatment in preparation for Phase 3 studies, and will collect information on problems that may interfere with treatment through this criterion.

22. Moved unblinding to after the second experimental session, rather than the third. This was done to decrease the amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether our treatment method will involve two rather than three experimental sessions.

23. CAPS score was raised to 60 from 50. The CAPS score cutoff was raised to 60 in order to work with more severe PTSD cases and to avoid floor effects.

24. The Amendment clarifies that a single consent form will cover Stage 1 and Stage 2. The revision was made so that enrollment includes the possibility of entering stage 2. Subjects who are eligible for stage 2 and do not wish to enroll can withdraw from the study.

25. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.

26. The amounts of MDMA encapsulated for Stage 1 has been updated to: 125 mg, 62.5 mg, 50 mg, and 12.5 mg. Previously, 125 mg, 62.5 mg, 50 mg, and 25 mg, were to be created. Section 8.0 has been revised to accommodate changes in dosing strategy for Stage 1 and Stage 2. New tables and text were provided for clarity to describe the various doses of study drug to be employed, and drug labels were revised in accordance with Health Canada regulations.

27. Section 9.1 and 9.2 were revised to match the Sponsor's new web-based randomization program requirements that will enable real-time drug accountability and randomization tracking.

28. Reference to Emergency Unblinding Envelopes has been removed, as the site should now contact the sponsor, if needed. If there is an emergency requiring knowledge of subject's condition assignment, the blind may be broken for an individual subject. The investigator may be provided with the condition assignment in case of emergency through the web-based randomization system. At any time the unblinded Randomization Monitor can be contacted if assistance is needed.

29. Section 9.4 Visit Descriptions have been re-written for clarity and to align with the new study design and assessments.

30. Section 10.0 "Removal of Subjects from Therapy or Assessment" has been updated with language to provide clarification on study procedures relating to collecting follow-up data on subjects removed from the study. Subjects removed

from the study may still be assessed at long-term follow up if possible for an intent-to-treat analysis. This analysis will address the potential that outcomes for the study will only be assessed in subjects who are likely to complete the study.

31. Section 12.0 Data Analysis has been updated to reflect the new study design and primary and secondary endpoints.

32. Section 12.1 Statistical Power has been revised to calculate power using comparator dose and full dose and information drawn from publications of data from sponsor-supported studies. The statistical power has been updated to reflect new information concerning sponsor-supported research and the comparator dose.

33. Section 13.0 is no longer titled “Monitoring for Toxicity”. Plans for Risk Mitigation were moved from the Appendix to Section 13.0, and it is now titled “Risk Mitigation”. The section was shortened to include only relevant information to the protocol. All other more specific and in-depth information is contained in the Investigator’s Brochure. In line with recently completed and published MDMA/PTSD studies, the potential for toxicity during experimental sessions was found to be minimal and adequately covered under Section 16.0 “Risks of Participation,” Likewise, Section 13.1 “Medical Emergencies” has been updated with information on number of experimental sessions and that adverse events during sponsor-supported studies generally resolved without requiring medical intervention.

34. Section 14.0 “Adverse Events” has updated contact information for medical monitors, describes the use of memory aid cards for the interval between final stage 1 or stage 2 visits and long-term follow up, and details the types of adverse events collected during the course of the study. The AE collection information was updated to provide information related to study staff and requirements for AE collection during the long term follow up. In addition, all AEs related to changes in psychiatric status will be collected throughout the study to provide for further capturing of psychiatric AEs.

35. Section 14.3, previously titled “Commonly Expected Side Effects” is now titled “Spontaneously Reported Reactions.” These expected reactions were updated with the most recent information and MDMA program collection. They are referred to as reactions with the understanding that the side effect profile of MDMA-assisted psychotherapy will only be determined post-approval.

36. Concomitant Medication collection and tapering instructions have been updated. A table containing commonly prescribed psychiatric medications and their halfMAPS lives is provided. Memory aid card information is now provided. This section has been updated to match the amended AE collections, particularly during the interval after the final stage 1 or stage 2 site visit and long-term follow up, and to provide clarity and information on all medications and tapering of pre-study medications throughout the protocol. The table permits informed estimation of

appropriate tapering procedures.

37. Section 14.5 Clinical Laboratory Assessments has been updated to reflect the full panel of tests to be performed for thorough medical evaluation prior to enrollment and accurate assessment of adverse events that could be related to treatment.

38. Section 15.0 Study Monitoring, Auditing and Documentation has been updated with new template language. Language was added to this section to provide consistency across MAPS studies and compliance with GCP.

39. Section 16 "Risks of Participation" has been revised for clarification, to include risk mitigation information previously under other sections and to encompass the literature and data from Sponsor-supported research. The risk section contains relevant information on the risks of receiving MDMA. Information originally in "Risk Mitigation" is contained within this section.

40. The section "Risk/Benefit Analysis" is no longer present in the protocol. The section was removed in line with sponsor protocol template design. The risks and benefits of the research are detailed in the "Introduction" and "Risks" sections. A thorough Risk/Benefit Analysis is not possible in a single pilot study with this sample size, and would be influenced by findings from multiple studies. As such, the Risk/Benefit Analysis will be conducted on an ongoing basis across multiple Phase 2 studies supported by the sponsor and is likely to change across the duration of this study.

41. Section 18.0 Confidentiality was revised to reflect the Sponsor's updated procedures and requirements for ensuring confidentiality of study data kept in digital media.

42. Section 22.0 Record Retention describing the conditions of record storage and responsibilities of the investigator concerning length of record retention has been added in compliance with agency regulations.

43. Section 21.0 "Publication Policy" was added to the protocol to include the Sponsor's updated publication policy in line with previous and future publications of Phase 2 pilot studies in the clinical development plan.

44. The section that was previously Chemistry and Manufacturing and Control has been removed as it is contained in the Investigator's Brochure in line with the sponsor's new protocol template.

45. Appendices describing facilities and visit by visit descriptions have been removed from the protocol. Study procedures are now described in a visit by visit fashion to improve compliance with the protocol. Facilities are only listed in the title page and are no longer part of the protocol template.

46. Draft case report forms are no longer present as an appendix. Draft case report forms are no longer part of the protocol template as the sponsor plans on utilizing Electronic Data Capture (EDC) for this study.2. **OVERALL ASSESSMENT**

The proposed changes include, among others: move of the unblinding to after the second rather than third experimental session decreasing exposure of the patients assigned to the comparator group, decrease of the initial dose in Stage 2 to 100 mg from 125 mg, stricter inclusion/exclusion criteria, including raising of CAPS (severity of PTSD) score from 50 to 60 (see points 19, 21, 23), addition of several scales measuring various effects of the study drug (see point16) and introduction of a follow-up at 1 year, all of which potentially contribute to increase in patients safety during this study. The comparator dose is changed from 25 mg with an optional 12.5 mg supplemental dose to 50 mg with the optional 25 mg supplemental dose; that for the consistency amongst protocols. That dose has been used previously as a comparator and is acceptable.

Overall the proposed changes do not adversely affect patients' safety and therefore are acceptable. NOL is proposed for this amendment.

Subject: Recommendation for Inspection

From/De: Dr. Beata Wiatrowska Clinical Group II	Date: 05/09/13
File Number	9427-M2544-21C
Control Number	167090
Protocol Number	MP-4
Protocol Title	A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada
Recommendation for inspection	No
Priority for inspection	N/A
Rationale for the recommendation Rationale may include: <ul style="list-style-type: none"> - phase in the drug development process - complexity of the CT design - inadequate information in the protocol - subject population - level of risk to patients - novel therapies/dosage forms - clear deviations from reporting requirements - frequent protocol deviations - themes or trends - trial size - small/inexperienced sponsor - other (provide details) 	



Therapeutic Products Directorate
 Direction des produits thérapeutiques

To / A: [Dr. Carole Legare], Director, Office of Clinical Trials	Security – Classification – de sécurité: HC Protected
From / De: [Paul Smeaton], Manager, Clinical Trials Quality Division, Office of Clinical Trials	Date: [2013-08- 23.]

Subject / Quality Overall Summary – Chemical Entities Clinical Trial Application – Phase II
Objet: QOS - CTA GRP(PQ)-01-1(v1): Draft Date 2008/04/07

Brand (Proprietary) Name of Drug Product	MDMA	
Proper, Common or Non-proprietary Name of Drug Substance	MDMA ; 3,4 methylenedioxyamphetamine	
Manufacturer / Sponsor	Multidisciplinary Association for Psychedelic Studies	
Therapeutic Classification		
Dosage Form(s) and Strength(s)	Capsule 12.5 mg; 25 mg; 50 mg; 62.5 mg 100mg and 125mg	
Route(s) of Administration	Oral	
Type of Submission / Phase of Trial	CTA_ Amendment	Phase-I I
TPD Target Date	2013-09-07	
Control No. / File No.	167090	9427-M2544 - 21C
Contact Information	Phone: [REDACTED]	

Reviewer Recommendation	This submission IS recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information		
Reviewer Name	K.Rajkumar	Review Hours	1.5h
Reviewer Signature		Completion Date	2013-08- 23
Panel / Team Leader Signature.			
Report Access	I:\DPQ\Submission\CTA\HIJKLM\Multidisciplinary associates for psychedelic studies\MDMA\167090 cta-2013r01a.doc		
References	Parent CTA 127822		
Attachments			

<Brand name>

1

DRAFT QOS-CE (CTA - Phase II) (2008/04/07)

Evaluator's Introduction/Discussion:

This is a review of response to our Clarifax dated August 19, 2013.

Comment 1

You are requested to revise Section P3.1 to include the number of 100mg capsules manufactured. It is understood that a total of 108 capsules of all strengths will be used in this Canadian clinical trial, please confirm.

Sponsor's Response

See Attachment (hard copy).

Reviewer's comment

According to the response 15 capsules of 100mg strength and a total of 120 capsules of different strengths are made for this clinical trial. This response is considered acceptable.

Comment 2

It is noted in Section P that the weight of each filled capsule is 236.5 ± 1.5 mg whereas, in Section P3.3 the weight of 12.5mg strength is reported as 371.7mg. Please explain this discrepancy.

Sponsor's Response

See Attachment (hard copy).

Reviewer's comment

According to the response, only the blinded capsules has a weight of 236.5 ± 1.5 mg. Since the 12.5mg strength is being administered in open label experiments the weight differs from blinded capsules.

Comment 3

You are requested to justify the change in drug product container closure system from amber glass bottles to clear cellophane packaging. A discussion on the level of protection offered by the proposed container closure system against light, should be included.

Sponsor's Response

See Attachment (hard copy).

Reviewer's comment

The sponsor states that as the molecule does not possess any extended conjugated olefinic bond nor any chemical group that would be expected to be unstable in the presence of light. Furthermore the response claims that one clinical trial from 2003-2009 was completed and five clinical trials are ongoing using MDMA packaged in clear cellophane, as study drug. The response also states amber glass vials were proposed in the parent CTA as that is what the Kerrisdale Pharmacy had available at the time. This issue will not be pursued any further.



Therapeutic Products Directorate
 Direction des produits thérapeutiques

To / A: [Dr. Carole Legare], Director, Office of Clinical Trials	Security – Classification – de sécurité: HC Protected
From / De: [Paul Smeaton], Manager, Clinical Trials Quality Division, Office of Clinical Trials	Date: [2013-08- 19.]

Subject / Quality Overall Summary – Chemical Entities Clinical Trial Application – Phase II
Objet: QOS - CTA GRP(PQ)-01-1(v1): Draft Date 2008/04/07

Brand (Proprietary) Name of Drug Product	MDMA	
Proper, Common or Non-proprietary Name of Drug Substance	MDMA ; 3,4 methylenedioxyamphetamine	
Manufacturer / Sponsor	Multidisciplinary Association for Psychedelic Studies	
Therapeutic Classification		
Dosage Form(s) and Strength(s)	Capsule 12.5 mg; 25 mg; 50 mg; 62.5 mg 100mg and 125mg	
Route(s) of Administration	Oral	
Type of Submission / Phase of Trial	CTA_ Amendment	Phase-I I
TPD Target Date	2013-09-07	
Control No. / File No.	167090	9427-M2544 - 21C
Contact Information	Phone: [REDACTED]	

Reviewer Recommendation	This submission <IS NOT> recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information		
Reviewer Name	Udai Gill	Review Hours	6. + 1
Reviewer Signature		Completion Date	2013-08- 19
Panel / Team Leader Signature			
Report Access	I:\DPQ\Submission\CTA\HIJKLM\Multidisciplinary associates for psychedelic studies\MDMA\167090 cta-2013r01a.doc		
References	Parent CTA 127822		
Attachments	 C:\167090.pdf		

Evaluator's Introduction/Discussion:

This is a review of a phase II CTA- Amendment for a protocol No. MP-4: (amendment 1, version 2)

Title: A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada

Study subjects: 12

Drug product: each capsule contains Active + lactose to reach equivalent weight of 236.5mg ±1.5 mg per capsule.

Compounding is done at Kerrisdale pharmacy in Vancouver BC.
Capsules and lactose certified BSE/TSE free.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION SPONSOR:

We have the following comments with respect to your CTA-amendment for MDMA capsules, Control No. 167090::

- 1. It is understood that total of 108 capsules are manufactured for this clinical study therefore you are requested to revise section P.3.1(manufacture) to include the number of MDMA capsules for 100mg strength.**
- 2. It is noted that the each filled capsule weight is 236.5 mg ± 1.5 mg , section P.1drug product but filled 12.5mg strength capsules weight (371.7mg) is significant different than the other strengths, section P.3.3, Batch formula. Please explain.**
- 3. It is not that the container closure system for drug product is changed to clear cellophane packaging from original amber glass bottle (vials) containing 3gm silica gel desiccant. Please provide a justification for this change.**

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-
Resistant Posttraumatic Stress Disorder (PTSD) - Canada
Amendment 1 Version 2**

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC, University of Victoria

Study Number: M-P4

Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title:

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC, University of Victoria

Co-Investigators: Andrew Feldmar; Zach Walsh, Ph.D R. Psych. Assistant Professor, Department of Psychology, University of British Columbia

Expected Study Dates Sept 15, 2013 – May 2016

Approved by: IRB Services, Ontario Committee, July 12, 2013

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 125 mg (full dose-initial dose), 100 mg (active dose Stage 2-initial dose), 62.5 (full dose-supplemental dose), 50 mg (comparator-initial dose; also active dose Stage 2-supplemental dose), 25 mg (comparator- supplemental dose, and optional titration initial dose for Stage 2), 12.5 mg (optional titration supplemental dose, Stage 2), [Full dose strength capsules are used in Stage 1. Supplemental doses are used in both stages and are administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose; Titration dosing occurs in Stage 2, See Table 1 and 2 for dosage by visit.]

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

Primary Efficacy and Safety Objectives: Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

Safety Objectives: The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (CSSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.
- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

Secondary Objectives:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI)

- at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint

In specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

Study Design and Duration

3.5 Purpose

This Phase 2 pilot study is a randomized, double-blind, dose comparison study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment. After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.

A therapy team will conduct psychotherapy visits according the treatment manual provided. The team will include two licensed therapists who will work together as cotherapists.

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months
- Comparator dose subjects who complete Stage 2: 18 months.

Number of Centres

Assessments of PTSD symptoms and neurocognitive function will also be performed

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the primary study endpoint.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with chronic, treatment-resistant PTSD and with a CAPS score of 60 or higher. Treatment resistance is defined as being unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to inability to tolerate psychotherapy and/or pharmacotherapy. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all of the inclusion criteria without meeting any of the exclusion criteria. Participants must reside in Canada.

Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 50, 62.5, 100 and 125 mg. The initial full dose of MDMA is 125 mg and the supplemental full dose is 62.5 mg. The initial comparator dose is 50 mg, and the supplemental comparator dose is 25 mg. The initial active dose for the first Stage 2 session consists of an initial dose of 100 mg and a supplemental dose of 50 mg, with optional titration doses of 25 mg initial and 12.5 mg supplemental dose available in the second and third open-label experimental sessions of Stage 2. MDMA has been obtained from Lipomed AG. All doses of MDMA will be compounded with the inactive substance lactose to ensure that all the blinded capsules weigh the same amount.

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [1-6]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [3, 11, 12]. The initial full 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 drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25 mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions. The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.

The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

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 1.5 to 2.5 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 the supplemental dose of MDMA is contraindicated or not necessary.

There will be not be any changes in dose regimen across the first two blinded sessions. Full dose participants will receive the same dose regimen during a third session in an open-label context after unblinding per protocol. Subjects in the comparator dose condition will not complete Stage 1, but will continue to Stage 2. In Stage 2, they will receive the active dose for the first Stage 2 session, and they can receive the active or full dose during the second and third sessions via a clinical titration dosing strategy.

If the participant experiences hypertension that required clinical intervention or had a serious adverse event that is possibly or probably related to study drug, then no further doses of MDMA will be administered.

S Drug Substance

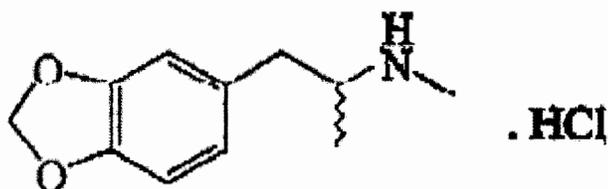
S.1 General Information

The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. [REDACTED] with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by [REDACTED] Switzerland. On January 30, 2006, a quality control analysis was performed by [REDACTED]. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94.1 B5.5 with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually by [REDACTED] between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N- Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report submitted for in Modules 2 and 3 of the CTA approved on March 17, 2009, control # 127822).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.

Step 2: MDA-nitrostyrol + LiAlH₄ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [redacted]. Specifications of manufacture, including solvent and procedures, are translated in the second report of [redacted] in Modules 2 and 3 for CTA approved on March 17, 2009, control # 127822.

S.2.3 Control of Materials

See above and contained in report by [redacted], p. 1

S.3 Characterization:

Batch number is [redacted]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED] One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2 of report supplied in Modules 2 and 3 of CTA approved March 17, 2009, control # 127822).

Validation: From manufacturer, data available upon request ([REDACTED] p. 1).

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] (see attachment and reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(Max)}=1\ 234\ +/-\ 1\ nm$

$E_{mol} = 3800\ +/-\ 500$

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by Brenneisen:

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He1.2 mL/min
Derivatization: MBTFA
Injection: 250 C, splitless 1 µL
Detection: full scan

Identity (HPLC-DAD): TR = 5.8 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289
(M⁺, MDMA-TFA) 154 (basepeak) 162, 289 (M⁺) MDMA-TFA
Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from [REDACTED]

S.4.4 Batch Analysis:

As listed above, the batch is [REDACTED]

Provided on manufacturer's data sheet

Appearance: Conforms to appearance
Identity: IR identical to reference
UV, in distilled water, $\lambda_{(MAX)}.1 = 234.0$ nm
 $\epsilon_{mol}.1 = 3939$
 $\lambda_{(Max)}.2 = 285.0$ nm
 $\epsilon_{mol}.2 = 3688$
Melting point = 148.9 to 149.7 C
Purity HPLC = 99.66%
Freebase content: 83.51%
Water content: 055%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: **Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%**
Tests for presence of heavy metals: **Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm**

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED], and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [REDACTED] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment 4 in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

[REDACTED] reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

[REDACTED] also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

In an analysis performed in February 2010, the material was 99.9% pure and there was no evidence of decomposition products (see attached document). Heavy metals were < 100 ppm, and residues below 1%.

P. Drug Product

The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: initial Stage 1 full dose of 125 mg; supplemental Stage 1 full dose of 62.5 mg; initial Stage 1 comparator dose of 50 mg, supplemental Stage 1 comparator dose of 25 mg; initial Stage 2 active dose of 100 mg; supplemental Stage 2 active dose of 50 mg; optional initial Stage 2 titration dose of 25 mg; optional supplemental Stage 2 titration dose of 12.5 mg. plus lactose to reach equivalent weight of 236.5 ± 1.5 mg per capsule for all blinded doses. There are no other ingredients in these capsules. The capsules were prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but have been compounded by Kerrisdale Pharmacy, in Vancouver, BC. The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies [1, 8, 11, 13-15] and on narrative reports of MDMA-assisted therapy [12, 16]. The dose of 125 mg from the same supply has been used in a previous sponsor-supported research study conducted in Switzerland [15]. The sponsor chose the comparator dose on the basis of research in people with PTSD and in healthy controls [4, 8, 13, 15], with 50 mg expected to exhibit some activity without producing the same degree of effects. The active dose or doses close to it have been used in studies in healthy controls and is expected to produce most but possibly not all of the effects produced by the full dose [6, 17-20]. The sponsor selected an inactive material to help maintain the blind by ensuring that all blinded doses are of equivalent weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

The encapsulation has been performed by a compounding pharmacist who has the appropriate skills. The MDMA

will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all blinded capsules have similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of blinded full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed in Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk, the licensed dealer, has encapsulated all doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy supplied the capsules and lactose. Compounded MDMA was weighed to the appropriate dose and placed in clear gelatin capsules, one dose per capsule. All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A "packing stat" was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. All 108 capsules are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose 125 mg (23 capsules), 50 mg (27 capsules), 62.5 mg (23 capsules), 25 mg (22 capsules), 12.5 mg (10 capsules) and a varying amount of lactose to maintain equal weight for all blinded doses.

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

Randomization will be performed via the use of a web-based randomization program. An unblinded randomization monitor will generate the randomization list at the beginning of the study. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions.

P.3.3 Batch Formula

lactose monohydrate are provided in the reports supplied by the manufacturer. passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA.

Full initial dose: 125 mg + 113.5 mg lactose

Full supplemental dose: 62.5 mg + 174.1 mg lactose

Active Stage 2 initial dose: 100 mg + 143.0 mg lactose

Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose
Comparator initial dose: 50 mg + 184.9 mg lactose
Comparator supplemental dose: 25 mg + 211.0 mg lactose
Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose
Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose
Capsules placed in individual inner envelopes, which are placed in a numbered primary container.

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all capsules of the product to ensure that blinded capsules are of equivalent weight.

The lactose used will be [REDACTED]

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is [REDACTED]

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, [REDACTED] lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of <= 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of clear capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and will be stored with the rest of the capsules in a separate closed bottle in Kerrisdale Pharmacy. Pharmacist Colin Holyk will test these capsules for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

P.7 Container Closure System

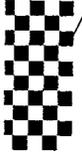
All doses of MDMA will be in the form of clear capsules. The MDMA capsules will be stored in clear cellophane packages. Each package (primary container) will be assigned a container number intended for use in the randomization process so as to maintain the double blind. All packages will be appropriately stored in the Kerrisdale Pharmacy.

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

A Attachments:

1. Attachments containing manufacturer sheets, requested analyses and certificates of suitability contained in Modules 2 and 3 submitted in CTA approved March 17, 2009, control # 127822

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects*. J Clin Psychopharmacol, 2000. **20**(4): p. 455-66.
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3. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations*. Behav Brain Res, 1996. **73**(1-2): p. 103-7.
4. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. **162**(4): p. 396-405.
5. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function*. Psychopharmacology (Berl), 2006. **187**(4): p. 467-75.
6. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA*. Psychopharmacology (Berl), 2001. **154**(2): p. 161-8.
7. de la Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans*. Br J Clin Pharmacol, 2000. **49**(2): p. 104-9.
8. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
9. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans*. J Pharmacol Exp Ther, 1999. **290**(1): p. 136-45.
10. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP*. Drug Alcohol Depend, 2003. **72**(1): p. 33-44.
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13. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder*. J Psychoactive Drugs, 2008. **40**(3): p. 225-36.
14. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study*. J Psychopharmacol, 2011. **25**(4): p. 439-52.
15. Oehen, P., et al., *A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)*. J Psychopharmacol, 2013. **27**(1): p. 40-52.
16. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.
17. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss*. Psychopharmacology (Berl), 2010. **209**(1): p. 69-76.
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Health Products and Food Branch
Direction générale des produits de santé et des aliments

Therapeutic Products Directorate

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TO/À

Name/Nom: _____ Date: August 19, 2013
Organization/Organisme Multidisciplinary Association for Psychedelic Studies
Tel./Tél: _____ Fax/Télécopieur: 831-429-6370
No. of pages, including this page/N°. de pages, incluant cette page: 2

FROM/DE

Name/Nom: Dr. Rajkumar Kumarathasan E-mail/Courrier élec.: rajkumar.kumarathasan@hc-sc.gc.ca
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RE: Phase II CTA for Methylenedioxymethamphetamine Capsules 12.5mg, 25mg, 50mg, 62.5mg, 100mg and 125mg, Control No. 167090

In accordance with the Therapeutic Products Directorate's policy on *Management of Drug Submissions*, we request clarification of the points on the following page(s) so that we can continue our evaluation of the Quality (Chemistry and Manufacturing) information in your submission.

Please provide a complete response within 2 calendar days of this communication via facsimile. The response should include the Directorate's comments and summary responses in a question and answer format. Where appropriate, the relevant portions of the Quality Summary template (e.g., QOS-CB(CTA)) should be used to summarize the new or revised information provided in the accompanying solicited information, such as updated stability data.

If the requested information is not received within the stated time frame, or the response is incomplete, then a **NOT SATISFACTORY NOTICE** will be issued. Please inform the undersigned as soon as possible, by fax, if you will be unable to provide a complete and timely response and prefer that a Notice be sent.

AUG. 19. 2013 2:52PM

HEALTH CANADA

NO. 1872 P. 2

Page 2 of 2

We have the following comments with respect to your CTA for methylenedioxymethamphetamine capsules 12.5mg, 25mg, 50mg, 62.5mg, 100mg and 125mg, Control No. 167090:

1. You are requested to revise Section P3.1 to include the number of 100mg capsules manufactured. It is understood that a total of 108 capsules of all strengths will be used in this Canadian clinical trial, please confirm.
2. It is noted in Section P that the weight of each filled capsule is 236.5 ± 1.5mg whereas, in Section P3.3 the weight of 12.5mg strength is reported as 371.7mg. Please explain this discrepancy.
3. You are requested to justify the change in drug product container closure system from amber glass bottles to clear cellophane packaging. A discussion on the level of protection offered by the proposed container closure system against light, should be included.



Rajkumar Kumarathasan, PhD.
Chemistry Advisor
Clinical Trials Quality Division
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RE: Phase II CTA for Methylenedioxyamphetamine Capsules 12.5mg, 25mg, 50mg, 62.5mg, 100mg and 125mg, Control No. 167090

Dear Dr. Kumarathasan,

This letter is in response to the request for clarification on the CTA-A Control No. 167090. The responses are listed in order of the request.

1. Please find attached to this letter the revision to Module 2 and 3 Quality Overall Summary, Section P3.1 as requested by Health Canada. A total of 120 capsules of different strengths, and not 108 as previously stated, have been prepared for this clinical trial. Please see below for the strengths and total numbers of capsules that have been manufactured for the study. These capsule counts are independent of study drug to be used for stability testing (N=4) as described in Section P.4.1.

Dose	Initial/Supplement	Blinded?	Required/Optional	Total Capsules
125mg	Initial	Blinded	Required	23
50mg	Initial	Blinded	Required	12
62.5mg	Supplement	Blinded	Optional	23
25mg	Supplement	Blinded	Optional	12
100mg	Initial	Open-Label	Required	15
25mg	Initial	Open-Label	Optional	10
50mg	Supplement	Open-Label	Optional	15
12.5mg	Supplement	Open-Label	Optional	10
TOTAL				120


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2. Section P3.1 has been revised to further clarify that only the doses to be used in blinded experimental sessions must be of equivalent weight in order to maintain the blind. The remaining doses are used for open-label experimental sessions in Stage 2 of the protocol. This statement is consistent with section P, which states "The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: initial Stage 1 full dose of 125 mg; supplemental Stage 1 full dose of 62.5 mg; initial Stage 1 comparator dose of 50 mg, supplemental Stage 1 comparator dose of 25 mg; initial Stage 2 active dose of 100 mg; supplemental Stage 2 active dose of 50 mg; optional initial Stage 2 titration dose of 25 mg; optional supplemental Stage 2 titration dose of 12.5 mg plus lactose to reach equivalent weight of 236.5 ± 1.5 mg per capsule for all blinded doses." This is also stated again in Section P as "The sponsor selected an inactive material to help maintain the blind by ensuring that all blinded doses are of equivalent weight."

The discrepancy noted by the agency between the weight of the 12.5mg capsule strength and the weight range of 236.5 ± 1.5 mg per blinded capsule is thus attributed to the fact that the 12.5mg dose strength is only intended for use in open label experimental sessions.

3. MDMA stability is affected by light. MDMA does not possess any of the chemical features that are often seen in light sensitive molecules. It does not have any extended conjugated olefinic bonds, nor any chemical group that would be expected to be unstable in the presence of light. To date, the sponsor has completed one clinical trial with the same drug supply lasting from 2006 to 2010, with annual stability testing conducted in Switzerland. The methylenedioxy ring remained stable, as indicated by stability reports from 2010 submitted with the CTA-A. In addition, the sponsor has completed one clinical trial from 2003 to 2009 in the U.S., and currently has 5 ongoing clinical trials with MDMA that are using the same clear cellophane packaging for study drug. The drug was not stored in dark amber vials for any of these clinical trials. At the time of submission of the parent CTA in 2008, dark amber vials were proposed to store the study drug as that is what the Kerrisdale Pharmacy had available at the time. Since the time of submission of the parent CTA, the sponsor has gathered empirical evidence that clear cellophane packaging, stored in a secure safe at room temperature, is sufficient to maintain optimal stability of study drug. Cellophane envelopes have clear advantages over dark amber vials for storage space as well as drug accountability purposes. Due to the initial dose and optional supplemental dosing regimen in experimental sessions, it is important to be able to package each capsule of study drug individually. This ensures that each capsule is stored in individual secondary containment. Cellophane envelopes are easier to transport and store than amber vials. As the study drug will need to be transported from the Kerrisdale Pharmacy to the Qualified Investigator's office for drug administration, it is crucial to ensure that capsules are transported in packaging that will not break if they are accidentally dropped. In addition, the study drug will be stored in a [redacted] that presents a controlled environment that will only be disrupted when [redacted] of study drug to the treatment room. The drug will be ingested by the subject on the same day as being removed [redacted] Hence



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storage in amber vials is not necessary and the Quality Overall Summary was amended in CTA-A.

We look forward to hearing confirmation from the agency that the review of the CTA-A, Control No. 167090 may proceed as revised with the information provided in this letter.

Sincerely,

[Redacted signature block]

[Redacted name]

of Clinical Research

MAPS

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada**

Amendment 1 Version 2

Sponsor: Multidisciplinary Association for Psychedelic Studies

**Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC,
University of Victoria**

Study Number: M-P4

Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents

Quality Overall Summary and Data

1

MAPS Study M-P4

2.3 Quality Overall Summary

1 Introduction

Study Title:

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC, University of Victoria

Co-Investigators: Andrew Foldmar, Zach Walsh, Ph.D R. Psych. Assistant Professor, Department of Psychology, University of British Columbia

Expected Study Dates Sept 15, 2013 – May 2016

Approved by: IRB Services, Ontario Committee, July 12, 2013

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 125 mg (full dose-initial dose), 100 mg (active dose Stage 2-initial dose), 62.5 (full dose-supplemental dose), 50 mg (comparator-initial dose; also active dose Stage 2-supplemental dose), 25 mg (comparator- supplemental dose, and optional titration initial dose for Stage 2), 12.5 mg (optional titration supplemental dose, Stage 2), [Full dose strength capsules are used in Stage 1. Supplemental doses are used in both stages and are administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose; Titration dosing occurs in Stage 2, See Table 1 and 2 for dosage by visit.]

Quality Overall Summary and Data

2

MAPS Study M-P4

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

Route of Administration: Oral**Indications:** For use in combination with therapy in people with PTSD**1(a) Excerpt from Protocol Synopsis (PSEAT)****Trial Objectives**

Primary Efficacy and Safety Objectives: Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

Safety Objectives: The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (CSSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.
- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.

- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

Secondary Objectives:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint

In specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

Study Design and Duration

3.5 Purpose

This Phase 2 pilot study is a randomized, double-blind, dose comparison study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment.

After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.

A therapy team will conduct psychotherapy visits according to the treatment manual provided. The team will include two licensed therapists who will work together as cotherapists.

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months
- Comparator dose subjects who complete Stage 2: 18 months.

Number of Centres

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the primary study endpoint.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with chronic, treatment-resistant PTSD and with a CAPS score of 60 or higher. Treatment resistance is defined as being unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to inability to tolerate psychotherapy and/or pharmacotherapy. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must

meet all of the inclusion criteria without meeting any of the exclusion criteria. Participants must reside in Canada.

Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 50, 62.5, 100 and 125 mg. The initial full dose of MDMA is 125 mg and the supplemental full dose is 62.5 mg. The initial comparator dose is 50 mg, and the supplemental comparator dose is 25 mg. The initial active dose for the first Stage 2 session consists of an initial dose of 100 mg and a supplemental dose of 50 mg, with optional titration doses of 25 mg initial and 12.5 mg supplemental dose available in the second and third open-label experimental sessions of Stage 2. MDMA has been obtained from Lipomed AG. All doses of MDMA will be compounded with the inactive substance lactose to ensure that all the blinded capsules weigh the same amount.

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [1-6]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [3, 11, 12]. The initial full 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 drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25 mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions. The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.

The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

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 1.5 to 2.5 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 the supplemental dose of MDMA is contraindicated or not necessary.

There will be not be any changes in dose regimen across the first two blinded sessions. Full dose participants will receive the same dose regimen during a third session in an open-label context after unblinding per protocol. Subjects in the comparator dose condition will not complete Stage 1, but will continue to Stage 2. In Stage 2, they will receive the active dose for the first Stage 2 session, and they can receive the active or full dose during the second and third sessions via a clinical titration dosing strategy.

If the participant experiences hypertension that required clinical intervention or had a serious adverse event that is possibly or probably related to study drug, then no further doses of MDMA will be administered.

S Drug Substance

S.1 General Information

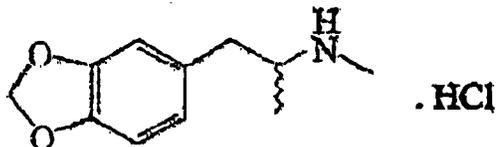
The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N, alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by

Switzerland. On January 30, 2006, a quality control analysis was performed by This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94.1 B5.5 with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually by between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report submitted for in Modules 2 and 3 of the CTA approved on March 17, 2009, control # 127822).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.

Step 2: MDA-nitrostyrol + LiAlH₄ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Quality Overall Summary and Data

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MAPS Study M-P4

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [REDACTED]. Specifications of manufacture, including solvent and procedures, are translated in the second report of [REDACTED] in Modules 2 and 3 for CTA approved on March 17, 2009, control # 127822.

S.2.3 Control of Materials

See above and contained in report by [REDACTED] p. 1

S.3 Characterization:

Batch number is : [REDACTED]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]. One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2 of report supplied in Modules 2 and 3 of CTA approved March 17, 2009, control # 127822).

Validation: From manufacturer, data available upon request [REDACTED] p. 1).

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] (see attachment and reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Quality Overall Summary and Data

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MAPS Study M-P4

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(Max)}$ = 1 234 +/- 1 nm

ϵ_{mol} = 3800 +/- 500

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by [REDACTED]

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μ m, 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μ L

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μ m

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

Injection: 250 C, splitless 1 μ L

Detection: full scan

Identity (HPLC-DAD): TR = 5.8 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA) 154 (basepeak) 162, 289 (M⁺) MDMA-TFA

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from [REDACTED]

S.4.4 Batch Analysis:

As listed above, the batch is [REDACTED]

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Quality Overall Summary and Data

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MAPS Study M-P4

Identity: IR identical to reference
UV, in distilled water, $\lambda_{(MAX).1} = 234.0$ nm
 $\epsilon_{mol.1} = 3939$
 $\lambda_{(MAX).2} = 285.0$ nm
 $\epsilon_{mol.2} = 3688$
Melting point = 148.9 to 149.7 C
Purity HPLC = 99.66%
Freebase content: 83.51%
Water content: 055%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%
Tests for presence of heavy metals: Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [redacted] and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [redacted] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, Nichols reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [redacted] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment 4 in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

In an analysis performed in February 2010, the material was 99.9% pure and there was no evidence of decomposition products (see attached document). Heavy metals were < 100 ppm, and residues below 1%.

P. Drug Product

The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: initial Stage 1 full dose of 125 mg; supplemental Stage 1 full dose of 62.5 mg; initial Stage 1 comparator dose of 50 mg; supplemental Stage 1 comparator dose of 25 mg; initial Stage 2 active dose of 100 mg; supplemental Stage 2 active dose of 50 mg; optional initial Stage 2 titration dose of 25 mg; optional supplemental Stage 2 titration dose of 12.5 mg plus lactose to reach equivalent weight of 236.5 ± 1.5 mg per capsule for all blinded doses. There are no other ingredients in these capsules. The capsules were prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but have been compounded by Kerrisdale Pharmacy, in Vancouver, BC. The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies [1, 8, 11, 13-15] and on narrative reports of MDMA-assisted therapy [12, 16]. The dose of 125 mg from the same supply has been used in a previous sponsor-supported research study conducted in Switzerland [15]. The sponsor chose the comparator dose on the basis of research in people with PTSD and in healthy controls [4, 8, 13, 15], with 50 mg expected to exhibit some activity without producing the same degree of effects. The active dose or doses close to it have been used in studies in healthy controls and is expected to produce most but possibly not all of the effects produced by the full dose [6, 17-20]. The sponsor selected an inactive material to help maintain the blind by ensuring that all blinded doses are of equivalent weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

The encapsulation has been performed by a compounding pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all blinded capsules have similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of blinded full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed in Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk, the licensed dealer, has encapsulated all doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy supplied the capsules and lactose. Compounded MDMA was weighed to the appropriate dose and placed in clear gelatin capsules, one dose per capsule. All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A "packing stat" was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. A total of 120 capsules have been created for use in this clinical trial. The 70 capsules used for blinded experimental sessions are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose 125 mg (23 capsules), 100 mg (15 capsules), 50 mg (27 capsules), 62.5 mg (23 capsules), 25 mg (22 capsules), 12.5 mg (10 capsules) and a varying amount of lactose to maintain equal weight for all blinded doses.

Berra Yazar 8/20/13 10:21 AM
 Deleted: All
 Berra Yazar 8/20/13 10:21 AM
 Deleted: 108

Dose	Initial/Supplement	Blinded?	Required/ Optional	Total Capsules
125mg	Initial	Blinded	Required	23
50mg	Initial	Blinded	Required	12
62.5mg	Supplement	Blinded	Optional	23
25mg	Supplement	Blinded	Optional	12
100mg	Initial	Open-Label	Required	15
25mg	Initial	Open-Label	Optional	10
50mg	Supplement	Open-Label	Optional	15
12.5mg	Supplement	Open-Label	Optional	10
TOTAL				120

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

Randomization will be performed via the use of a web-based randomization program. An unblinded randomization monitor will generate the randomization list at the beginning of the study. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions.

P.3.3 Batch Formula

lactose monohydrate are provided in the reports supplied by the manufacturer. passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA.

Full initial dose: 125 mg + 113.5 mg lactose

Full supplemental dose: 62.5 mg + 174.1 mg lactose

Active Stage 2 initial dose: 100 mg + 143.0 mg lactose

Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose

Comparator initial dose: 50 mg + 184.9 mg lactose

Comparator supplemental dose: 25 mg + 211.0 mg lactose

Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose

Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose

Quality Overall Summary and Data

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MAPS Study M-P4

Capsules placed in individual inner envelopes, which are placed in a numbered primary container.

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all capsules of the product to ensure that blinded capsules are of equivalent weight.

The lactose used will be [REDACTED]

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is [REDACTED].

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, [REDACTED] issued by the manufacturer, [REDACTED] lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of <= 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of clear capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and will be stored with the rest of the capsules in a separate closed bottle in Kerrisdale Pharmacy. Pharmacist Colin Holyk will test these capsules for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

P.7 Container Closure System

All doses of MDMA will be in the form of clear capsules. The MDMA capsules will be stored in clear cellophane packages. Each package (primary container) will be assigned a container number intended for use in the randomization process so as to maintain the

double blind. All packages will be appropriately stored in the Kerrisdale Pharmacy.

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

A Attachments:

1. Attachments containing manufacturer sheets, requested analyses and certificates of suitability contained in Modules 2 and 3 submitted in CTA approved March 17, 2009, control # 127822
1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects*. J Clin Psychopharmacol, 2000. 20(4): p. 455-66.
2. Freedman, R.R., C.E. Johanson, and M.E. Tancer, *Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2005. 183(2): p. 248-56.
3. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations*. Behav Brain Res, 1996. 73(1-2): p. 103-7.
4. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. 162(4): p. 396-405.
5. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function*. Psychopharmacology (Berl), 2006. 187(4): p. 467-75.
6. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA*. Psychopharmacology (Berl), 2001. 154(2): p. 161-8.
7. de la Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans*. Br J Clin Pharmacol, 2000. 49(2): p. 104-9.
8. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
9. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans*. J Pharmacol Exp Ther, 1999. 290(1): p. 136-45.
10. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP*. Drug Alcohol Depend, 2003. 72(1): p. 33-44.
11. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. J Psychoactive Drugs, 1986. 18(4): p. 319-27.

12. Stolaroff, M., *The Secret Chief Revealed: Conversations with a pioneer of the underground therapy movement*. 2004, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.
13. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder*. *J Psychoactive Drugs*, 2008. 40(3): p. 225-36.
14. Mithoefer, M.C., et al., *The safety and efficacy of (+/-)3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study*. *J Psychopharmacol*, 2011. 25(4): p. 439-52.
15. Oehen, P., et al., *A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxyamphetamin)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)*. *J Psychopharmacol*, 2013. 27(1): p. 40-52.
16. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.
17. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss*. *Psychopharmacology (Berl)*, 2010. 209(1): p. 69-76.
18. Farre, M., et al., *Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics*. *Psychopharmacology (Berl)*, 2004. 173(3-4): p. 364-75.
19. Ramaekers, J.G. and K.P. Kuypers, *Acute effects of 3,4-methylenedioxyamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol*. *Neuropsychopharmacology*, 2006. 31(5): p. 1048-55.
20. Bedi, G., et al., *Effects of MDMA on sociability and neural response to social threat and social reward*. *Psychopharmacology (Berl)*, 2009. 207(1): p. 73-83.

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada
Amendment 1 Version 2**

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC,
University of Victoria

Study Number: M-P4

Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents

	Health Canada / Santé Canada	Office of Clinical Trials
Screening Template for CTA-A		
CR File #: 9427-M2544-21C Date received in OCT : 2013.08.02 Review 1 Start Date: 2013.08.08 Study Phase: Phase II (30 day) Study Population: Males and Females Document I.D. #: <i>847977</i>	DSTS Control #: 167090 Due Date: 2013.09.07 Data Description: CL/2VO/1CD Clinical Division: Vol 1 Quality Division: Vol 2	
Attached Documents: <input type="checkbox"/> SOAD Form <input type="checkbox"/> CTSI Form <input type="checkbox"/> Other:		

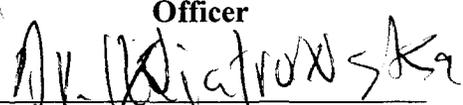
RECEIVED
AUG 12 2013

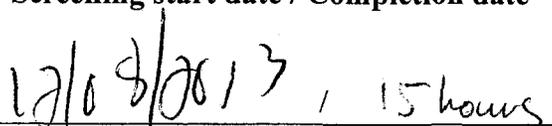
Product Name : MDMA Protocol # or Identifier: MP-4 Amendment type: Amendment # 1 to Protocol # MP-4 (Version 2) and Quality Amendment	
Therapeutic/Pharmacological Classification: Monoamine releaser and uptake inhibitor / for the treatment of Post-Traumatic Stress Disorder [Clinical Group II: CNS]	
Sponsor Name : MULITDISIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES	Country: USA

	Form	Route	Medicinal Ingredients	Strength / Unit	Basic Unit	F#
1	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	12.5 mg	CAP	1
2	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	25 mg	CAP	2
3	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	50 mg	CAP	3
4	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	62.5 mg	CAP	4
5	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	100 mg	CAP	4
6	CAP	ORL	METHYLENEDIOXYMETHAMPHETAMINE	125 mg	CAP	4

Screening Officer's Comment(s): IB is Edition 7, dated August 1st, 2013

Parent CTA # 127822 reviewed by:
 - Clinical Assessment Officer: Dr. BEATA WIATROWSKA / 2009.03.17
 - Quality Assessment Officer: UDAI GILL / 2009.03.09


Natasha Widmer - Screening Officer

Assessment Officer

2013.08.06 / 2013.08.09
 Screening start date / Completion date

 Assigned date / Review Hours



Health Canada
Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

Your file Votre référence

Our file Notre référence

12 August 2013

9427-M2544-21C

Clinical Research
Multidisciplinary Association for Psychedelic Studies
1215 Mission St.
SANTA CRUZ, CA 95060
USA
831-429-6362

**ACKNOWLEDGMENT
CLINICAL TRIAL AMENDMENT**

RE: AMENDMENT # 1 TO PROTOCOL # MP-4 (Version 2) and Quality Amendment

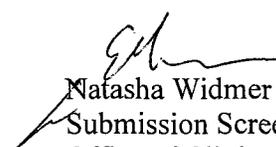
Dear [REDACTED]

This will confirm the receipt of your complete application on August 8, 2013, regarding your information and material to support the Clinical Trial Application Amendment (CTA/A) for **MDMA**, control number **167090**. Please note that a new control number has been assigned to this CTA/A. Any correspondence relating to the original CTA should be referenced to the original control number assigned.

Please note that additional information may be requested during the review stage.

This protocol amendment will be reviewed and a "Not Satisfactory Notice" or "No Objection Letter" will be issued within 30 days of the date of receipt of the information.

Yours sincerely,


Natasha Widmer
Submission Screening Officer
Office of Clinical Trials

NW/en

Canada



Re: Clarification Request for protocol # MP-4
@MAPS
to:
Natasha Widmer
2013-08-06 02:44 PM
Cc:

Received:
2013.08.08
-NAV

Show Details

History: This message has been replied to.

Dear Natasha

With Regards to clinical trial amendment application:

Product: MDMA
Protocol Number: MP-4
Sponsor: MULITDISIPLINARY ASSOCIATION FOR PSYCHEDELIC
STUDIES
Control Number: 167090 (parent CTA control # 127822)

Thank you for letting us know so quickly that we need a quality amendment.

will be preparing the following today in hard copy and electronic format for submission:

1) Quality Amendment

- Updated Quality Overall Summary for this Amendment with information for all dosage forms (100 mg, 50 mg, and 25 mg)
- The QOS introduction will be in MS Word format.
- A tracked changes version of the QOS as well as a final version.
- Any additional documents or appendices if applicable.

2) In box 82, on Appendix 3 of the submitted HC-SC 3011 form box 82 should have the protocol number/identifier "MP-4" . The Health Canada number was accidentally entered. Do we need to re-submit this or will this email serve as a correction to box 82.

Best Regards

of Clinical Research

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1215 Mission St.
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www.maps.org

On Tue, Aug 6, 2013 at 10:37 AM, Natasha Widmer <natasha.widmer@hc-sc.gc.ca> wrote:
Good afternoon Amy Emerson,

This is with regards to the clinical trial amendment application for:

Product: MDMA
Protocol Number: MP-4
Sponsor: MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC
STUDIES
Control Number: 167090 (parent CTA control # 127822)

According to the information captured in the e-Clinical Trials Manual, which includes the requirements from Part C, Division 5 of the Food and Drug Regulations, the following revision is necessary for the processing of this submission to continue into formal review.

1) You have recorded in the submitted Drug Submission Application (HC-SC 3011) form, three new strengths (100 mg, 50 mg, and 25 mg), which were not recorded on the initial form submitted with CTA control # 127822.

Additionally, the 20 mg strength is no longer recorded.

If the Drug Products being used in this trial have changed, a Quality Amendment will be required for these new dosage forms. Therefore:

Please provide an updated Quality Overall Summary for this Amendment, which includes information for all dosage forms to be used in this trial. Please note the QOS introduction must be in MS Word format. If possible, it would be greatly appreciated if a tracked changes version of the QOS was provided, to outline the changes that have been made. Please also include any additional documents or appendices to the Quality information, if applicable.

Please provide a hard and electronic copy of these Quality documents.

2) In box 82, on Appendix 3 of the submitted HC-SC 3011 form, you have recorded "control number 127822". This is not the protocol number that you had originally assigned to the trial. Please confirm that box 82 should have the protocol number/identifier "MP-4" recorded. Otherwise, explain.

Should you have any questions or comments, please feel free to contact me.

Kind regards,

Natasha Widmer
Regulatory Project Officer / Agent de projet réglementaire
Office of Clinical Trials / Bureau des essais cliniques

Therapeutic Products Directorate / Direction des produits thérapeutiques
Health Canada / Santé Canada
Telephone: (613) 948-4344
Fax: (613) 946-7996



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Your file Votre référence

Our file Notre référence

17 March 2009

9427-M2544-21C

Rick Doblin PhD
President
Multidisciplinary Association for
Psychedelic Studies
3 Francis Street,
BELMONT, Massachusetts
USA 02478-2218
(617) 484-8711

No Objection Letter RE: Protocol # MP-4

Dear Dr. Doblin:

I am pleased to inform you that the information and material to support your Clinical Trial Application for **MDMA**, control number **127822**, received on February 16, 2009, have been reviewed and we have no objection to your proposed study.

I would remind you of the necessity of complying with the *Food and Drug Regulations*, Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials.

You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice*.

Please note that for drugs marketed in Canada and in clinical trials, any serious and unexpected adverse drug reaction occurring inside or outside Canada should be reported to both MHPD and TPD until completion of the trial then the reports should be send to MHPD only.

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Yours sincerely,

Elizabeth Komsta, M.Sc, Ph.D.
A/Manager - Clinical Trials Group II
Office of Clinical Trials



Health Canada Santé Canada

Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

REQUEST FOR ADDITIONAL INFORMATION

If you receive this fax in error, please advise the sender immediately.
Si vous recevez cette télécopie par erreur, veuillez en aviser immédiatement l'expéditeur.

TO/À
Name/Nom: Dr. Rick Doblin, PhD Date: March 5, 2009

Organization/Organisme: MAPS

Tel./Tél.: 617-484-8711 Fax/Télécopieur: 617-484-8427

No. of Pages, including this page/N^o de pages, incluant cette page: 2

FROM/DE
Name/Nom: Beata Wiatrowska, M.D. E-Mail/Courier électronique: beata_wiatrowska@hc-sc.gc.ca

Tel./Tél.: 613-941-2132 Fax/Télécopieur: 613-952-9656

TITLE Division/Unit	Clinical Trials & Special Access Programme/ Programme des essais cliniques et accès spécial aux médicaments	TITRE Division/Unité
Bureau	Bureau of Pharmaceutical Assessment / Bureau de l'évaluation des produits pharmaceutiques	Bureau
Directorate	Therapeutic Products Directorate / Direction Des Produits Therapeutiques	Direction
Room		Pièce
Building	Finance Building/ Edifice Finance	Édifice
Location	Tunney's Pasture/Pré Tunney	Lieu
Address Locator	0202C1	Localisateur d'adresse
City/Province	Ottawa, Ontario	Ville/Province
Postal Code	K1A 1B6	Code postal

Website/site Web : www.hc-sc.gc.ca/hpb-dgps/therapeut

In accordance with Division 5 of the Food and Drug Regulations, we request clarification of the points on the following page so that we can continue our evaluation of your Clinical Trial Application (CTA) or CTA Amendment for:

Product:MDMA
Protocol Number:MP-4
Control Number: 127822
File Number: 9427-M2544-21C
Received in the Bureau on:16/02/09

Please provide a complete response within **2 working days** from the date of this request **via facsimile** to the sender. If the requested information is not received within 2 working days, a Not Satisfactory Notice may be issued.

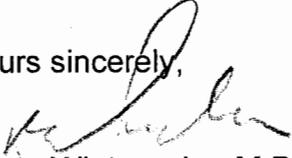
Comment:

Re: Informed consent:

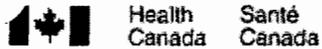
1. I am correct in the addiction section the time-frame for people who recently had problems with drug abuse, from 30 days to 6 months.
2. Re: possible brain damage section: Please explain in simple terms what was the "small change" that was seen in the brain scans of people who took ecstasy in recreational setting

I would appreciate receiving your response in a paper (via fax), as well as an electronic (via e-mail) version.

Yours sincerely,



Beata Wiatrowska, M.D., FRCP(C)



To: Dr. John Patrick Stewart	Security – Classification: HC Protected
From: Dr. B. Wiatrowska	Date: 17/03/09

**Subject: Protocol Safety and Efficacy Assessment Template
 Clinical Trial Application – Evaluation Report**
Effective Date: 2008-03-01

Type of Submission / Phase of Trial	CTA	
Target Date	18/03/09	
Control Number / File Number	127822	0427-42544-21C

REVIEWER	
Recommendation	This Clinical Trial Application (CTA) is recommended for clearance with respect to Safety and Efficacy Information.
Name	Dr. B. Wiatrowska
Signature	
Date Review Completed	17/03/09
Review Time	7.5 hours

MANAGER	
Decision / Date	Agree with above recommendation.
Manager's Name	Dr. E. Komsta <i>Made 17/09</i>
Manager's Signature	

Canada

1. INTRODUCTION

(Information to be included in this section can be extracted from the PSEAT prepared by the sponsor)

A. SUMMARY OF PRODUCT INFORMATION		
Proprietary Name of Drug Product	MDMA	
Non-proprietary or Common Name of Drug Substance	Ecstasy	
Sponsor	MAPS	
Dosage Form(s)	capsules	
Strength(s)	12.5, 25, 62.5, 125 mg	
Route of Administration	oral	
Proposed Indication(s)	MDMA assisted psychotherapy for PTSD	
B. INVESTIGATOR'S BROCHURE (if applicable)		
Date and Version/Edition Number	Dec 2007, updated in response to Clarifax	
Cut-off date for data included in this version/edition of the Investigator's Brochure	As above	
C. CONTACT INFORMATION		
Contact Person/Name	Dr. Rick Doblin	
Telephone and Fax Number, including area code	Tel. 617-484-8711	Fax 617-484-8427
Email Address	Rick@maps.org	

Email Address	
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2. INVESTIGATOR'S BROCHURE

(The relevant sections should be filled using a check mark)

	Acceptable	Not Acceptable
Date of Issue	*	
Rationale for Drug Development	*	
Drug Formulation	*	
Pharmacodynamics	*	
Pre-clinical Pharmacokinetics/ Pharmacodynamics	*	
Pre-clinical Toxicology	*	
Information on Patient Exposure, Duration of Study, Location of Study, Drug Dosage	*	
Efficacy	*	
Safety (Summary of ADRs: Deaths, Serious, Other)	*	

Protocol Synopsis 1 MAPS Study: MP-4

Study Synopsis

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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 5, 2008

Protocol Synopsis 2 MAPS Study: MP-4

PI: Ingrid Pacey

Background and Rationale

Background: 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). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems.

PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population

of the US. To date the treatment of PTSD has primarily been psychotherapeutic, 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 eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD [4]. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with 3,4-methylenedioxymethamphetamine (MDMA), a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy.

MDMA is a ring-substituted phenethylamine that bears structural and pharmacological similarities to amphetamines and the psychedelic compound mescaline. However, it possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [8-11]. MDMA was initially patented by Merck as an intermediary product and then

rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. 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 [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e. g. 16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22].

In

Protocol Synopsis 3 MAPS Study: MP-4

PI: Ingrid Pacey

contrast, all available Phase I and Phase 2 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. 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.

Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. 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"

[8]. 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 [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25].

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. Though the

psychopharmacology and neuropsychological underpinnings of the therapeutic effects of

MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli.

Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the 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 [28]. A one-year+ follow-up study is currently underway.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be 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.

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PI: Ingrid Pacey

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

The proposed pilot study will employ a randomized, double-blind, active placebocontrolled

design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of

125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA

1.5 to 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 during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression

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PI: Ingrid Pacey

symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the

study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a

total of about 8 months.

Number of Centres

List of Investigators

Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She 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 will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.

Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. 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. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She

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PI: Ingrid Pacey

is a clinical psychologist who has 15 years of experience and has conducted psychiatric diagnostic and competency assessments.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD who score 50 or higher on the Clinician-Administered PTSD Scale (CAPS). The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all the inclusion criteria listed below without meeting any exclusion criteria. Participants must reside in Canada.

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 [32, 33].

4. Participants must be willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.

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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 nonsteroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).

c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other

medications approved by the research team).

8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.

9. Participants must be willing to remain overnight at [REDACTED] 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

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PI: Ingrid Pacey

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 [34], 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.

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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 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

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PI: Ingrid Pacey

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 assignment 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 Protocol Synopsis 11 MAPS Study: MP-4

PI: Ingrid Pacey

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 openlabel.

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 arrive [redacted] 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.

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PI: Ingrid Pacey

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 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	Presudy	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	14	21	28	35	42	49	56	63	70	77	84	91	98	105	112	119							
Visit Timing and Windows Post telephone																								
(Post-consent, may be same day (-/+3 d))																								
Post V4 Post V5 post V6																								
24 h post-experim.																								
Break 1																								
Between V6 and V11 Post-V9 +3-5 wks post V6																								
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 V16																								
Study Staff	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew	Ingrid	Andrew		
Physician	Ingrid	Andrew	IA	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	X	X	X	X	X	X	X	X	
Psychotherapy-No Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
General Well-Being	X	X	X	X	X	X	X	X	X	X	X	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	X	X																					
Blood Pressure	X	X	X	X																				
Pulse	X	X	X	X																				
Body Temperature	X	X	X	X																				
SUD	X	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	X	X	X	X	X	X	X	X	X	X	
Adverse Events Requiring Dr																								

General Well-Being 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
Adverse Events Requiring Dr Visit X X X X X X X X X X X X
RRPQ X
End Stage 2
*=if appropriate

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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 reside near [REDACTED] 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 [REDACTED]

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

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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

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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 openlabel

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, Protocol Synopsis 17 MAPS Study: MP-4

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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

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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.

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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

reatment 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 antiinflammatory

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

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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

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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

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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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4. INFORMED CONSENT FORM

(The relevant sections should be filled using a check mark)

	Acceptable	Not Acceptable
Full Disclosure of Risk	*	
Clarity of Language	*	
Description of Procedure	*	
Confidentiality for Patient	*	
Lack of Bias	*	
Placebo Disclosure (if applicable)	*	

5. OVERALL ASSESSMENT

Current Problems/Concerns:

Below find a list of questions and requests posed to the sponsor with the first submission of the protocol followed by the current requests and the sponsor's answers (the initial application was withdrawn as the sponsor needed more time to answer chemistry and manufacturing questions).

Reviewer's Discussion/Summary:

**Response to Clarifax t: control #126833, sent as electronic mail
 Sent to Rick Doblin on January 16, 2009 from Beata Wiatrowska, M.D., FRCP(C)**

1. Please provide updated information on studies of MDMA-assisted psychotherapy for PTSD and/or for potentially life threatening illness, if available.

All 21 participants in the MAPS-sponsored US study of MDMA-assisted psychotherapy in people with PTSD have completed the study. A long-term follow-up will soon be launched. A preliminary data analysis found a greater decrease in PTSD symptoms after MDMA-assisted psychotherapy than after psychotherapy and inactive placebo. No drug-related serious adverse events (SAEs) occurred during this study. As of January 20, 2009, the MAPS-sponsored Swiss study of MDMA-assisted psychotherapy in people with PTSD has completed treatment of ten of twelve subjects. The eleventh subject has just been enrolled, and a potential twelfth and final subject is in the screening process. The MAPS-sponsored MDMA/PTSD study in Israel has so far completed treating two subjects and has enrolled a third subject. The second subject had PTSD for over 40 years, from the 1967 "Six Day" War, and after treatment has very few symptoms. No drug-related serious adverse events occurred during either the Swiss or Israeli MDMA/PTSD studies.

The study of MDMA-assisted psychotherapy in people with anxiety associated with advanced-stage cancer, conducted at McLean Hospital, Harvard Medical School, has enrolled one participant. This subject had a remarkably successful outcome in terms of reduced anxiety and pain and reported enhance communications with his family.

2. Please provide more detailed reasons for the Swiss Government revoking permission to conduct MDMA assisted psychotherapy.

In 1988, the Swiss Ministry of Health gave permission to a small group of Swiss psychiatrists (members of the Swiss Medical Society for Psycholytic Therapy-SAEPT) to administer MDMA and lysergic acid diethylamide (LSD) to their Swiss patients within a psychotherapeutic context. Permission was revoked in 1993, for reasons completely unrelated to the administration of MDMA or LSD in psychotherapy.

The Swiss Ministry of Health revoked permission after one of the Swiss psychiatrists conducted a group psychedelic therapy session in France, where he had no permit to do so. During the group session, he administered different psychedelic substances to different participants. Tragically, one of the participants in this event died after receiving the psychedelic compound ibogaine (not administered in combination with any other drug). The Swiss government subsequently closed the Swiss program in which LSD and MDMA were permitted to be used in patients, at first temporarily and then permanently. A brief account of these events can be found in the attached letter from Swiss psychiatrist Dr. Peter Gasser, President of SAEPT.

3. a) What is the abuse/addiction potential of MDMA?

b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA-assisted psychotherapy sessions?

c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dextedrine etc.)?

- a) MDMA possesses moderate abuse liability.
- b) The estimated risk of abuse of MDMA after completing a trial of MDMA-assisted psychotherapy is very low. Dr. Mithoefer is aware of one subject in his study who used MDMA after the completion of the study. Afterwards, she said she would never do that again since she didn't feel it was as productive as when she was under the supervision of trained therapists.
- c) Comparisons between one drug and another are viewed by some as controversial, but examining human behavior and self-administration in animals suggests that MDMA has lower abuse potential than psychostimulants.

These issues are addressed in more detail at several points in the study protocol, on pp. 45-46 and again on p. 87, with excerpts below.

Abuse Liability (from pp. 45-46)

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at night clubs and parties in the early to mid-1980s. MDMA possesses abuse liability, and this is discussed in “Additional information.” Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. Mithoefer and colleagues are in the process of conducting a long-term follow-up of participants who took part in the study of MDMA-assisted psychotherapy that will address this question. Mithoefer reported that anecdotally it appeared that people did not develop problems with MDMA/ecstasy abuse and that a number of participants volunteered that they would never seek out ecstasy outside a legal, controlled therapeutic setting. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted.”

Abuse Liability (from p. 87)

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

4. Re: Inclusion criterion #2a: Please change the criterion 2a so that in addition to an unsuccessful course of appropriate psychotherapy a participant must have had at least one unsuccessful attempt at treatment with SSRI or mirtazapine or MAOI, and that treatment must have constituted an adequate trial (lasting for at least 3 months at optimal doses or the patient could not tolerate the treatment, i.e. the patients who simply

refused a trial of any of the approved form of pharmacotherapy would not be eligible for this study).

We agree without reservation to expand the inclusion criteria to include people treated with pharmacotherapies other than SSRIs.

However, we believe that potential subjects who did not successfully resolve their symptoms after psychotherapy and who have refused pharmacotherapy, should continue to be enrolled in the study. People who refuse pharmacotherapy have made a legitimate decision concerning their health care and have the right to make those decisions. For those patients, it remains true that, for them, currently available treatments have not been of sufficient therapeutic efficacy.

Based on substantial evidence, risk of study participation is not large. There are no significant safety reasons to exclude patients who have failed on psychotherapy and refuse pharmacotherapy. We would prefer to continue to enroll any subjects who have failed on psychotherapy but refused pharmacotherapy.

5. Re: Inclusion criterion #2b: Please clarify that being a veteran with PTSD symptoms that have persisted for no less than 1 year but no more than 5 years would only qualify to participate in the study if this veteran also meets criterion #2a.

That is correct; all veterans must meet all criteria including #2a to be enrolled in the study. This original inclusion criteria was written in 2001, when MAPS was seeking approval for the first US MDMA/PTSD study. We would like to revise this inclusion to permit enrollment of veterans with PTSD of no more than ten years duration. This revision is proposed upon recognition that people in the US MDMA/PTSD study had PTSD for an average of 19 years before enrolling in the study and were still successfully treated, even a subject receiving disability payments. Canadian soldiers with PTSD may have experienced combat-related PTSD prior to 2004, such as in Afghanistan in UN peacekeeping missions.

6. Re: Exclusion criterion #10: Please extend the time that the participant must be in remission for substance abuse or dependence (except caffeine and nicotine) to 12 months- i.e. full sustained remission, if substance abuse or dependence was an issue.

We would prefer to retain a six-month exclusion period for active substance abuse. Participation in MDMA-assisted psychotherapy reduces rather than increases the risks of substance abuse due to the focus on resolving subjects' underlying psychological issues.

Upwards of 40% of people with PTSD also report a lifetime diagnosis of alcohol or substance abuse (Brady and Sinha 2005). As noted above, the risk of abuse of MDMA within a psychotherapy context is low. The study of MDMA-assisted psychotherapy in the US excluded people reporting a diagnosis of substance abuse within 60 days, without any abuse or dependence occurring afterwards. Given the significant number of people with PTSD reporting

past alcohol or substance abuse in the past and the low risk of abuse from study participation, we believe that maintaining the current six-month diagnosis exclusion will allow for greater ease of recruitment and will also result in a more representative sample being recruited.

Kathleen Brady MD, a Professor of Psychiatry at the Medical University of South Carolina and the Associate Dean for Clinical and Translational Research, an internationally recognized expert on PTSD and dual diagnosis, wrote a letter to Canadian IRB Services in support of an exclusion using the 60-day period. We agreed to a compromise and extended the exclusion to six months. We request the same compromise in our Canadian MDMA/PTSD study.

7. Re: Informed Consent:

- a) Re: risks of MDMA: Please provide the percentage of people expected to experience each of the listed potential adverse effects.
- b) Please clarify that people who had recently (in the last 365 rather than 60 days) problems with drug abuse should not take part in this study.
- c) Please provide what is the average expected increase in blood pressure and heart rate.

a) Percentages for most commonly reported side effects range from 40% to 70%, as stated in the current ICF, while less commonly experienced effects occurred in at least 13% of participants in Phase 1 studies. Percentages can be viewed in an attached document.

Some of the findings of potential risks are derived from studies reporting inferential and not descriptive statistics, as with changes in perception and immunological effects, In these cases, exact percentages cannot be provided but are presumed to be greater than 50%.

None of the serious adverse events listed as occurring with ecstasy users have occurred in MDMA Phase I studies of over 400 people or in any of the MDMA/PTSD Phase II studies with about 36 people treated to date. We provide percentages of people likely to experience a given adverse effect if the information is available. If desired, an estimated percentage can be made from studies presenting data as inferential statistics.

- b) We will clarify the IC however you require, after you have reviewed our request to retain the current exclusion of subjects with active substance abuse in the prior 6 months.
- c) From previous studies of 365 people and using identical or similar doses of MDMA, average increase in SBP was 30-35 mmHg and average increase in DBP was 15-20 mmHg. Average elevation in heart rate was 18-20 beats per minute (BPM).

The cited attachments are available as a hard copy.

The questions and sponsor's responses were discussed with Dr. E. Komsta.

Response to Clarifax sent March 5, 2009 to Rick Doblin, Ph.D

“1. Please correct in the addiction section the time-frame for people who recently had problems with drug abuse from 60 days to 6 months”

The correction has now been made on Page 10, it was an inadvertent error.

“2. Re: possible brain damage section: Please explain in simple terms what was the “small change” in the brain scans of people who took ecstasy in recreational settings.”

The change was a decrease in region-specific cerebral blood volume in the dorsolateral prefrontal cortex. The researchers who found the change hypothesized that it was either due to transient reduction in a type of serotonin receptor or a sign of reduced function in this area.

We added the following statement:

“Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area.”

Reviewer’s Discussion/Summary:

	Applicable	Not Applicable
Non-Clinical and Clinical Safety & Efficacy Assessment Completed:	*	
Reason: [If the drug has not been reviewed previously, there is a substantial amount of new information that has not been captured in the PSEAT-CTA, or this is a new indication, the Non-clinical and Clinical Safety & Efficacy Assessment should be completed as appropriate.]		

This pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve adult patients with treatment-resistant posttraumatic stress disorder.

Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive 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 cotherapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the

morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression symptoms six weeks after the third open-label session.

Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

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.

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.

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.

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.

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.

COMMENT:

The rationale for the proposed study of MDMA- assisted psychotherapy is sound. The study design including proposed doses of MDMA follow the previous pilot studies in US and Switzerland. Safety issues are addressed adequately. NOL is proposed for this study.

NON-CLINICAL AND CLINICAL SAFETY & EFFICACY ASSESSMENT

Overview

(+/-) 3,4-methylenedioxyamphetamine (MDMA, 3,4-methylenedioxy-nmethylamphetamine, N-methyl-3,4-methylenedioxyamphetamine,) has the chemical formula of $C_{11}H_{15}NO_2$. It is a phenylisopopylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in 1912 as an intermediate chemical involved in the production of the stytic hydrastinine (Freudenmann et al. 2006). No significant investigations examined the pharmacological, physiological or psychological effects of MDMA until the 1950s, when the US Army administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991), and there are records of a police seizure of MDMA in the early 1970s that suggests either intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Some have estimated that up to 4000 people underwent MDMA-assisted psychotherapy in North America prior to its placement in Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001). A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986; Greer and Tolbert 1986), including Greer and Tolbert's study of MDMA in a psychotherapeutic context. However, controlled human studies of MDMA did not

commence until early to mid-1990s, with the publication of research conducted by Grob and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006; Mithoefer 2006; Oehen 2006).

Pharmacological and toxicological effects

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see

also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use

high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear.

MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture.

The nature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978),

and an a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973).

Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al.

2003). Typically, human trials have used doses between 1 and 2 mg/kg.

Pharmacokinetics and biological disposition

MDMA is metabolized in the liver and has a half-life of seven to nine hours (de la Torre et al. 2004), though a half-life of 11 hours has been reported (Pizarro et al. 2004) and is distributed throughout the body (De Letter et al. 2004), though a study in rats reported

greater disposition in brain than in plasma (Chu et al. 1996). After 100 mg MDMA, T_{max} is reached at 2 hours, at a time close to peak physiological and subjective effects, and urinary recovery over a 24 hour period is 15% (de la Torre et al. 2004). The pharmacokinetics of MDMA have been primarily characterized by a group of Spanish researchers, with the exception of one publication from researchers in the Netherlands. The Spanish team first reported nonlinear pharmacokinetics for MDMA, findings that are confirmed in recent studies in nonhuman primates (Mechan et al. 2006). MDMA is metabolized by several CYPD enzymes, including but not limited to CYP2D6, CYP1A2 and CYP3A4. Monoamine oxidase and catechol-O-methyltransferase (COMT) also metabolize MDMA.

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

1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004;

Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% (de la Torre et al. 2004). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Safety and effectiveness in humans obtained from prior clinical studies

When Merck first patented MDMA, it was solely as an intermediate step toward the production of another compound (Freudenmann et al. 2006), and there were no early clinical investigations of MDMA. Published accounts of MDMA-assisted psychotherapy first appeared during the time of hearings for the scheduling of MDMA (Adamson 1985). Shortly afterwards, the only published study of MDMA-assisted therapy appeared, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986). These accounts suggested that, when combined with

psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a lifethreatening

illness. The Swiss government permitted psychotherapists to conduct MDMA-assisted psychotherapy between 1988 and 1993 (Gasser 1994; Widmer 1998). These therapists reported that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration. The Swiss

psychotherapists did not publish any formal analyses of the treatment. Permission to conduct MDMA-assisted psychotherapy in Switzerland was revoked due to events unrelated to the safety or efficacy of MDMA and due to the lack of any published research results.

Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after

MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001).

A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway to study the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006).

Possible Risks and Side Effects

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of

hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

Common Adverse Effects and Side Effects

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies of MDMA are listed in Table 2 and include reduced appetite, dizziness,

tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance,

Investigator's Brochure: MDMA MAPS: 12/2007

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dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas

(Harris et al. 2002). Other less common side effects include parasthesias (unusual body sensations) such as tingling sensations, or feeling hot or cold. These effects are transient

and recede with the waning of drug effects. One study found that women were more likely than men to experience most commonly reported side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating (Liechti et al. 2001b).

Sub-acute effects appearing 24 to 48 hours (1 to 2 days) after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related

sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with subacute effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006).

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of

impaired serotonin function or verbal memory after exposure to one to three doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggest that this risk is minimal after a low number of exposures. While there may also be risks related to psychological well-being such as increased symptoms of anxiety or depression, support for these long-term

effects are even less strong than for the previously listed changes.

Abuse Potential

The US Drug Enforcement Administration (DEA) placed MDMA in Schedule 1, the most restrictive schedule reserved for compounds with high abuse potential and no medical value, and most other nations followed the lead of the US in making MDMA a tightly controlled substance. Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less

Investigator's Brochure: MDMA MAPS: 12/2007

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intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses

moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens

but lesser than for psychostimulants.

Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et

al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al.

2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al. 1999).

Reproductive and Developmental Toxicity

Previous research supported a possible link between ecstasy use and birth defects (McElhatton et al. 1999), while an epidemiological study conducted in 2004 in a large cohort of pregnant women in England failed to support this link, at least in respect to a specific cardiac defect (Bateman et al. 2004). However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant (Ho et al. 2001).

Several teams of researchers have performed studies of developmental toxicity in rodents

(see for example (Koprach et al. 2003a; Koprach et al. 2003b; Piper and Meyer 2004; Williams et al. 2005). In some studies, the researchers administered large, repeated doses

to pregnant rats, and in others, the MDMA was administered to neonatal rats. The researchers did not report gross structural abnormalities in rats exposed to high doses of

MDMA in utero. However, studies of MDMA in neonatal rats found changes in numbers of serotonin or dopamine cells and impaired learning or memory, particularly when MDMA was administered from the 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et

al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose

of MDMA in young rats also produced less of an increase in BT and fewer signs of "serotonin syndrome" when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable

to some effects of MDMA.

Research trial data

Information is being gathered and prepared. Side effects reported in the first clinical trials

are similar to those reported in controlled studies, though anxiety may be more prevalent,

due in part to the condition under study and in part to the nature of the setting, as participants are encouraged to confront emotionally upsetting thoughts, memories and feelings. In this setting anxiety is not chiefly viewed as a side effect, but as an element of

the underlying disorder and the therapeutic process.

March 6, 2009

Response to Clarifax sent March 5, 2009 to Rick Doblin, Ph.D
From Beata Wiatrakowska M.D. FRCP(C)
Tel: 613- 941-2132 Fax: 613-952-9656
Study Control# 127822
File # 9247-M2554-21C

Dear Dr. Wiatrakowska,

I am responding to the fax you sent yesterday, after requesting that the contents be sent again because the second page of the facsimile was illegible.

“1. Please correct in the addiction section the time-frame for people who recently had problems with drug abuse from 60 days to 6 months”

The correction has now been made on Page 10, it was an inadvertent error.

“2. Re: possible brain damage section: Please explain in simple terms what was the “small change” in the brain scans of people who took ecstasy in recreational settings.”

The change was a decrease in region-specific cerebral blood volume in the dorsolateral prefrontal cortex. The researchers who found the change hypothesized that it was either due to transient reduction in a type of serotonin receptor or a sign of reduced function in this area.

We added the following statement:

“Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area.”

Please find along with this fax the pages of relevant text from the informed consent with changes made. I will also send a copy of this letter and the entire informed consent form containing these revisions via email.

Sincerely,

Rick Doblin Ph.D.
Rick@maps.org

March 6, 2009

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From Beata Wiatrakowska M.D. FRCP(C)
Tel: 613- 941-2132 Fax: 613-952-9656
Study Control# 127822
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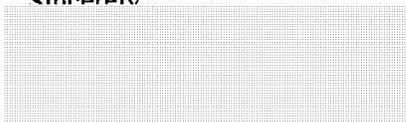
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We added the following statement:

"Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood flow found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it could be a sign of reduced function in this area."

Please find along with this fax the pages of relevant text from the informed consent form and the changes made. I will also send a copy of this letter and the entire informed consent form containing these revisions via email.

Sincerely,



Rick Doblin Ph.D.
Rick@maps.org

Risks from MDMA

Changes in vision, hearing or other senses: In previous studies in which MDMA was given to volunteers, including a total of about 365 subjects without emotional disorders and 21 with PTSD, most subjects reported experiencing minor changes in vision and hearing, such as sounds seeming closer or farther away than usual, or objects seeming brighter than usual, with these changes lasting 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness.

Blood pressure and heart rate. These effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate.

Blood pressure rose well above normal levels in a few subjects (a little less than 5%) after MDMA was given in previous studies, but these subjects did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in individuals with pre-existing heart or blood vessel defects. These serious problems could include heart attack or stroke. We will screen all potential subjects for preexisting heart problems before they are allowed to be in this study. This doesn't guarantee that no heart problems will occur, but it does greatly reduce the risk of this happening.

Anxious or jittery feeling: Some subjects in previous studies reported feeling over-stimulated or anxious. It usually lasted less than 30 minutes. Due to your PTSD, you may be more likely to have severe anxiety or panic attacks. Letting yourself accept and feel those emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study doctors will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask the attendant to call the study doctors immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study doctors may require you to stay in a nearby hospital.

Serious problems and death: There have been some serious problems, and even deaths, associated with the use of Ecstasy outside of controlled clinical or laboratory settings. Serious problems have included high fever, drinking too much liquid, convulsions, and liver damage. Some recreational users of Ecstasy have become severely anxious, depressed or paranoid (thinking that other people are against them). Since you will be receiving moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur during or after the experimental

session, but this does not guarantee that they could not occur. If they do occur, the study doctors are prepared to respond to these problems.

Insomnia & drowsiness: In previous studies, less than 40% of subjects have reported insomnia (difficulty sleeping), and feeling tired, irritable, or drowsy for as long as 3 days after MDMA.

Mood: Some after-effects of MDMA may be noticeable up to 2 or 3 days later. While some subjects feel that their mood is better, others feel it is worse.

Immune System: You will probably have a less active immune system for 2 or 3 days after MDMA. This may make you more likely to become sick with a cold or other infection during this time.

Addiction: There is a small chance that you will become dependent on (addicted to) MDMA. One study found that up to 6% of people using Ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory.

People who have recently (in the last 6 months) had problems with drug abuse should not take part in this study.

There may be unknown side effects or risks from the use of MDMA.

Possible Brain Damage

Experiments in rats and monkeys show that high and repeated doses of MDMA can change brain cells that release a chemical called serotonin; in mice only, the affected cells release dopamine. The changes include loss of the part of the cell (called "axons") that connects different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult tests of memory. Recent studies in monkeys and rodents suggest that the doses in studies finding damaged axons are too high to reflect typical human doses of ecstasy or MDMA used in studies.

Many studies found that people who had used Ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use Ecstasy and performed less well on tests of planning and impulse control. These differences are not great, but they have lasted for at least a year after people had stopped taking Ecstasy. Not all studies have found Ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use Ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take ecstasy than people without these problem

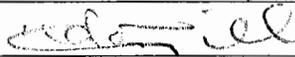
Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA, and did not see any changes in the brain, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area. Findings from these studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a medical laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few ecstasy tablets in a recreational setting with people who did not take them found less improvement in memory in the people who took ecstasy, and no other changes in thinking or planning. It is believed that the amount of MDMA you will receive will not produce any lasting changes in recall or planning ahead, though this cannot be guaranteed. You will not get a second dose of MDMA if they believe you are showing signs of memory problems.

Health Products and Food Branch
Direction générale des produits de santé et des aliments
QUALITY EVALUATION SUMMARY – CTAs
(QES-CTA)

E.1 SUBMISSION SUMMARY	
Proprietary (Brand) Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	MDMA ; 3,4 methylenedioxymethamphetamine
Company (Manufacturer/Sponsor) Name	Multidisciplinary Association for Psychedelic Studies
Dosage Form(s)	Capsule
Strength(s)	12.5 mg (active placebo); 25 mg(active placebo);62.5 mg (supplemental dose); and 125 mg (<u>initial dose</u>)
Route of Administration	Oral
Contact Information	Rick Doblin Phone: 617-484-8711; Fax: 617-484-8427

Type of Submission (and Phase for CTAs)	Phase-I I- Clarifax Response	
TPD Target Date	200 9-03-18	
Control Number / File Number	12 7822	9427-M2544 - 21C
Number of Volumes	C/T one folder Bin 2 dated 2009-02- 16	
Lead Clinical Bureau/Division	Office of clinical trials	

Recommendation	This submission IS** recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information.		
1st Reviewer(s)	Udai Gill	Review Hours	1 / 1
Start Date	2009-03-09	Completion Date	2009-03-09
Signatures	1st Reviewer(s)		
	2nd Reviewer(s)		
Report Access	I:\DPQ\Submission\CTA\HIJKLMMultidisciplinary associates for psychedelic studies\MDMA\127822 cta-2009-r02.doc		
References			

Attachments	Clarifax response
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**commitment to provide information on the active placebo and drug product batch numbers, batch analysis, date of manufacture and analysis and manufacturing site, prior to dosing study.

Evaluator's Introduction/Discussion:

This is a review of a phase II CTA for a protocol No. MP-4: 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

Dose 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.

Dosing: An Experimental 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.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION SPONSOR

We have the following comments with respect to your Phase II CTA for MDMA, strengths at 12.5 mg, 25mg, 62.5mg and 125mg per capsule, Control no. 127822:

Comment 1. The following comments concern the specifications and batch analysis of the drug product.

- a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.

Response: See attachment

Evaluation: The sponsor has agreed to provide the drug product specifications. This is sufficient at this stage.

- b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis. Alternatively, you may provide a commitment to provide this information prior to dosing.

Response: See attachment

Evaluation: The sponsor has agreed to provide all above information on the lot of drug product used in this clinical trial prior to dosing.

2. Please provide a commitment that the stability (includes tests for appearance, assay, related substances/degradation products and dissolution) of one of the active placebo will be monitored throughout the duration of the clinical trial.

Response: See attachment

Evaluation: The sponsor has agreed to provide a commitment that one of the active placebo will be monitored throughout the duration of the clinical trial. This is considered acceptable.

Response to Clarifax
Prepared by Rajkumar Kumarabasan, Ph.D.
Chemistry Advisor
Clinical Trials Quality Division
Office of Clinical Trials
5th Floor, Highland Cross, Tower B
3615
1400 Scott Street
Ottawa, Ontario
Canada K1A 6K9
Tel: 613-941-6059
Fax: 613-954-3867

March 3, 2009

This information is prepared in response to Clarifax issued to Rick Doolin on March 3, 2009 for a Clinical Trial Application for a study with the drug substance (product) MIDMA.
Protocol Number: MP-4
Control Number: 127822

Dear Rajkumar Kumarabasan, Ph.D.,

Please find the answers to your queries below.

1. a. Please provide the drug product specifications that includes tests and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units, and dissolution.

TEST	METHOD	ACCEPTANCE CRITERIA
Appearance	Visual	White
Identity	HPLC	Conform to Standards
Assay	HPLC	Conform to Standards 90-110%
Related Substances	HPLC	Report Results
Degradation		
Uniformity of Dosage Units	weight	Report Results
Dissolution	USP	Report Results

Above is the chart that you requested.

1.b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture, and date of analysis. Alternatively, you may provide a commitment to provide this information prior to dosing.

I pledge and commit to provide all of the above listed information (batch number, batch size, date and site of manufacture and date of analysis) prior to dosing.

2. Please provide a commitment that the stability (includes tests for appearance, assay, related substances/degradation products and dissolution) of one of the active placebo will be monitored throughout the duration of the clinical trial.

I pledge and commit that the stability (includes tests for appearance, assay, related substances/degradation products and dissolution) of one of the active placebo capsules will be monitored throughout the duration of the clinical trial.

TEST	METHOD	ACCEPTANCE CRITERIA
Appearance	Visual	White
Assay	HPLC	Conforms to Standards NO-1 HPLC
Related Substances	HPLC	Report Results
Degradation		
Dissolution	USP	Report Results

I think I've now responded to all of the issues you raised in your CLM file of 3/3/09.


Rick Doherty, Ph.D.

Rick Doherty, Ph.D.
MAPS President



Canac

Health Products and Food Branch
Direction générale des produits de santé et des aliments

Therapeutic Products Directorate

Direction des produits thérapeutiques

OUR MISSION: We contribute to the health of Canadians and to the effectiveness of the health care system by regulating pharmaceuticals and medical devices and by providing Canadians with access to information to make informed choices.

NOTRE MISSION : Nous contribuons à l'amélioration de santé des Canadiens et à l'efficacité du système de soins de santé en réglementant les produits pharmaceutiques et les matériels médicaux et en offrant aux Canadiens un accès à l'information pour qu'ils puissent faire des choix éclairés.

If you receive this fax in error, please advise the sender immediately.
Si vous recevez cette télécopie par erreur, veuillez en aviser immédiatement l'expéditeur.

TO/À

Name/Nom : Dr. Rick Doblin Date : March 3, 2009

Organization/Organisme : Multidisciplinary Association for Psychedelic Studies

Tel./Tél. (617) 484-8711

Fax/Télécopieur : (617) 484-8427

No. of Pages, including this page/N^o de pages, incluant cette page : 2

FROM/DE

Name/Nom : Dr. Rajkumar Kumarathasan E-Mail/Courriel : rajkumar_kumarathasan@hc-sc.gc.

Tel./Tél. : (613) 941-6059 Fax/Télécopieur : (613) 954-8867

TITLE	Chemistry Advisor / Conseiller de Chimie	TITRE
Division	Clinical Trials Quality Division / Division de la qualité pour les essais cliniques	Division
Directorate	THERAPEUTIC PRODUCTS DIRECTORATE / DIRECTION DES PRODUITS THÉRAPEUTIQUES	Direction
Office	Office of Clinical Trials / Bureau des essais cliniques	Bureau
Room	5012	Pièce
Location	5 th Floor - Holland Cross, 1600 Scott Street, Tower B	Lieu
Address Locator	3105	Localisateur d'adress
City/Province	Ottawa, Ontario	Ville/Province
Postal Code	K1A 0K9	Code postal

Web site/site Web : http://hc-sc.gc.ca/dhp-mps/index_e.html / http://hc-sc.gc.ca/dhp-mps/index_f.html

RE: Phase II CTA for MDMA 12.5 mg, 25 mg, 62.5mg and 125 mg , Control No. 127822:

In accordance with the Therapeutic Products Directorate's policy on *Management of Drug Submissions*, we request clarification of the points on the following page(s) so that we can continue our evaluation of the Quality (Chemistry and Manufacturing) information in your submission.

Please provide a complete response within 2 calendar days of this communication via facsimile. The response should include the Directorate's comments and summary responses in a question and answer format. Where appropriate, the relevant portions of the Quality Summary template (e.g., QOS-CE(CTA)) should be used to summarize the new or revised information provided in the accompanying solicited information, such as updated stability data.

If the requested information is not received within the stated time frame, or the response is incomplete, then a NOT SATISFACTORY NOTICE will be issued. Please inform the undersigned as soon as possible, by fax, if you will be unable to provide a complete and timely response and prefer that a Notice be sent.

We have the following comments with respect to your CTA for MDMA
12.5mg, 25mg, 62.5mg and 125mg, Control 127822:

1. The following comments concern the specifications and batch analysis of the drug product.
 - a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.
 - b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis. Alternatively, you may provide a commitment to provide this information prior to dosing.
2. Please provide a commitment that the stability (includes tests for appearance, assay, related substances/degradation products and dissolution) of one of the active placebo will be monitored throughout the duration of the clinical trial.

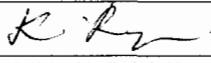


Rajkumar Kumarathasan, PhD.
Chemistry Advisor
Clinical Trials Quality Division
Office of Clinical Trials

Health Products and Food Branch
Direction générale des produits de santé et des aliments
QUALITY EVALUATION SUMMARY – CTAs
(QES-CTA)

E.1 SUBMISSION SUMMARY	
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Company (Manufacturer/Sponsor) Name	Multidisciplinary Association for Psychedelic Studies
Dosage Form(s)	Capsule
Strength(s)	12.5 mg (active placebo); 25 mg(active placebo);62.5 mg (supplemental dose); and 125 mg (<u>initial dose</u>)
Route of Administration	Oral
Contact Information	Rick Doblin Phone: 617-484-8711; Fax: 617-484-8427

Type of Submission (and Phase for CTAs)	Phase-I I	
TPD Target Date	200 9-03-18	
Control Number / File Number	12 7822	9427-M2544 - 21C
Number of Volumes	C/T one folder Bin 2 dated 2009-02- 16	
Lead Clinical Bureau/Division	Office of clinical trials	

Recommendation	This submission IS NOT recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information.		
1st Reviewer(s)	Udai Gill	Review Hours	10 hrs + 2
Start Date	2009-02-23	Completion Date	2009-02-27
Signatures	1st Reviewer(s)		
	2nd Reviewer(s)		
Report Access	I:\DPQ\Submission\CTA\HIJKLM\Multidisciplinary associates for psychedelic studies\MDMA\127822 cta-2009-r01.doc		
References			

Attachments	EDQM certificates, Lactose, DS information
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This is a review of a phase II CTA for a protocol No. MP-4: A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Dose 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.

Dosing: An Experimental 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.

Placebo: Active Placebo (low dose MDMA + Lactose); active placebo doses are 12.5 mg and 25mg. 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.

Drug Substance:

The drug substance, MDMA [(+/-)3,4 – methylenedioxyamphetamine. HCl] is sourced from Lipomed AG, Switzerland. MDMA batch No. MDM-94-HC/94.1B5.5 . The sponsor has provided recent testing results for heavy metals and residue on ignition and results are considered acceptable (attachment). Rest of the results are provided in drug manufacturer's report. The current C of A for the drug substance including results for impurities.

The sponsor has indicated that the study API will be shipped in brown bottle with a white screw cap. The drug substance seems to have good stability as per provided information and analysis performed over certain periods.

Drug Product:

The drug product is compounded at Kerrisdale pharmacy, Vancouver BC. Racemic MDMA is 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. The active placebo capsules contain lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

The drug product is compounded at Kerrisdale pharmacy, Vancouver BC. All 108 capsules will have equivalent weight. Each dose 12.5 mg (15 capsules); 25mg (15 capsules) , 62.5mg (39 capsules), and 125 mg (39 capsules).

The sponsor will be asked to provide the specifications for the drug product, batch No used in this study and test results.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION

SPONSOR

We have the following comments with respect to your Phase II CTA for MDMA, strengths at 12.5 mg, 25mg, 62.5mg and 125mg per capsule, Control no. 127822:

1. The following comments concern the specifications and batch analysis of the drug product.

- a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.**
- b. You are requested to provide the batch No and test results for all strengths of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis. If not available at this time, a commitment to submit this information prior to first dosing should be provided.**

2. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the active placebo will be monitored throughout the duration of the clinical trial.

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MB.BS. FRCP[C]

Study Number: M-P4

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 21, 2008

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 12.5 mg (active placebo supplemental dose), 25 mg (active placebo-initial dose), 62.5 (experimental dose-supplemental dose), 125 mg (experimental dose-initial dose). Supplemental dose administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

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 either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 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 during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling

participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

The study will take place at one center in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, will take place at the offices of the principal investigator, Dr. Ingrid Pacey. Assessments of PTSD symptoms and neurocognitive function will be performed in the offices of the independent rater, Dr. Karen Tallman, located at the same street address as the offices of the principal investigator.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD and with a CAPS score of 50 or higher. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all of the inclusion criteria listed below without meeting any of the exclusion criteria. Participants must reside in Canada.

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 [1-3]. 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 [4, 5] 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 [5].

As described above, capsules containing the initial dose of MDMA will be administered in [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.

S Drug Substance

S.1 General Information

The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N, -alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by [REDACTED]

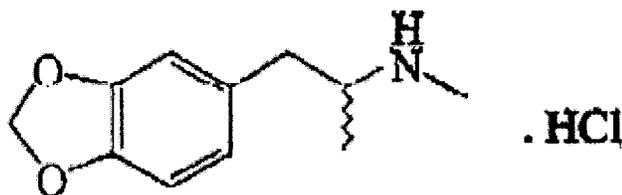
[REDACTED] On January 30, 2006, a quality control analysis was performed by [REDACTED]. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94.1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-

methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.

Step 2: MDA-nitrostyrol + $LiAlH_4$ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [REDACTED]

[REDACTED] Specifications of manufacture, including solvent and procedures, are translated in the second report of [REDACTED]

S.2.3 Control of Materials

See above and contained in report by [REDACTED] p. 1

S.3 Characterization:

Batch number is [REDACTED]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]

[REDACTED] One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2).

Validation: From manufacturer, data available upon request [REDACTED]

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] and listed above.

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(\text{Max})}$ = 1 234 +/- 1 nm

ϵ_{mol} = 3800 +/- 500

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by Brenneisen:

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

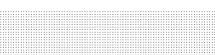
Injection: 250 C, splitless 1 μL

Detection: full scan

Identity (HPLC-DAD): TR = 7 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA)

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from 

S.4.4 Batch Analysis:

As listed above, the batch is MDM-94-HC/94.1B5.5.

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

UV, in distilled water, $\lambda_{(MAX).1} = 234.0$ nm

$\epsilon_{mol.1} = 3939$

$\lambda_{(Max).2} = 285.0$ nm

$\epsilon_{mol.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%

Freebase content: 83.51%

Water content: 055%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 100 ppm

Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: **Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%**

Tests for presence of heavy metals: **Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm**

More details are presented in the attached report (in German).

>> The sponsor has provided test results for ignition residue and heavy metals. This is considered acceptable.

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED] and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and

opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [REDACTED] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment number 4, listed below).

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

[REDACTED] reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

[REDACTED] also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

P. Drug Product

The drug product will consist of 00 opaque gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: Experimental dose initial dose 125 mg MDMA per capsule; experimental dose supplemental dose 62.5 mg MDMA per capsule; active placebo initial dose 25 mg MDMA plus lactose to reach equivalent weight of 125 mg capsule per capsule; active placebo supplemental dose 12.5 mg MDMA plus lactose to reach weight of 62.5 mg per capsule. There are no other ingredients in these capsules. The capsules will be prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but will be compounded by Kerrisdale Pharmacy, a Vancouver-area pharmacist. The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies (2, 4) and on narrative reports of MDMA-assisted therapist (as Adamson and Metzner 1980; Stolaroff 2004). A dose of 125 mg has been used in a previous sponsor-supported research study conducted in the US (3). The sponsor chose the active placebo dose on the basis of a previous research study (4), with 25 mg expected to produce very few effects. The sponsor selected an inactive material to help maintain the blind by ensuring that all doses are of equal weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

The principal investigator will transport the MDMA to Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk will encapsulate experimental and active placebo doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy will supply the capsules and lactose. MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all 108 capsules have equivalent weights. All capsules will contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X39) and a varying amount of lactose to maintain equal weights.

The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses.

The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, the randomization monitor selects a number from amongst a set of cards based on the list, and that number is the bottle number used for that participant.

P.3.3 Batch Formula

lactose monohydrate are provided in the reports supplied by the manufacturer. passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Opaque 00 gelatin capsules will be filled with the appropriate dose of MDMA.

Experimental initial dose: 125 mg

Experimental supplemental dose: 62.5 mg

Active Placebo initial dose: 25 mg + approximately 100 mg lactose or appropriate amount so that full weight = 125 mg

Active placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg
Capsules placed in numbered bottles

>> The information on the batch formula is considered acceptable.

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all “active placebo” doses of the product. Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA capsules are of equal weight.

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, , issued by the manufacturer, lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of <= 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of opaque capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

>> The sponsor has not provided specifications or batch analysis results. The sponsor will be asked to provide the specifications and results for the batches of the drug product used in this clinical trial study.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and stored with the rest of the capsules in a separate closed bottle . will bring them to the pharmacist every six months for stability assessment and to make sure they will dissolve appropriately. Samples of the

compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

>> ** The sponsor commits to monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis.

>>The sponsor will be asked to place one of the active placebo on stability testing program.

P.7 Container Closure System

All doses of MDMA will be in the form of opaque capsules. The MDMA capsules will be stored in amber glass bottles (vials) containing one 3 gram silica gel desiccant in each bottle. Each bottle will be assigned a number intended for use in the randomization process so as to maintain the double blind. All bottles will be appropriately stored in the offices of the principal investigator.

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

A Attachments:

1. Lipomed manufacturer's specification and batch analysis
2. Quality Analysis of [REDACTED] pp. 1-2 concern this batch of MDMA and p. 3 concerns capsules produced for a sponsor-supported study in Switzerland
3. Additional details of manufacture provided by Lipomed and translated by [REDACTED] and additional tests performed by Interlab Belp
4. Original reports from Interlab Belp and Lipomed (German)
5. Stability report of [REDACTED] referring to different source and batch of MDMA but supporting long-term stability
6. Certificate of suitability for capsules
7. Letter associated with certificate of suitability for capsules to be used in this study
8. Product description for lactose ordered in this study
9. Certificate of suitability of lactose ordered for study
10. Batch analyses for the lactose used in this study
11. Certification that the lactose is BSE/TSE free

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation]*. J Clin Psychopharmacol, 2000. **20**: 455-66.
2. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. J Psychoactive Drugs, 1986. **18**: 319-27.

3. Mithoefer, M., *MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): Eleventh update on study progress*. MAPS Bulletin, 2008. **17**: 11-12.
4. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
5. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. **162**: 396-405.

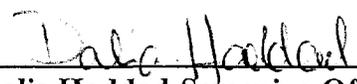
	Health Canada / Santé Canada	Office of Clinical Trials
Screening Template for CTA - 30-day default review		
CR File #: 9427-M2544-21C Date received in OCT : 2009.02.16 Review 1 Start Date: 2009.02.16 Study Phase: Phase II-30 day Study Population: Males, Females Document I.D. #: <i>520609</i>	DSTS Control #: 127822 Due Date: 2009.03.18 Data Description: CL/2VO/2CD Clinical Division: Vol. # 1 Quality Division: Vol. # 2	
PSEAT Format: PDF		
PSEAT Template Path: <i>\\seribn55\mdma_mars\New Work\127822-cta.doc</i>		

Product Name : MDMA	
Protocol # or Identifier: MP-4	
Protocol Title: 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	
Therapeutic/Pharmacological Classification: Monoamine releaser and uptake Inhibitor [Clinical Group II : CNS]	
Sponsor Name : Multidisciplinary Association for Psychedelic Studies	Country: USA

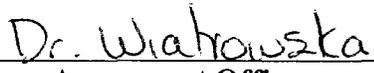
#	Form	Route	Medicinal Ingredients	Strength / Unit	Basic Unit	F#
1	CAP	ORL	UNASSIGNED	12.5 mg	CAP	1
2	CAP	ORL	UNASSIGNED	20 mg	CAP	2
3	CAP	ORL	UNASSIGNED	62.5 mg	CAP	3
4	CAP	ORL	UNASSIGNED	125 mg	CAP	4

Comparator Product: Active Placebo (Low Dose MDMA + Lactose)
Screening Officer's Comment(s): - This is a re-submission of ctrl # 126833 - IB (December 2007)

Previous related submission, CTA control# 126833 (WITHDRAWN), reviewed by: N/A
- Clinical Assessment Officer: DR. BEATA WIATROWSKA / 2009.01.23 - Quality Assessment Officer: UDAI GILL / 2009.01.23



Dalia Haddad-Screening Officer



Assessment Officer

2009.02.16 / 2009.02.16

 Screening start date / Completion date

Feb 17, 2009 /

 Assigned date / Review Hours



Health Canada
Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

Your file Votre référence

Our file Notre référence

16 February 2009

9427-M2544-21C

Rick Doblin PhD
President, MAPS
3 Francis St.
BELMONT, MA 02478-2218
USA

ACKNOWLEDGEMENT CLINICAL TRIAL APPLICATION
RE: PROTOCOL# MP-4

Dear Dr. Doblin:

This will confirm the receipt of your complete application on February 16, 2009, regarding your information and material to support a Clinical Trial Application (CTA) for **MDMA**, control number **127822**. You are requested to refer to the file number and control number in any communication relating to this application.

Please note that additional information may be requested during the review stage.

You are reminded that under paragraph C.05.006 (1) (b) of the Food and Drug Regulations, the sale of a new drug for clinical testing is prohibited if, within 30 days after the date of receipt of the complete submission, the Director has sent a notice by registered mail that the Clinical Trial Application is not satisfactory.

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/en



Health Canada
Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

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Our file Notre référence

23 January 2009

9427-M2544-21C

Rick Doblin, Ph.D.
President, MAPS
Multidisciplinary Association for Psychedelic Studies
3 Francis Street
BELMONT, MA
USA 024-78-2218
617-484-8711

Acknowledgement of Withdrawal

Re: Protocol # M-P4

Dear Dr. Doblin:

Thank you for your letter dated January 23, 2009, advising us of your decision to withdraw the Clinical Trial Application for **MDMA**, control number **126833**.

Your application has been withdrawn according to this notice.

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/mh

Canada

DOC ID # 547219



Rick Doblin <rick@maps.org>

2009-01-23 10:07 AM

To Hicham Chafak <Hicham_Chafak@hc-sc.gc.ca>

cc Rajkumar_Kumarathanan@hc-sc.gc.ca, Ilsa Jerome
<ilsa@maps.org>

bcc

Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol #
MP-4, Control Number: 126833

Dr. Chafak,

I'm writing to withdraw MAPS CTA Control Number 126833. We will resubmit once we have all the required Chemistry information.

I assume that we will still hear back from Dr. Beata Wiatrowska regarding our discussions about protocol design. We submitted a reply to her Clarifax on January 20 and am awaiting a response. Should I wait to hear from her and then let her know that we have withdrawn our CTA due to the need for additional Chemistry information, or should I proceed in a different manner?

Sincerely,

Rick Doblin, Ph.D.
MAPS President



Hicham
Chafak/HC-SC/GC/CA
2009-01-23 09:04 AM

To Rick Doblin <rick@maps.org>
cc Rajkumar_Kumarathanan@hc-sc.gc.ca
bcc

Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol #
MP-4, Control Number: 126833

Dr. Rick Doblin,

The information provided is not sufficient. Therefore please withdraw this
CTA

without prejudice and resubmit at a later date.

Send me an e-mail or fax requesting the withdrawal of this CTA. This should
be sent today (by noon)

Hicham Chafak
Office of Clinical Trials/Bureau des Essais Cliniques
CTQD
613-957-4149

This message and any attachments are solely for the intended recipient. If you are not the intended
recipient -- Please immediately and permanently delete.

Rick Doblin <rick@maps.org>



Rick Doblin <rick@maps.org>

2009-01-22 05:00 PM

To Rajkumar Kumarathanan
<Rajkumar_Kumarathanan@hc-sc.gc.ca>
cc Hicham Chafak <Hicham_Chafak@hc-sc.gc.ca>

Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol #
MP-4, Control Number: 126833

Dr. Kumarathanan,

I am submitting information as requested. I am not sure if it is
sufficient since we do not yet have the synthesis information which we
should be receiving tomorrow from Lipomed. We also do not have the
batch information for the lactose since the pharmacist has not yet
ordered the specific batch that will be used in the capsules. We should
be receiving information in about ten days about residue on ignition and
heavy metals from Interlab Belp, Switzerland.

Attached is information about the capsules and lactose.

If you feel this information is not sufficient, I withdraw MAPS' CTA,
Control Number: 126833. If so, we will resubmit once we have all the
required Chemistry information.

Sincerely,

Rick Doblin, Ph.D.
MAPS President
> Dear Dr. Doblin,

>
> We have not received a satisfactory response(as discussed on January 14,
> 2009) for comments 1, 2a, 4, 5, 6, 7 and 8 of the Clarification Request
> sent on January 12, 2009, yet. As per the telephone request by Dr. Hicham
> Chafak, Health Canada, on January 21, 2009, please provide a satisfactory
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> provide a satisfactory response, you are requested to withdraw this CTA
> without prejudice and resubmit at a later date in order to avoid the
> issuance of Not Satisfactory Notice.

>
> Thanks

>
> Rajkumar Kumarathasan, PhD.
> Chemistry Advisor
> Clinical Trials Quality Division
> Office of Clinical Trials, TPD
> Tel.:(613) 941-6059

>
>
> ----- Forwarded by Rajkumar Kumarathasan/HC-SC/GC/CA on 2009-01-22 10:48
> AM -----

>
> Rajkumar Kumarathasan/HC-SC/GC/CA
> 2009-01-14 10:22 AM

>
> To
> rick@maps.org
> cc

>
> Subject
> Re: Clarification Request:MAPS MDMA/PTSD Protocol # MP-4, Control Number:
> 126833

>
>
>
>
>
> Dear Dr. Doblin,

>
> Please ensure that a complete satisfactory response is submitted by
> January 21, 2009 (noon). Alternatively, you may withdraw the CTA and
> resubmit when the requested information is available.

>
> Thanks

>
> Rajkumar Kumarathasan, PhD.
> Chemistry Advisor
> Clinical Trials Quality Division
> Office of Clinical Trials, TPD
> Tel.:(613) 941-6059

>
>
>
>
>
> Rick Doblin <rick@maps.org>
> 2009-01-14 01:09 AM

>
> To
> Rajkumar Kumarathasan <Rajkumar_Kumarathasan@hc-sc.gc.ca>

> cc
> [REDACTED]
> Subject
> Re: Clarification Request:MAPS MDMA/PTSD Protocol # MP-4, Control Number:
> 126833
>
>
>
>
>
> Dr. Kumarathasan,
>
> As I suggested might be the case in my email to you on 1/12/09, it turns
> out that we will definitely not be able to respond to all the Chemistry
> questions you asked in your Clarification request by 1/14/09. I'm not
> sure exactly how long it will take us to reply. I'll let you know our
> time frame as soon as we figure that out.
>
> I'm going traveling for MAPS work from Wed. January 14 until Tuesday,
> January 20. If you will be sending any communications during that time
> (and also after), I'd appreciate receiving them via email in Word format
> rather than or in addition to fax. I hope this is not an extra burden on
> you and am grateful for the time it takes you to switch from fax to email.
>
> Sincerely,
>
> Rick Doblin, Ph.D.
> MAPS President
>
>
>

 - Response Clarifax 126833-2 1-23-09-2.doc  - Lactose_productsafety_303329.pdf  -
Certificate of sutability Capsules 2009.pdf

Response to Clarifax
Posted by Rajkumar Kumarathasan
Chemistry Advisor, Clinical Trials Quality Division
Therapeutic Projects Directorate,
Office of Clinical Trials,
5012
Holland Cross, Tower B
3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9
Tel: 613-941-6059
Fax: 613-954-8867
rajkumar_kumarathasan@hc-sc.gc.ca

January 22, 2009

Protocol Number: MP-4
Control Number: 126833

Dear Dr. Kumarathasan,

Please find below the questions excerpted from the clarifax sent to Rick Doblin on January 12, 2009, and our response to these questions below. In addition, we have located and are now working with a compounding pharmacist, Colin Holyk of Kerrisdale Medical Centre, 5591 West. Blvd, Vancouver BC, V6M 3W6. His telephone number is 604-261-0333.

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.

Details of synthesis are presented in section S.2.1 of the Chemistry, Manufacture and Quality section and are reproduced from page 1 of the CMC document from [REDACTED] from July 23, 2008. Though currently unavailable, [REDACTED] indicated that details of synthesis will be available on Friday, January 24, 2009.

2. The following comments concern the specifications and batch analysis of the drug substance.

- a. **You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.**
- b. **It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.**

a). Interlab Belp, Switzerland will assess the MDMA on tests and limits for residue on ignition and heavy metals following Ph.Eur. It will take eight to 12 days to obtain results for these tests. We pledge to provide the test results prior to administering MDMA to any study participants.

b) We will be using the same batch [REDACTED] analyzed on July 13, 2008. The batch is listed as MDMA-94.1 B5.5, as seen on S1 (p. 4) and the Lipomed data sheet.

3. Please revise Section S6 to include the description of the drug substance container closure system.

The drug substance will be contained in a brown glass bottle with a white, tightly closing cap. The MDMA will be sent from the [REDACTED] within this brown glass bottle.

4. Please report the quality standard for lactose (eg. USP/NF) in Section P.4.

The lactose used will be Lactose Monohydrate [REDACTED]
See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is [REDACTED]

Revision of P.4 would this appear:

“P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all “active placebo” doses of the product. The lactose will be lactose monohydrate purchased from [REDACTED] The quality standard will be [REDACTED] Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA capsules are of equal weight.

5. The following comments concern the specifications and batch analysis of the drug product.

a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.

b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis.

As described on p. 2 of all product safety sheets for lactose monohydrate issued by the manufacturer, [REDACTED] lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water.

The pharmacist has not yet ordered a specific batch of lactose.

6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.

The MDMA capsules will be stored in amber glass bottles (vials) containing one 3 gram silica gel desiccant in each bottle.

7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.

MDMA is an extremely stable molecule, and no dissolution is expected during the course of the study (See S.7, and response to Question #6, above). The study is expected to last about two years or less. Given the evidence, we believe that continued monitoring of the drug product for degradation is not necessary.

We will monitor the stability of capsules during the study. We will create four additional capsules specifically for stability testing. We will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be stored with the rest of the capsules in a separate closed bottle [redacted] will bring them to the pharmacist every six months for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.

The attached certificate of suitability is available from the manufacturer and provided by pharmacist Colin Holyk.

If you need any additional information, please let me know and I will be glad to provide it.

Sincerely,

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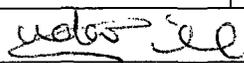
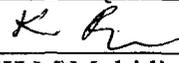
Deleted: 1

Rick Doblin, Ph.D.
MAPS President

Health Products and Food Branch
Direction générale des produits de santé et des aliments
QUALITY EVALUATION SUMMARY – CTAs
(QES-CTA)

E.1 SUBMISSION SUMMARY	
Proprietary (Brand) Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	MDMA ; 3,4 methylenedioxymethamphetamine
Company (Manufacturer/Sponsor) Name	Multidisciplinary Association for Psychedelic Studies
Dosage Form(s)	Capsule
Strength(s)	12.5 mg; 20 mg; 62.5 mg; and 125 mg;
Route of Administration	Oral
Contact Information	Rick Doblin Phone: 617-484-8711; Fax: 617-484-8427

Type of Submission (and Phase for CTAs)	Phase-I I- Clarifax response ; <u>Withdrawn</u>	
TPD Target Date	200 9-01-23	
Control Number / File Number	126833	9427-M2544 - 21C
Number of Volumes	C/T one folder Bin 2 dated 200 8-12-24	
Lead Clinical Bureau/Division	Office of clinical trials	

Recommendation	This submission has been withdrawn with respect to the Quality (Chemistry and Manufacturing) information.		
1st Reviewer(s)	Udai Gill	Review Hours	1 hr
Start Date	200 9-01-07	Completion Date	2009-01- 23
Signatures	1st Reviewer(s)		
	2nd Reviewer(s)		
Report Access	I:\DPQ\Submission\CTA\HIJKLMMMultidisciplinary associates for psychedelic studies\MDMA\126833 cta-2009-r02.doc		
References	Withdrawn by the sponsor		
Attachments	Clarifax response		

Evaluator's Introduction/Discussion:

This is a review of a phase II CTA for a protocol No. MP-4: 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

The CTA control number 126833 is withdrawn by the sponsor as per attached response.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION SPONSOR

We have the following comments with respect to your Phase II CTA for MDMA, strengths at 12.5 mg, 25mg, 62.5mg and 125mg per capsule, Control no. 126627:

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.
2. The following comments concern the specifications and batch analysis of the drug substance.
 - a. You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.
 - b. It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.
3. Please revise Section S6 to include the description of the drug substance container closure system.
4. Please report the quality standard for lactose (eg. USP/NF) in Section P.4.
5. The following comments concern the specifications and batch analysis of the drug product.
 - a. Please provide the drug product specifications that includes test and

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- b. **You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis**

6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.

7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.

8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.

Sponsor's Response

Rick Doblin
<rick@maps.org>

2009-01-23 10:07 AM

To Hicham Chafak <Hicham_Chafak@hc-sc.gc.ca>

cc Rajkumar_Kumarathanan@hc-sc.gc.ca, Ilsa Jerome
<ilsa@maps.org>

Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol
t # MP-4, Control Number: 126833

Dr. Chafak,

I'm writing to withdraw MAPS CTA Control Number 126833. We will resubmit once we have all the required Chemistry information.

I assume that we will still hear back from Dr. Beata Wiatrowska regarding our discussions about protocol design. We submitted a reply to her Clarifax on January 20 and am awaiting a response. Should I wait to hear from her and then let her know that we have withdrawn our CTA due to the need for additional Chemistry information, or should I proceed in a different manner?

Sincerely,

Rick Doblin, Ph.D.
MAPS President

Rick Doblin
<rick@maps.org>
2009-01-22 05:00 PM

To Rajkumar Kumarathasan
<Rajkumar_Kumarathasan@hc-sc.gc.ca>
cc Hicham Chafak <Hicham_Chafak@hc-sc.gc.ca>
Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol
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Attached is information about the capsules and lactose.

If you feel this information is not sufficient, I withdraw MAPS' CTA, Control Number: 126833. If so, we will resubmit once we have all the required Chemistry information.

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Rick Doblin, Ph.D.
MAPS President

> Dear Dr. Doblin,
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> issuance of Not Satisfactory Notice.

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> Thanks

>

> Rajkumar Kumarathasan, PhD.

> Chemistry Advisor
> Clinical Trials Quality Division
> Office of Clinical Trials, TPD
> Tel.:(613) 941-6059
>
> ----- Forwarded by Rajkumar Kumarathasan/HC-SC/GC/CA on 2009-01-22
10:48
> AM -----
>
> Rajkumar Kumarathasan/HC-SC/GC/CA
> 2009-01-14 10:22 AM
>
> To
> rick@maps.org
> cc

> Subject
> Re: Clarification Request:MAPS MDMA/PTSD Protocol # MP-4, Control
Number: 126833

> Dear Dr. Doblin,
>
> Please ensure that a complete satisfactory response is submitted by
> January 21, 2009 (noon). Alternatively, you may withdraw the CTA
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> Chemistry Advisor
> Clinical Trials Quality Division
> Office of Clinical Trials, TPD
> Tel.:(613) 941-6059
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> Rick Doblin <rick@maps.org>
> 2009-01-14 01:09 AM
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> Ilsa Jerome <ilsa@maps.org>
> Subject
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> Sincerely,
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> Rick Doblin, Ph.D.
> MAPS President

 - Response Clarifax 126833-2 1-23-09-2.doc  -

Lactose_productsafety_303329.pdf  - Certificate of suitability Capsules 2009.pdf



Health Santé
 Canada Canada

To: Dr. John Patrick Stewart
From: Dr. B. Wiatrowska

Security – Classification: HC Protected
Date: 22/01/2009

Subject: Protocol Safety and Efficacy Assessment Template
 Clinical Trial Application – Evaluation Report
Effective Date: 2008-03-01

Type of Submission / Phase of Trial	CTA	
Target Date	23/01/09	
Control Number / File Number	126833	

REVIEWER	
Recommendation	This Clinical Trial Application (CTA) is recommended for clearance with respect to Safety and Efficacy Information.
Name	Dr. B. Wiatrowska
Signature	
Date Review Completed	22/01/09
Review Time	30 hours

MANAGER	
Decision / Date	Agree with above recommendation.
Manager's Name	Dr. E. Komsta
Manager's Signature	

Canada

1. INTRODUCTION

(Information to be included in this section can be extracted from the PSEAT prepared by the sponsor)

A. SUMMARY OF PRODUCT INFORMATION		
Proprietary Name of Drug Product	MDMA	
Non-proprietary or Common Name of Drug Substance	Ecstasy	
Sponsor	MAPS	
Dosage Form(s)	capsules	
Strength(s)	12.5, 25, 62.5, 125 mg	
Route of Administration	oral	
Proposed Indication(s)	MDMA assisted psychotherapy for PTSD	
B. INVESTIGATOR'S BROCHURE (if applicable)		
Date and Version/Edition Number	Dec 2007, updated in response to Clarifax	
Cut-off date for data included in this version/edition of the Investigator's Brochure	As above	
C. CONTACT INFORMATION		
Contact Person/Name	Dr. Rick Doblin	
Telephone and Fax Number, including area code	Tel. 617-484-8711	Fax 617-484-8427
Email Address	Rick@maps.org	

2. INVESTIGATOR'S BROCHURE

(The relevant sections should be filled using a check mark)

	Acceptable	Not Acceptable
Date of Issue	*	
Rationale for Drug Development	*	
Drug Formulation	*	
Pharmacodynamics	*	
Pre-clinical Pharmacokinetics/ Pharmacodynamics	*	
Pre-clinical Toxicology	*	
Information on Patient Exposure, Duration of Study, Location of Study, Drug Dosage	*	
Efficacy	*	
Safety (Summary of ADRs: Deaths, Serious, Other)	*	

3. PROTOCOL SUMMARY

(Information to be included in this section can be extracted from the PSEAT prepared by the sponsor)

Study Synopsis

A Randomized, Active Placebo-controlled Pilot Study of 3,4-

methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects

with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 5, 2008

Background and Rationale

Background: 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). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population of the US. To date the treatment of PTSD has primarily been psychotherapeutic, 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 eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD [4]. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with 3,4-methylenedioxyamphetamine (MDMA), a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy.

MDMA is a ring-substituted phenethylamine that bears structural and pharmacological similarities to amphetamines and the psychedelic compound mescaline. However, it possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [8-11]. MDMA was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. 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 [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e. g. 16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22].

In

contrast, all available Phase I and Phase 2 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. 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.

Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. 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"

[8]. 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 [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25].

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. Though the psychopharmacology and neuropsychological underpinnings of the therapeutic effects of

MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli.

Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and

colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the 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 [28]. A one-year+ follow-up study is currently underway.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be 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.

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

The proposed pilot study will employ a randomized, double-blind, active placebocontrolled

design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive 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 cotherapist

team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session

on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via

Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression

symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the

study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a

total of about 8 months.

Number of Centres

The study will take place at one location in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, will take place at the offices of the principal

investigator, Dr. Ingrid Pacey. Assessments of PTSD symptoms and neurocognitive function will be performed in

This office is located in the same building as

List of Investigators

Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She 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 will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.

Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. 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. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She

is a clinical psychologist who has 15 years of experience and has conducted psychiatric diagnostic and competency assessments.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD who score 50 or higher on the Clinician-Administered PTSD Scale (CAPS). The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all the inclusion criteria listed below without meeting any exclusion criteria. Participants must reside in Canada.

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) 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 with PTSD symptoms that have persisted for no less than one year but no more than five 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 [32, 33].

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 nonsteroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).

c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).

8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.

9. Participants must be willing to remain overnight at [REDACTED] 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 [34], 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 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.

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 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 assignment 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 openlabel.

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 arrive ██████████ 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

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

reside [redacted] 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 [redacted]

[redacted] 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 antiinflammatory

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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4. INFORMED CONSENT FORM

(The relevant sections should be filled using a check mark)

	Acceptable	Not Acceptable
Full Disclosure of Risk	*	
Clarity of Language	*	
Description of Procedure	*	
Confidentiality for Patient	*	
Lack of Bias	*	
Placebo Disclosure (if applicable)	*	

5. OVERALL ASSESSMENT

Current Problems/Concerns:

Response to Clarifax t: control #126833, sent as electronic mail

Sent to Rick Doblin on January 16, 2009 from Beata Wiatrowska, M.D., FRCP(C)

1. Please provide updated information on studies of MDMA-assisted psychotherapy for PTSD and/or for potentially life threatening illness, if available.

All 21 participants in the MAPS-sponsored US study of MDMA-assisted psychotherapy in people with PTSD have completed the study. A long-term follow-up will soon be launched. A

preliminary data analysis found a greater decrease in PTSD symptoms after MDMA-assisted psychotherapy than after psychotherapy and inactive placebo. No drug-related serious adverse events (SAEs) occurred during this study. As of January 20, 2009, the MAPS-sponsored Swiss study of MDMA-assisted psychotherapy in people with PTSD has completed treatment of ten of twelve subjects. The eleventh subject has just been enrolled, and a potential twelfth and final subject is in the screening process. The MAPS-sponsored MDMA/PTSD study in Israel has so far completed treating two subjects and has enrolled a third subject. The second subject had PTSD for over 40 years, from the 1967 "Six Day" War, and after treatment has very few symptoms. No drug-related serious adverse events occurred during either the Swiss or Israeli MDMA/PTSD studies.

The study of MDMA-assisted psychotherapy in people with anxiety associated with advanced-stage cancer, conducted at McLean Hospital, Harvard Medical School, has enrolled one participant. This subject had a remarkably successful outcome in terms of reduced anxiety and pain and reported enhanced communications with his family.

2. Please provide more detailed reasons for the Swiss Government revoking permission to conduct MDMA assisted psychotherapy.

In 1988, the Swiss Ministry of Health gave permission to a small group of Swiss psychiatrists (members of the Swiss Medical Society for Psycholytic Therapy-SAEPT) to administer MDMA and lysergic acid diethylamide (LSD) to their Swiss patients within a psychotherapeutic context. Permission was revoked in 1993, for reasons completely unrelated to the administration of MDMA or LSD in psychotherapy.

The Swiss Ministry of Health revoked permission after one of the Swiss psychiatrists conducted a group psychedelic therapy session in France, where he had no permit to do so. During the group session, he administered different psychedelic substances to different participants. Tragically, one of the participants in this event died after receiving the psychedelic compound ibogaine (not administered in combination with any other drug). The Swiss government subsequently closed the Swiss program in which LSD and MDMA were permitted to be used in patients, at first temporarily and then permanently. A brief account of these events can be found in the attached letter from Swiss psychiatrist Dr. Peter Gasser, President of SAEPT.

3. a) What is the abuse/addiction potential of MDMA?

b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA-assisted psychotherapy sessions?

c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dexedrine etc..)??

- a) MDMA possesses moderate abuse liability.
- b) The estimated risk of abuse of MDMA after completing a trial of MDMA-assisted psychotherapy is very low. [REDACTED] is aware of one subject in his study who used MDMA after the completion of the study. Afterwards, she said she would never do that

again since she didn't feel it was as productive as when she was under the supervision of trained therapists.

- c) Comparisons between one drug and another are viewed by some as controversial, but examining human behavior and self-administration in animals suggests that MDMA has lower abuse potential than psychostimulants.

These issues are addressed in more detail at several points in the study protocol, on pp. 45-46 and again on p. 87, with excerpts below.

Abuse Liability (from pp. 45-46)

MDMA is classified as a Schedule I compound, largely on the basis of its growing popularity at night clubs and parties in the early to mid-1980s. MDMA possesses abuse liability, and this is discussed in "Additional information." Whether or not MDMA's abuse potential will negatively affect people with PTSD exposed to MDMA when given along with psychotherapy is an open question for which there is of yet no direct data. [REDACTED] and colleagues are in the process of conducting a long-term follow-up of participants who took part in the study of MDMA-assisted psychotherapy that will address this question. [REDACTED] reported that anecdotally it appeared that people did not develop problems with MDMA/ecstasy abuse and that a number of participants volunteered that they would never seek out ecstasy outside a legal, controlled therapeutic setting. People with PTSD undergoing MDMA-assisted psychotherapy are likely to experience painful and frightening emotions during these sessions and memories related to the original traumatic incident in addition to or even instead of increased positive mood or euphoria. As a result, it seems unlikely that people with PTSD undergoing this emotionally challenging experimental intervention will find the experience pleasurable or safe enough to pursue MDMA use in unsupervised and uncontrolled settings. Diversion is not an issue because MDMA will only be administered under the supervision of the principal investigator and no take-home doses will be permitted."

Abuse Liability (from p. 87)

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests

that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

4. Re: Inclusion criterion #2a: Please change the criterion 2a so that in addition to an unsuccessful course of appropriate psychotherapy a participant must have had at least one unsuccessful attempt at treatment with SSRI or mirtazapine or MAOI, and that treatment must have constituted an adequate trial (lasting for at least 3 months at optimal doses or the patient could not tolerate the treatment, i.e. the patients who simply refused a trial of any of the approved form of pharmacotherapy would not be eligible for this study).

We agree without reservation to expand the inclusion criteria to include people treated with pharmacotherapies other than SSRIs.

However, we believe that potential subjects who did not successfully resolve their symptoms after psychotherapy and who have refused pharmacotherapy, should continue to be enrolled in the study. People who refuse pharmacotherapy have made a legitimate decision concerning their health care and have the right to make those decisions. For those patients, it remains true that, for them, currently available treatments have not been of sufficient therapeutic efficacy.

Based on substantial evidence, risk of study participation is not large. There are no significant safety reasons to exclude patients who have failed on psychotherapy and refuse pharmacotherapy. We would prefer to continue to enroll any subjects who have failed on psychotherapy but refused pharmacotherapy.

5. Re: Inclusion criterion #2b: Please clarify that being a veteran with PTSD symptoms that have persisted for no less than 1 year but no more than 5 years would only qualify to participate in the study if this veteran also meets criterion #2a.

That is correct; all veterans must meet all criteria including #2a to be enrolled in the study. This original inclusion criteria was written in 2001, when MAPS was seeking approval for the first US MDMA/PTSD study. We would like to revise this inclusion to permit enrollment of veterans with PTSD of no more than ten years duration. This revision is proposed upon recognition that people in the US MDMA/PTSD study had PTSD for an average of 19 years before enrolling in the study and were still successfully treated, even a subject receiving disability payments. Canadian soldiers with PTSD may have experienced combat-related PTSD prior to 2004, such as in Afghanistan in UN peacekeeping missions.

6. Re: Exclusion criterion #10: Please extend the time that the participant must be in remission for substance abuse or dependence (except caffeine and nicotine) to 12 months- i.e. full sustained remission, if substance abuse or dependence was an issue.

We would prefer to retain a six-month exclusion period for active substance abuse. Participation in MDMA-assisted psychotherapy reduces rather than increases the risks of substance abuse due to the focus on resolving subjects' underlying psychological issues.

Upwards of 40% of people with PTSD also report a lifetime diagnosis of alcohol or substance abuse (Brady and Sinha 2005). As noted above, the risk of abuse of MDMA within a psychotherapy context is low. The study of MDMA-assisted psychotherapy in the US excluded people reporting a diagnosis of substance abuse within 60 days, without any abuse or dependence occurring afterwards. Given the significant number of people with PTSD reporting past alcohol or substance abuse in the past and the low risk of abuse from study participation, we believe that maintaining the current six-month diagnosis exclusion will allow for greater ease of recruitment and will also result in a more representative sample being recruited.

Kathleen Brady MD, a Professor of Psychiatry at the Medical University of South Carolina and the Associate Dean for Clinical and Translational Research, an internationally recognized expert on PTSD and dual diagnosis, wrote a letter to Canadian IRB Services in support of an exclusion using the 60-day period. We agreed to a compromise and extended the exclusion to six months. We request the same compromise in our Canadian MDMA/PTSD study.

7. Re: Informed Consent:

- a) Re: risks of MDMA: Please provide the percentage of people expected to experience each of the listed potential adverse effects.
- b) Please clarify that people who had recently (in the last 365 rather than 60 days) problems with drug abuse should not take part in this study.
- c) Please provide what is the average expected increase in blood pressure and heart rate.

a) Percentages for most commonly reported side effects range from 40% to 70%, as stated in the current ICF, while less commonly experienced effects occurred in at least 13% of participants in Phase 1 studies. Percentages can be viewed in an attached document.

Some of the findings of potential risks are derived from studies reporting inferential and not descriptive statistics, as with changes in perception and immunological effects. In these cases, exact percentages cannot be provided but are presumed to be greater than 50%.

None of the serious adverse events listed as occurring with ecstasy users have occurred in MDMA Phase I studies of over 400 people or in any of the MDMA/PTSD Phase II studies with about 36 people treated to date. We provide percentages of people likely to experience a given adverse effect if the information is available. If desired, an estimated percentage can be made from studies presenting data as inferential statistics.

- b) We will clarify the IC however you require, after you have reviewed our request to retain the current exclusion of subjects with active substance abuse in the prior 6 months.

c) From previous studies of 365 people and using identical or similar doses of MDMA, average increase in SBP was 30-35 mmHg and average increase in DBP was 15-20 mmHg. Average elevation in heart rate was 18-20 beats per minute (BPM).

The cited attachments are available as a hard copy.

The questions and sponsor's responses were discussed with [REDACTED]

Reviewer's Discussion/Summary:

	Applicable	Not Applicable
Non-Clinical and Clinical Safety & Efficacy Assessment Completed:	*	
Reason: [If the drug has not been reviewed previously, there is a substantial amount of new information that has not been captured in the PSEAT-CTA, or this is a new indication, the Non-clinical and Clinical Safety & Efficacy Assessment should be completed as appropriate.]		

This pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve adult patients with treatment-resistant posttraumatic stress disorder.

Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive 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 cotherapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

Participants in the active placebo condition will have the opportunity to enroll in an openlabel study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression symptoms six weeks after the third open-label session.

Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

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.

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.

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.

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.

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.

COMMENT:

The rationale for the proposed study of MDMA- assisted psychotherapy is sound. The study design including proposed doses of MDMA follow the previous pilot studies in US and Switzerland. Safety issues are addressed adequately. NOL is proposed for this study.

NON-CLINICAL AND CLINICAL SAFETY & EFFICACY ASSESSMENT

Overview

(+/-) 3,4-methylenedioxyamphetamine (MDMA, 3,4-methylenedioxy-nmethylamphetamine, N-methyl-3,4-methylenedioxyamphetamine,) has the chemical formula of $C_{11}H_{15}NO_2$. It is a phenylisopopylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in 1912 as an intermediate chemical involved in the production of the styptic hydrastinine (Freudenmann et al. 2006). No significant investigations examined the pharmacological, physiological or psychological effects of MDMA until the 1950s, when the US Army administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991), and there are records of a police seizure of MDMA in the early 1970s that suggests either intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Some have estimated that up to 4000 people underwent MDMA-assisted psychotherapy in North America prior to its placement in Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001). A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986; Greer and Tolbert 1986), including Greer and Tolbert's study of MDMA in a psychotherapeutic context. However, controlled human studies of MDMA did not commence until early to mid-1990s, with the publication of research conducted by Grob and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006; Mithoefer 2006; Oehen 2006).

Pharmacological and toxicological effects

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use

high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear. MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture. The nature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978),

and an a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al.

2003). Typically, human trials have used doses between 1 and 2 mg/kg.

Pharmacokinetics and biological disposition

MDMA is metabolized in the liver and has a half-life of seven to nine hours (de la Torre et al. 2004), though a half-life of 11 hours has been reported (Pizarro et al. 2004) and is distributed throughout the body (De Letter et al. 2004), though a study in rats reported greater disposition in brain than in plasma (Chu et al. 1996). After 100 mg MDMA, T_{max} is reached at 2 hours, at a time close to peak physiological and subjective effects, and urinary recovery over a 24 hour period is 15% (de la Torre et al. 2004). The pharmacokinetics of MDMA have been primarily characterized by a group of Spanish researchers, with the exception of one publication from researchers in the Netherlands. The Spanish team first reported nonlinear pharmacokinetics for MDMA, findings that are confirmed in recent studies in nonhuman primates (Mechan et al. 2006). MDMA is metabolized by several CYPD enzymes, including but not limited to CYP2D6, CYP1A2 and CYP3A4. Monoamine oxidase and catechol-O-methyltransferase (COMT) also metabolize MDMA.

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called α -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-

methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al.

1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004;

Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% (de la Torre et al. 2004). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Safety and effectiveness in humans obtained from prior clinical studies

When Merck first patented MDMA, it was solely as an intermediate step toward the production of another compound (Freudenmann et al. 2006), and there were no early clinical investigations of MDMA. Published accounts of MDMA-assisted psychotherapy first appeared during the time of hearings for the scheduling of MDMA (Adamson 1985). Shortly afterwards, the only published study of MDMA-assisted therapy appeared, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986). These accounts suggested that, when combined with

psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a lifethreatening

illness. The Swiss government permitted psychotherapists to conduct MDMA-assisted psychotherapy between 1988 and 1993 (Gasser 1994; Widmer 1998). These therapists reported that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration. The Swiss psychotherapists did not publish any formal analyses of the treatment. Permission to conduct MDMA-assisted psychotherapy in Switzerland was revoked due to events unrelated to the safety or efficacy of MDMA and due to the lack of any published research results.

Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after

MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001). A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway to study the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006).

Possible Risks and Side Effects

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of

hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

Common Adverse Effects and Side Effects

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies of MDMA are listed in Table 2 and include reduced appetite, dizziness,

tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, Investigator's Brochure: MDMA MAPS: 12/2007

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dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas

(Harris et al. 2002). Other less common side effects include paresthesias (unusual body sensations) such as tingling sensations, or feeling hot or cold. These effects are transient

and recede with the waning of drug effects. One study found that women were more likely than men to experience most commonly reported side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating (Liechti et al. 2001b).

Sub-acute effects appearing 24 to 48 hours (1 to 2 days) after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related

sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with subacute

effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006).

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of

impaired serotonin function or verbal memory after exposure to one to three doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggest that this risk is minimal after a low number of exposures. While there may also be risks related to psychological well-being such as increased symptoms of anxiety or depression, support for these longterm

effects are even less strong than for the previously listed changes.

Abuse Potential

The US Drug Enforcement Administration (DEA) placed MDMA in Schedule 1, the most restrictive schedule reserved for compounds with high abuse potential and no medical value, and most other nations followed the lead of the US in making MDMA a tightly controlled substance. Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less

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intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA

possesses

moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens

but lesser than for psychostimulants.

Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al.

2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al.

1999).

Reproductive and Developmental Toxicity

Previous research supported a possible link between ecstasy use and birth defects

(McElhatton et al. 1999), while an epidemiological study conducted in 2004 in a large cohort of pregnant women in England failed to support this link, at least in respect to a specific cardiac defect (Bateman et al. 2004). However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant (Ho et al. 2001).

Several teams of researchers have performed studies of developmental toxicity in rodents

(see for example (Koprach et al. 2003a; Koprach et al. 2003b; Piper and Meyer 2004; Williams et al. 2005). In some studies, the researchers administered large, repeated doses

to pregnant rats, and in others, the MDMA was administered to neonatal rats. The researchers did not report gross structural abnormalities in rats exposed to high doses of

MDMA in utero. However, studies of MDMA in neonatal rats found changes in numbers of serotonin or dopamine cells and impaired learning or memory, particularly when MDMA was administered from the 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et

al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose of MDMA in young rats also produced less of an increase in BT and fewer signs of "serotonin syndrome" when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable

to some effects of MDMA.

Research trial data

Information is being gathered and prepared. Side effects reported in the first clinical trials

are similar to those reported in controlled studies, though anxiety may be more prevalent,

due in part to the condition under study and in part to the nature of the setting, as participants are encouraged to confront emotionally upsetting thoughts, memories and feelings. In this setting anxiety is not chiefly viewed as a side effect, but as an element of

the underlying disorder and the therapeutic process.



Health Canada Santé Canada

Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

REQUEST FOR ADDITIONAL INFORMATION

If you receive this fax in error, please advise the sender immediately.
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TO/À
Name/Nom: Dr. Rick Doblin Date: 16/01/09

Organization/Organisme: MAPS

Tel./Tél.: 617-484-8711 Fax/Télécopieur: 617-484-8427

No. of Pages, including this page/N° de pages, incluant cette page: 2

FROM/DE
Name/Nom: Beata Wiatrowska, M.D. E-Mail/Courier électronique: beata_wiatrowska@hc-sc.gc.ca

Tel./Tél.: 613-941-2132 Fax/Télécopieur: 613-952-9656

TITLE		TITRE
Division/Unit	Clinical Trials & Special Access Programme/ Programme des essais cliniques et accès spécial aux médicaments	Division/Unité
Bureau	Bureau of Pharmaceutical Assessment / Bureau de l'évaluation des produits pharmaceutiques	Bureau
Directorate	Therapeutic Products Directorate / Direction Des Produits Therapeutiques	Direction
Room		Pièce
Building	Finance Building/ Edifice Finance	Édifice
Location	Tunney's Pasture/Pré Tunney	Lieu
Address Locator	0202C1	Localisateur d'adresse
City/Province	Ottawa, Ontario	Ville/Province
Postal Code	K1A 1B6	Code postal
	Website/site Web : www.hc-sc.gc.ca/hpb-dgps/therapeut	

In accordance with Division 5 of the Food and Drug Regulations, we request clarification of the points on the following page so that we can continue our evaluation of your Clinical Trial Application (CTA) or CTA Amendment for:

Product:MDMA
Protocol Number:M-P4
Control Number: 126833
File Number: 9427-M2544-21C
Received in the Bureau on: 24/12/08

Please provide a complete response within **2 working days** from the date of this request **via facsimile** to the sender. If the requested information is not received within 2 working days, a Not Satisfactory Notice may be issued.

Comment:

1. Please provide an updated information on studies of MDMA- assisted psychotherapy for PTSD and/or for potenti / life threatening illness, if available.
2. Please provide more detailed reasons for the Swiss Government revoking permission to conduct MDMA assisted psychotherapy.
3.
 - a) What is the abuse/addiction potential of MDMA?
 - b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA assisted psychotherapy sessions?
 - c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dexedrine etc..)?
4. Re: Inclusion criterion #2a: Please change the criterion 2a so that in addition to an unsuccessful course of appropriate psychotherapy a participant must have had at least one unsuccessful attempt at treatment with SSRI or mirtazapine or MAOI, and that treatment must have constituted an adequate trial (lasting for at least 3 months at optimal doses or the patient could not tolerate the treatment, i.e. the patients who simply refused a trial of any of the approved form of pharmacotherapy would not be eligible for this study).
5. Re: Inclusion criterion #2b: Please clarify that being a veteran with PTSD symptoms that have persisted for no less than 1 year but no more than 5 years would only qualify to participate in the study if this veteran also meets criterion #2a.
6. Re: Exclusion criterion #10: Please extend the time that the participant must be in remission for substance abuse or dependence (except caffeine and nicotine) to 12 months- i.e. full sustained remission, if substance abuse or dependence was an issue.
7. Re: Informed Consent:
 - a) Re: risks of MDMA: Please provide the percentage of people expected to experience each of the listed potential adverse effects.
 - b) Please clarify that people who had recently (in the last 365 rather than 60 days) problems with drug abuse should not take part in this study.
 - c) Please provide what is the average expected increase in blood pressure and heart rate.

I would appreciate receiving your response in a paper (via fax), as well as an electronic (via e-mail) version.

Yours sincerely,

Beata Wiatrowska, M.D., FRCP(C)

Health Products and Food Branch
Direction générale des produits de santé et des aliments

Therapeutic Products Directorate

Direction des produits thérapeutiques

OUR MISSION: To ensure that the drugs, medical devices and other therapeutic products available in Canada are safe, effective and of high quality.

NOTRE MISSION : Faire en sorte que les médicaments, les matériels médicaux et les autres produits thérapeutiques disponibles au Canada soient sûrs, efficaces et de haute qualité.

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TO/À

Name/Nom: Dr. Rick Doblin Date: January 12, 2009
Organization/Organisme Multidisciplinary Association for Psychedelic Studies
Tel./Tél.: (617)484-8711 Fax/Télécopieur: (617)484-8427
No. of pages, including this page/N°. de pages, incluant cette page: 2

FROM/DE

Name/Nom: Dr. Rajkumar Kumarathasan E-mail/Courier élec.: rajkumar_kumarathasan@hc-sc.gc.ca
Tel./Tél.: (613) 941-6059 Fax/Télécopieur: (613) 954-8867

TITLE	Chemistry Advisor / Conseiller de Chimie	TITRE
Division	Clinical Trials Quality Division / Division de la qualité pour les essais cliniques	Division
Bureau	Office of Clinical Trials / Bureau des essais cliniques	Bureau
Location	5th Floor, Holland Cross, Tower B, 1600 Scott Street 5e étage, Holland Cross, Tour B, 1600 rue Scott	Lieu
City	Ottawa, Ontario	Ville
Postal Code	K1A 0K9	Code postal
Address Locator	3105A	Localisateur d'adresse

RE: Phase II CTA for MDMA 12.5mg, 25mg, 62.5mg and 125mg , Control 126833

In accordance with the Therapeutic Products Directorate's policy on *Management of Drug Submissions*, we request clarification of the points on the following page(s) so that we can continue our evaluation of the Quality (Chemistry and Manufacturing) information in your submission.

Please provide a complete response **within 2 calendar days** of this communication **via facsimile**. The response should include the Directorate's comments and summary responses in a question and answer format. Where appropriate, the relevant portions of the Quality Summary template (e.g., QOS-CE(CTA)) should be used to summarize the new or revised information provided in the accompanying solicited information, such as updated stability data.

If the requested information is not received within the stated time frame, or the response is incomplete, then a **NOT SATISFACTORY NOTICE will be issued**. Please inform the undersigned as soon as possible, by fax, if you will be unable to provide a complete and timely response and prefer that a Notice be sent.

We have the following comments with respect to your CTA for MDMA 12.5mg, 25mg, 62.5mg and 125mg, Control 126833:

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.
2. The following comments concern the specifications and batch analysis of the drug substance.
 - a. You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.
 - b. It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.
3. Please revise Section S6 to include the description of the drug substance container closure system.
4. Please report the quality standard for lactose (eg. USP/NF) in Section P.4.
5. The following comments concern the specifications and batch analysis of the drug product.
 - a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.
 - b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis.
6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.
7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.
8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.

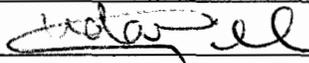
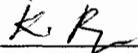


Rajkumar Kumarathasan, PhD.
Chemistry Advisor
Clinical Trials Quality Division
Office of Clinical Trials

Health Products and Food Branch
Direction générale des produits de santé et des aliments
QUALITY EVALUATION SUMMARY – CTAs
(QES-CTA)

E.1 SUBMISSION SUMMARY	
Proprietary (Brand) Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Product	MDMA
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	MDMA ; 3,4 methylenedioxymethamphetamine
Company (Manufacturer/Sponsor) Name	Multidisciplinary Association for Psychedelic Studies
Dosage Form(s)	Capsule
Strength(s)	12.5 mg; 20 mg; 62.5 mg; and 125 mg;
Route of Administration	Oral
Contact Information	Rick Doblin Phone: 617-484-8711; Fax: 617-484-8427

Type of Submission (and Phase for CTAs)	Phase-I I	
TPD Target Date	200 9-01-23	
Control Number / File Number	126833	9427-M2544 - 21C
Number of Volumes	C/T one folder Bin 2 dated 200 8-12-24	
Lead Clinical Bureau/Division	Office of clinical trials	

Recommendation	This submission IS NOT recommended for clearance with respect to the Quality (Chemistry and Manufacturing) information.		
1st Reviewer(s)	Udai Gill	Review Hours	10 hrs + 2
Start Date	200 9-01-07	Completion Date	2009-01-19 
Signatures	1st Reviewer(s)		
	2nd Reviewer(s)		
Report Access	I:\DPQ\Submission\CTA\HIJKLMMultidisciplinary associates for psychedelic studies\MDMA\126833 cta-2009-r01.doc		
References			
Attachments			

Evaluator's Introduction/Discussion:

This is a review of a phase II CTA for a protocol No. MP-4: A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Dose 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.

Dosing: An Experimental 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.

Placebo: Active Placebo (low dose MDMA + Lactose); active placebo doses are 12.5 mg and 25mg. 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.

Drug Substance:

The drug substance, MDMA [(+/-)3,4 – methylenedioxyamphetamine. HCl] is sourced from Lipomed AG, Switzerland. MDMA batch No. MDM-94-HC/94.1B5.5 . The sponsor will be asked to provide a current C of A for the drug substance including results for impurities. The sponsor will be asked to revise the container closure system information in S6. The information in stability testing section is not complete and stability testing data is not provided.

Drug Product:

The drug product is compounded at Kripps Health Care RX pharmacy, Vancouver BC. Racemic MDMA is 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. The active placebo capsules contain lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

The drug product is compounded at Kripps Health Care RX pharmacy, Vancouver BC.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION

SPONSOR

We have the following comments with respect to your Phase II CTA for MDMA, strengths at 12.5 mg, 25mg, 62.5mg and 125mg per capsule, Control no. 126627:

1. Please provide the narrative description of the drug substance synthesis that includes all reagents and solvents used in each step of the manufacturing process.
2. The following comments concern the specifications and batch analysis of the drug substance.
 - a. You are requested to revise the specifications to include tests and limits for residue on ignition and heavy metals, and report the results for the batch to be used in this clinical trial.
 - b. It is understood that the drug substance batch # MDM-94-HC will be used in this Canadian clinical trial. Please confirm. If you intend to use a different batch, the batch analysis of the new batch should be provided.
3. Please revise Section S6 to include the description of the drug substance container closure system.
4. Please report the quality standard for lactose (eg. USP/NF) in Section P.4.
5. The following comments concern the specifications and batch analysis of the drug product.
 - a. Please provide the drug product specifications that includes test and limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.
 - b. You are requested to provide the batch analysis of the drug product batches to be used in this Canadian clinical trial. This should include the batch number, batch size, date and site of manufacture and date of analysis
6. Please provide the description of the container closure system, and proposed storage conditions and shelf life of the drug product.
7. Please provide a commitment that the stability (appearance, assay, related substances/degradation products and dissolution) of the drug product will be monitored throughout the duration of the clinical trial.
8. You are requested to provide the certificate of suitability issued to the manufacturers of gelatin to be used in this clinical trial.

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MB.BS. FRCP[C]

Study Number: M-P4

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 21, 2008

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 12.5 mg (active placebo supplemental dose), 25 mg (active placebo-initial dose), 62.5 (experimental dose-supplemental dose), 125 mg (experimental dose-initial dose). Supplemental dose administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

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 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 during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling

participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

The study will take place at one center in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, will take place [REDACTED]. Assessments of PTSD symptoms and neurocognitive function will be performed [REDACTED].

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD and with a CAPS score of 50 or higher. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all of the inclusion criteria listed below without meeting any of the exclusion criteria. Participants must reside in Canada.

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 [1-3]. 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 [4, 5] 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 [5].

As described above, capsules containing the initial dose of MDMA will be administered in the offices of Dr. Pacey 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.

S Drug Substance

S.1 General Information

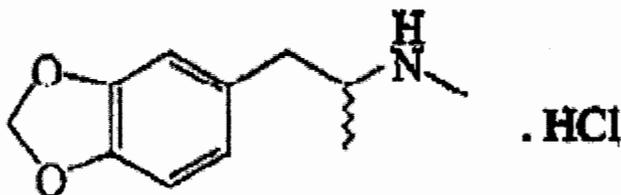
The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by [redacted] Switzerland. On January 30, 2006, a quality control analysis was performed by [redacted] This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no [redacted] with no decomposition products detectable and a HPLC purity >98%.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-

methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was [REDACTED]

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol

Step 2: MDA-nitrostyrol + LiAlH₄ -> MDA

Step 3: MDA + methylchloroformiate -> MDA-methylcarbamate

Step 4: MDA-methylcarbamate + LiAlH₄ -> MDMA

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within the report provided by [REDACTED]

S.2.3 Control of Materials

See above and contained in report by [REDACTED]

S.3 Characterization:

Batch number is [REDACTED]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]. One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2).

Validation: From manufacturer, data available upon request [REDACTED]

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] and listed above.

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(\text{Max})} = 1\ 234 \pm 1\ \text{nm}$
 $\epsilon_{\text{mol}} = 3800 \pm 500$
Melting Point: $149 \pm 3\ \text{C}$
Purity HPLC = 98.5%
Free base content = > 82.5%
Water content: $0.3 \pm 0.3\%$
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by [REDACTED]

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

Injection: 250 C, splitless 1 μL

Detection: full scan

Identity (HPLC-DAD): TR = 7 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M^+ , MDMA-TFA)

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from [REDACTED]

S.4.4 Batch Analysis:

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

UV, in distilled water, $\lambda_{(\text{MAX}).1} = 234.0\ \text{nm}$

$\epsilon_{\text{mol}.1} = 3939$

$\lambda_{(\text{MAX}).2} = 285.0\ \text{nm}$

$\epsilon_{\text{mol}.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%
Freebase content: 83.51%
Water content: 055%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 2000 ppm

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug, with or without inactive ingredient, will be placed in opaque capsules and these will be stored in bottles stored by the principal investigator.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED] and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

[REDACTED] reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

[REDACTED] also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

P. Drug Product

The drug product will consist of capsules containing racemic 3,4-methylenedioxyamphetamine (MDMA) in the following dosages: Experimental dose initial dose 125 mg MDMA per capsule; experimental dose supplemental dose 62.5 mg MDMA per capsule; active placebo initial dose 25 mg MDMA plus lactose to reach equivalent weight of 125 mg capsule per capsule; active placebo supplemental dose 12.5 mg MDMA plus lactose to reach weight of 62.5 mg per capsule. There are no other ingredients in these capsules. The capsules will be prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but will be compounded by a Vancouver-area pharmacist.

The sponsor has based dosage on previous research studies (2, 4) and on narrative reports of MDMA-assisted therapist (as Adamson and Metzner 1980; Stolaroff 2004). A dose of 125 mg has been used in a previous sponsor-supported research study conducted in the US (3). The sponsor chose the active placebo dose on the basis of a previous research study (4), with 25 mg expected to produce very few effects. The sponsor selected an inactive material to help maintain the blind by ensuring that all doses are of equal weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

Capsules will be compounded at a pharmacy in British Columbia. The study drug will be compounded and will not be re-synthesized. The encapsulation will be performed by an individual possessing the appropriate skills, as a pharmacist. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all capsules have similar weights. All capsules will contain the exact weight of MDMA and a varying amount of lactose to maintain equal weights between active placebo and experimental dose capsules.

P.3.3 Batch Formula

Opaque capsules will be filled with the appropriate dose of MDMA.

Experimental initial dose: 125 mg

Experimental supplemental dose: 62.5 mg

Active Placebo initial dose: 25 mg + approximately 100 mg lactose or appropriate amount so that full weight = 125 mg

Active placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg

Capsules placed in numbered bottles

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all “active placebo” doses of the product. Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA capsules are of equal weight.

P.4.1. Specifications

All doses of MDMA will be in the form of opaque capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

P.7 Container Closure System

All doses of MDMA will be in the form of opaque capsules. The capsules will be within plastic bottles with caps. Each bottle will be assigned a number intended for use in the randomization process so as to maintain the double blind. Each bottle will contain All bottles will be appropriately stored in the offices of the principal investigator.

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

A Attachments:

1. Lipomed sheet listing specifications and batch analysis
2. Quality Analysis of [REDACTED]; pp. 1-2 concern this batch of MDMA and p. 3 concerns capsules produced for a sponsor-supported study in Switzerland
3. Stability report of [REDACTED] referring to different source and batch of MDMA but supporting long-term stability

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation]*. J Clin Psychopharmacol, 2000. **20**: 455-66.
2. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. J Psychoactive Drugs, 1986. **18**: 319-27.
3. Mithoefer, M., *MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): Eleventh update on study progress*. MAPS Bulletin, 2008. **17**: 11-12.
4. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
5. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. **162**: 396-405.



Health Canada / Santé Canada

Office of Clinical Trials

Screening Template for CTA - 30-day default review

CR File #: 9427-M2544-21C Date received in OCT : 2008.12.22 Review 1 Start Date: 2008.12.24 Study Phase: Phase II-30 day Study Population: Males, Females Document I.D. #: 543517	DSTS Control #: 126833 Due Date: 2009.01.23 Data Description: CL/2VO/2CD Clinical Division: Vol. # 1 Quality Division: Vol. # 2	
PSEAT Format: PDF		
PSEAT Template Path: <i>1:30/4/05 \ MWOP \ MDMA_MAPS \ NewWork \ 126833_cta.doc</i>		

Product Name : **MDMA**

Protocol # or Identifier: **M-P4 ct**

Protocol Title: 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

Therapeutic/Pharmacological Classification: Monoamine releaser and uptake Inhibitor
[Clinical Group II : CNS]

Sponsor Name : Multidisciplinary Association for Psychedelic Studies	Country: USA
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	Form	Route	Medicinal Ingredients	Strength / Unit	Basic Unit	F#
1	CAP	ORL	UNASSIGNED	12.5 mg	CAP	1
2	CAP	ORL	UNASSIGNED	20 mg	CAP	2
3	CAP	ORL	UNASSIGNED	62.5 mg	CAP	3
4	CAP	ORL	UNASSIGNED	125 mg	CAP	4

Comparator Product: Active Placebo (Low Dose MDMA + Lactose)

Screening Officer's Comment(s):
 - IB (December 2007)

Previous related submission, CTA <control#>, reviewed by: N/A

 Dalia Haddad-Screening Officer	2008.12.22 / 2008.12.24 Screening start date / Completion date
 Assessment Officer	Jan 05/09 / 30h Assigned date / Review Hours

Response to Clarifax
Posted by Dalia Haddad
Submission Screening Officer, Submission Management Unit
Office of Clinical Trials, Therapeutic Projects Directorate,
5th Floor, Holland Cross, Tower B
3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9
Tel: 613-948-8274
Fax: 613-946-7996
dalia_haddad@hc-sc.gc.ca

December 23, 2008

This information is prepared in response to Clarifax issued to Rick Doblin on Dec 22, 2008 for a Clinical Trial Application for a study with the drug substance (product) MDMA.

Protocol Number: MP-4
Control Number: 126833

Dear Ms. Dalia Haddad,

Please find the answers to your queries below:

Excerpt from the Clarifax sent to Rick Doblin on 22 Dec 2008

1. It is mentioned that the MDMA and the active Placebo will be encapsulated. Please provide information on the following:

- The type of capsules used
- Brief description on the encapsulating process
- Are the capsules BSE/TSE free?
- Where will the encapsulating taking place?

Responses to each query are listed below.

- Capsules will be 00 opaque gelatin capsules.
- The principal investigator will transport the MDMA [redacted] will encapsulate experimental and active placebo doses of MDMA at [redacted]. The pharmacy will supply the capsules and lactose. MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all 108 capsules have equivalent weights. All capsules will contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X39) and a varying amount of lactose to maintain equal weights.

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Deleted: between active placebo and experimental dose capsules. The study will enroll eight people in the experimental dose condition and four people in the active placebo condition, and all four of these participants may enroll in an open-label study segment. Assuming one drop-out in each condition, the study will require 15 capsules with 12.5 mg MDMA, 15 capsules of 25 mg MDMA, 27 capsules with 62.5 mg MDMA and, for open-label sessions, 12 capsules with 62.5 mg MDMA and 12 capsules with 125 mg MDMA.

Deleted: The 12 subjects in the study will require X capsules with 12.5 mg MDMA, X capsules with 25 mg MDMA, X capsules of 62.5 mg MDMA and X capsules of 125 mg MDMA. These numbers assume all 4 subjects randomized initially to the low dose/placebo group enter into the open-label Stage 2 with full dose MDMA, and that there are two drop-outs, one from the full dose MDMA group and one from the low dose/placebo group.

The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses.

The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, the randomization monitor selects a number from amongst a set of cards based on the list, and that number is the bottle number used for that participant.

- Yes, the lactose and gelatin capsules will be BSE/TSE free.

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- The encapsulation will take place at [REDACTED]. Encapsulation will be performed by [REDACTED] in the presence of the principal investigator, who will possess the appropriate license.

Formatted: Bullets and Numbering

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If you need any additional information, please let me know and I will be glad to provide it

Sincerely,

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Rick Doblin, Ph.D.
MAPS President



Health
Canada

Santé
Canada

Therapeutic Products Directorate

5th Floor, Holland Cross, Tower B

Address Locator# 3105A

OTTAWA, Ontario

K1A 0K9

Your file Votre référence

Our file Notre référence

24 December 2008

9427-M2544-21C

Rick Doblin, Ph.D.
President, MAPS
Multidisciplinary Association for Psychedelic Studies
3 Francis Street
BELMONT, MA
USA 02478-2218
617-484-87711

**ACKNOWLEDGEMENT CLINICAL TRIAL APPLICATION
RE: PROTOCOL# M-P4**

Dear Dr. Doblin:

This will confirm the receipt of your complete application on December 24, 2008, regarding your information and material to support a Clinical Trial Application (CTA) for **MDMA**, control number **126833**. You are requested to refer to the file number and control number in any communication relating to this application.

Please note that additional information may be requested during the review stage.

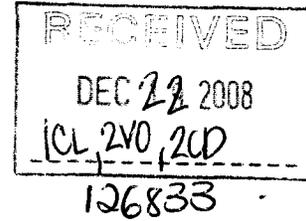
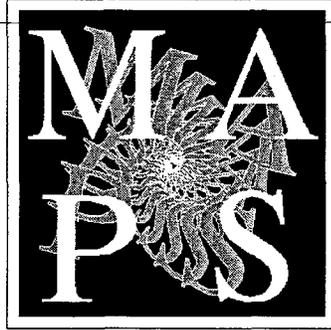
You are reminded that under paragraph C.05.006 (1) (b) of the Food and Drug Regulations, the sale of a new drug for clinical testing is prohibited if, within 30 days after the date of receipt of the complete submission, the Director has sent a notice by registered mail that the Clinical Trial Application is not satisfactory.

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/mh

Canada



December 18, 2008

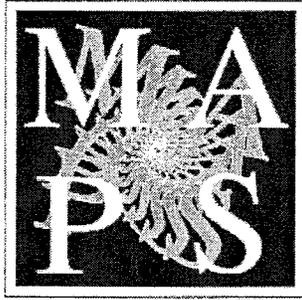
Dr. John Patrick Stewart
Acting Director,
Office of Clinical Trials
Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator: 3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9

Dear Dr. Stewart,

Enclosed is a Clinical Trial Application (CTA) for a Phase 2 study entitled, "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." The principal investigator for the study is Dr. Ingrid Pacey MB BS FRCP[C], Vancouver, British Columbia. The enclosed forms, investigator's brochure, protocol, consent materials and chemistry information are presented for review for this CTA. This protocol and associated informed consent have already been reviewed and approved by IRB Services, Aurora, Ontario, Canada.

The sponsor of the study is the Multidisciplinary Association for Psychedelic Studies (MAPS), a US-based non-profit research and educational organization working to develop MDMA into a prescription medicine for use in combination with psychotherapy. The enclosed application is for an investigation that is part of an international series of Phase 2 studies, the protocols of which have all been submitted to FDA as part of MAPS IND #63-384. MAPS has successfully completed an MDMA/PTSD pilot study in the US in 21 subjects and is sponsoring ongoing MDMA/PTSD studies in Switzerland and Israel, each to enroll 12 subjects and estimated to be completed around the end of 2009. Our Canadian MDMA/PTSD is an attempt to replicate our US results. Our Canadian MDMA/PTSD is an attempt to replicate our US results.

Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org



MAPS has also helped to initiate a study of MDMA-assisted psychotherapy for people with anxiety related to a cancer diagnosis, taking place at McLean Hospital, Harvard Medical School.

I look forward to hearing from you regarding the results of your review.

Sincerely

Rick Doblin PhD
President, MAPS

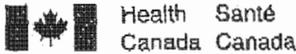
Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org

09/06/2013 09:48

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TPD-OCT

PAGE 02/02



Health Santé
Canada Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

SEP 03 2013

9427-M2544-21C

Your file Votre référence

Our file Notre référence

Clinical Research
Multidisciplinary Association for Psychedelic Studies
1215 Mission St.
SANTA CRUZ, CA
95060 USA

No Objection Letter RE: Amendment # 1 to Protocol # MP-4 (Version 2) and Quality Amendment

Dear [REDACTED]

This is to advise you that the data concerning your Clinical Trial Application for MDMA, control number 167090 which were received on August 8, 2013, have been reviewed and we have no objection to the amendment to the study. Please note that a new control number has been assigned to this Clinical Trial Application Amendment only. Any correspondence relating to the original CTA should be referenced to the original control number assigned. I would remind you of the necessity of complying with the *Food and Drug Regulations*, Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice*.

Please note that Health Canada has implemented electronic reporting of adverse drug reactions and is currently in pilots with some sponsors. Those sponsors who have an established electronic connection with Canada Vigilance Production stream should submit their reports using the distribution rules provided to them by Health Canada, and reporting to multiple directorates is no longer required. For the sponsors who have not yet established this connection, they should continue submitting their reports to the applicable directorate by fax or by courier. The following website provides further clarification on Health Canada's adverse drug reactions reporting requirements for clinical trials:
http://www.hc-sc.gc.ca/dhp-mpps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.pdf

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Yours sincerely,

Léo Bouthillier, Ph.D.
Manager - Clinical Trials Group II
Office of Clinical Trials

LB/en

Sponsor: **Multidisciplinary Association for Psychedelic Studies (MAPS)**
Protocol Title: **“A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of
Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada”**

Protocol Number: MP-4

Health Canada File#: **9247-M2554-21C** Health Canada Control#: **127822**

July 31, 2013

CTA-A



Multidisciplinary Association for Psychedelic Studies
1215 Mission Street, Santa Cruz, CA 95060 USA
Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370

July 31, 2013

Office of Clinical Trials
Therapeutic Products Directorate
Health Canada
5th Floor, Holland Cross, Tower B
Address Locator: 3105A
1600 Scott St.
Ottawa
Ontario K1A 0K9
Canada

Re: **Study #MP-4** “A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada”
Health Canada File#: **9247-M2554-21C** Health Canada Control#: **127822**

Dear Office of Clinical Trials, Therapeutic Products Directorate

Please find along with this letter a clinical trial application amendment for the study listed above, Control number 127822. The amendment application consists of the following documents, in order and listed in a table of contents:

- 1.1 Table of Contents
- 1.2 Application Information
 - 1.2.1 Drug Submission Application Form (HC/SC 3011)
 - 1.2.3 Investigator’s Brochure
 - 1.2.5 Study Protocols
 - 1.2.5.1 Amendment 1 Version 2 Summary of Changes
 - 1.2.5.2 Amendment 1 Version 2 Synopsis and Protocol
 - 1.2.5.3. Most recently authorized protocol
 - 1.2.6 Informed Consent Documents
 - 1.2.6.1 REB Approval and Letter of Attestation
 - 1.2.6.2 Version 2 Main Consent
 - 1.2.6.3 Version 3 Video Consent
 - 1.2.7 Clinical Trial Site Information
- [1.3] Electronic Information (to be contained on a compact disc mailed along with this letter]



Multidisciplinary Association for Psychedelic Studies

1215 Mission Street, Santa Cruz, CA 95060 USA

Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370

Please do not hesitate to call me if you have any further questions.

Thank you very much for your assistance,

Sincerely,

[Redacted signature block]
[Redacted signature block]
[Redacted signature block] Clinical Research

Drug Submission Application							
Part 1 - Manufacturer/Sponsor and Drug Product Information							
Health Canada Use Only:	1. Submission No.			2. Responsible Area		3. File No.	
						4. Date of Receipt	
						YYYY	MM
						DD	
5. Type of Submission Clinical Trial Application – Amendment			6. Number of Volumes / Compact Discs 1			7. Schedule Schedule III	
8. Brand or Proprietary or Product Name (should be the same as the brand name on the product label): None							
9. Proper, Common or Non-Proprietary Name : 3,4-methylenedioxyamphetamine (MDMA)							
A) Manufacturer/Sponsor (In cases where a DIN/Notice of Compliance (NOC) is issued, this will be the DIN/NOC Owner) (For CTA, CTA-A, VIND and VIND-AM, refer to attached Guidance)							
10. Company Code MAPS		11. Manufacturer/Sponsor Name (Full Legal Name - No Abbreviations): Multidisciplinary Association for Psychedelic Studies					
12. Street/Suite 1215 Mission St.		13. City/Town Santa Cruz		14. Prov./State CA	15. Country USA	16. Postal/ZIP Code 95060	
Contact Person for Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this is the DIN/NOC Owner contact)							
17. Name		18. Telephone No.		19. Fax No. 831-429-6370		20. Language Preferred X English	
21. Title Clinical Research		22. E-mail @maps.org					
B) Contact for THIS Drug Submission							
23. Company Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies							
24. Street/Suite/Post Office Box 1215 Mission St.		25. City/Town : Santa Cruz		26. Prov./State CA	27. Country USA	28. Postal/ZIP Code 95060	
29. Name		30. Telephone No.		31. Fax No. 831-429-6370		32. Language Preferred X English	
33. Title Clinical Research		34. E-mail @maps.org					
C) Regulatory Mailing Address (Complete where a DIN is to be issued, refer attached Guidance) Same as A Above							
35. Company Name (Full Name - No Abbreviations) Same as above							
36. Street/Suite/Post Office Box		37. City/Town		38. Prov./State	39. Country	40. Postal/ZIP Code	
Regulatory Mailing Contact				Same as A Above			
41. Name Same as above		42. Telephone No.		43. Fax No.		44. Language Preferred X English	
45. Title		46. E-mail					
D) Canadian Importer (Complete ONLY where Address in A is not in Canada. EXCEPTION for CTAs, see footnote)¹						Same as C Above	

¹ For clinical trial applications (human drugs), if clinical trial drugs are to be imported into Canada, importers should be authorized by the sponsor, **regardless of the sponsor's location**. Appendix 1 should be completed and submitted for each importer in Canada. Canadian importer(s) must be located within Canada. Refer to the attached guidance and the “Guidance for Clinical Trial Sponsors” for roles and responsibilities.

47. Name of Importer (Full Name - No Abbreviations) Colin Holyk, Kerrisdale Pharmacy				
48. Street/Suite/Post Office Box 5591 West Blvd	49. City/Town Vancouver	50. Province BC	51. Country CANADA	52. Postal Code V6M 3W6

E) Address to which the Drug Notification Form (DNF)/NOC are to be sent: Same As Above: A: B: C: D:

53. Related Submissions (referred to in this submission):

A) Type	Control No.	Brand Name	Manufacturer/Sponsor Name	File No.	Date Cleared
---------	-------------	------------	---------------------------	----------	--------------

Associated DIN(s) :

Reason for Submission:

Attach separate sheets (same format) if necessary. Number of pages attached: _____

Part 2 - Drug Product Formulation Information

54. Proposed Shelf Life 20 years 0 months at 22 °C.

55. Country(ies) of Manufacture: Switzerland

56. Medicinal (Active) Ingredient(s) - If the ingredient was sourced from Animal/Human, complete and submit Appendix 4.

CAS No. (if applicable)	Ingredient Name	Standard	Strength	Units	Per	Calculated as Base?		Animal/ Human Source	
						<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	3,4-methylenedioxymethamphetamine	USP	125	mg	capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Same as above	USP	100	mg	capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Same as above	USP	62.5	mg	Capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Same as above	USP	50	mg	capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Same as above	USP	12.5	mg	Capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Same as above	USP	25	mg	capsule	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

57. Non-medicinal Ingredient(s) - If the ingredient was sourced from Animal/Human, complete and submit Appendix 4.

For formulation variations pertaining to the same DIN (for example [e.g.] multiple flavourings, colours, fragrances), fill out the variant name and list all the non-medicinal ingredients for each variant type.

Variant Type [if applicable]: _____

CAS No. (if applicable)	Ingredient Name	Standard	Strength	Units	Per	Animal/ Human Source	
	A) Preservatives					<input type="checkbox"/> Yes	<input type="checkbox"/> No
						<input type="checkbox"/> Yes	<input type="checkbox"/> No
	B) Colouring Agents					<input type="checkbox"/> Yes	<input type="checkbox"/> No
						<input type="checkbox"/> Yes	<input type="checkbox"/> No
	C) Other²						
	Lactose		12.5-150	mg	capsule	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
						<input type="checkbox"/> Yes	<input type="checkbox"/> No
	D) Capsule Shell Ingredients (if applicable)						
	Gelatin		1		capsule	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
						<input type="checkbox"/> Yes	<input type="checkbox"/> No

²

For products regulated solely by Division 1: state the purpose of any non-medicinal ingredient(s) included under "Other"

58. Animal and/or Human Sourced Material(s) Used at Any Stage in the Manufacture of the Drug - If the material was sourced from Animal/Human, complete and submit Appendix 4.

CAS No. (if applicable)	Material Name	Standard	Present in Final Container	
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No

59. Is any ingredient listed under Section 56 or 57 a Nanomaterial? No

If Yes, provide the name of the ingredient:

60. Dosage Form: white, crystalline powder

61. Container Type Clear uncoloured gelatin capsules Package Size : 03

62. Therapeutic/Pharmacological Classification : Monoamine releaser and uptake inhibitor; Entactogen

63. Route(s) of Administration: Oral

64. Drug Product 9 Biologic / Radiopharmaceutical Pharmaceutical Disinfectant Drug and Medical Device

65. Drug Use Human [9 Paediatric (0-18 years of age) Adult] Radiopharmaceutical Veterinary
 Disinfectant [Hospital Food Processing Medical Instruments Domestic Barn Institutional/Industrial Contact Lens]

66. Is this a Non-prescription drug to which one or more Schedule A claims apply? Yes No

If Yes, complete and attach the Schedule A Form (Appendix 5).

67. Proposed Indication/Use: Facilitating psychotherapy for the treatment of Post-Traumatic Stress Disorder

68. Proposed Dosage (by age / species - include maximum daily dose)

Full dose condition: 125mg +62.5mg at t+1.5-2.5h Min 125mg, max 187.5mg

Comparator dose condition: 50mg + 25mg at t+1.5-2.5h Min 50mg, max 75mg

Open-label titration (Stage 2): 100mg to 125mg + 50mg to 62.5mg at 1.5-2.5h Min 100mg, max 150mg

69. Draft of Proposed Canadian Labels (inner and outer) enclosed? Yes No Package Insert enclosed? Yes No

For CTAs, CTA-As, VINDs and VIND-AMs labels should not be submitted unless requested by the appropriate Directorate.

70. Rationale for all SNDS, SANDS, (all human drug types); Veterinary Supplemental New Drug Submission (VSNDs), Veterinary Supplemental Abbreviated New Drug Submission (VSANDs) (all veterinary drug types); or for biological drug DIN submissions

- | | |
|--|---|
| <input type="checkbox"/> New route of administration, dosage form and/or strength | <input type="checkbox"/> Replace sterility test with process parametric release |
| <input type="checkbox"/> New claims/use, indications, recommended administration or dosage regime | <input type="checkbox"/> Confirmatory studies |
| <input type="checkbox"/> Change in formulation or method of manufacturing with clinical/bio data | <input type="checkbox"/> Other (please specify): _____ |
| <input type="checkbox"/> Change in drug substance/product (site, method, equipment, process control) | |

_____ on a separate attached sheet.

Date: 2013/05/29

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Complete Sections 72 - 74 for Veterinary Products only			
72. Species and Subtypes Recommended for use _____ _____ _____	73. Used for treatment of food-producing animals? 9 Yes 9 No		
	74. Withdrawal Time Species	Days	Hours
	_____ _____ _____	_____ _____ _____	_____ _____ _____

I, the undersigned, certify that the information and material included in this drug submission application is accurate and complete³.

75. Name of Authorized Signing Official _____	76. Signature _____	77. Date		
		YYYY	MM	DD
		2	0	1
		3	0	7
		2	3	
78. Title Director of Clinical Research	NO.	80. Fax No. (831) 429-6370		
81. Name of Company to which the Authorized Signing Official Belongs				

³

If the signing official is a third party acting on behalf of the manufacturer/sponsor identified in section 11, a letter of authorization, signed by the manufacturer/sponsor (section 11), must be filed with the completed submission application form (see Appendix 2).

Appendix I - for Clinical Trial Applications and Amendments only

**Template Authorisation for a Third Party to Import the
New Drug Described in this Clinical Trial Application or Amendment⁴**

I, _____ authorize Colin Holyk of Kerrisdale Pharmacy
: _____
(list each applicable importer [name and address].

add more space as necessary or attach a list of importers)

attached list of importers Yes No

to import the new drug for the purposes of the clinical trial described within this application.

Signed: _____

Print name: _____

Title: _____ Clinical Research

Clinical Trial Sponsor: Multidisciplinary Association for Psychedelic Studies
:

Date: 7/23/13

⁴

Submit with application if the clinical trial sponsor is authorizing one or more third parties to import the new drug for the purposes of the clinical trial described within this application. An authorisation is required for each clinical trial application. As additional importers are identified, additional copies of Appendix I should be provided to Health Canada. If the importer has not changed when a clinical trial application amendment is filed, Appendix I does not need to be re-submitted.

23 Jul 2013 9:02AM

HP LASERJET FAX

6047347242

p. 2

Health Canada

Form HC-SC 3011

**Appendix 3 - Clinical Trial Application Information
(for Clinical Trial Applications for human drugs only)**

82. Clinical Trial Protocol Number (must be assigned) control number 127822	83. Clinical Trial Protocol Title 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
84. Is the investigational product obtained from the Canadian market? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No DIN(s): _____ Country(ies) obtained: Switzerland	
85. Anticipated Clinical Trial Composition (check all that apply): Paediatric population (0-18 years of age) Females Males <input checked="" type="checkbox"/> Adult population <input checked="" type="checkbox"/> Females <input checked="" type="checkbox"/> Males	86. Phase of Clinical Trial (check appropriate box): Phase I - bioequivalence study (7-day administrative target) Phase I - study in healthy humans (30-day default) Phase I - other (30-day default) <input checked="" type="checkbox"/> Phase II (30-day default) Phase III (30-day default) Other (please specify):
87. Information regarding Research Ethics Board that has refused to approve the protocol and/or informed consent form enclosed? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Not known at this time	
88. Clinical Trial Site Information Form enclosed for all sites known at time of application? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No sites are known at this time	

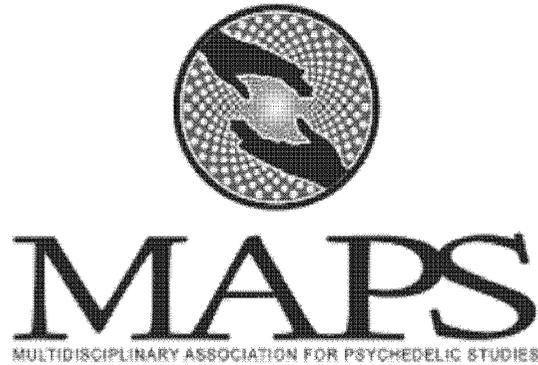
In respect of the clinical trial identified in Appendix 3 of this Drug Submission Application form we certify that:

- The information and material contained in, or referenced by, this application are complete and accurate and are not false or misleading.
- If requested by Health Canada, additional information or samples required to assess this application will be provided within two calendar days following receipt of the request from Health Canada.
- The clinical trial will be conducted and the drug used in accordance with the protocol and the requirements set out in Division 5 of the *Food and Drug Regulations*. The clinical trial will be conducted in accordance with good clinical practices.
- The trial or amendment will not commence at any site until receipt of a No Objection Letter from the Therapeutic Products Directorate or the Biologics and Genetic Therapies Directorate of Health Canada, or the elapse of 30 calendar days following receipt of the complete application by Health Canada, whichever comes first, and the receipt of the Research Ethics Board Approval.
- Records will be maintained for a period of 25 years and will be accessible for on-site inspection by Health Canada Inspectors.

89. Senior Medical Officer or Scientific Officer in Canada Ingrid Pacey MBBS FRCPC(C)	90. Tel. No. and Address 604-732-9309 2369 West Ave Vancouver BC	91. Signature 	92. Date YYYY MM DD 20 07 23
93. Senior Executive Officer 	94. Tel. No. 831-429-8362	95. Signature 	96. Date YYYY MM DD 20 11 30 7 23

Date: 2013/05/29

8 of 20



INVESTIGATOR'S BROCHURE

SPONSOR: Multidisciplinary Association for Psychedelic Studies

PRODUCT: 3,4-methylenedioxymethamphetamine (MDMA)

IND #: 63,384

EDITION: 7th Edition

RELEASE DATE: August 1, 2013

REPLACES: 6th Edition, dated September 7, 2010

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2. List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI-II	Beck Depression Inventory II
C	Celsius
CAPS	Clinician Administered PTSD Scale
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
EMA	European Medicines Agency
LD50	Lethal dose in 50% of cases
LSD	d-lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MP-1	Sponsor's first Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD

PRN	As needed
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

3. Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a U.S.-based non-profit research and educational organization supporting research of the therapeutic potential of MDMA (3,4-methylenedioxy-N-methylamphetamine). MAPS is sponsoring clinical trials to test medical uses of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety related to autism, pain and anxiety related to terminal illnesses and further research into its potential for therapeutic applications. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of psychotherapy. This Investigator's Brochure (IB) describes the physical, chemical, and pharmacological characteristics of MDMA, its effects in nonclinical and clinical studies, and the safety profile of MDMA-assisted psychotherapy. This IB focuses on research and information relevant to researchers and regulators engaged in clinical trials with MDMA.

MDMA is a ring-substituted phenethylamine that produces anxiolytic and prosocial effects through release of the monoaminergic neurotransmitters with the greatest effect on serotonin, followed by norepinephrine and dopamine. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session. Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders such as PTSD and possibly social anxiety more generally. MDMA may provide a much-needed option in the treatment of PTSD and other conditions associated with anxiety.

A substantial amount of data, both clinical and nonclinical, has been collected over nearly a century of research on the physiological and psychological effects of MDMA in humans and animals. Estimates from animal data suggest a LD50 in humans between 10 - 20 mg/kg [1]. Due to a wide range of responses to identical milligram per kilogram (mg/kg) dosing [2], possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses that are equivalent to between 1 and 2 mg/kg (active doses in studies range from 75mg to 187.5mg) to achieve a more consistent response between subjects. The pharmacokinetics of MDMA in humans have been characterized using oral doses of up to 150 mg MDMA. Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Unexpected and expected serious adverse events involving administration of MDMA in government-approved clinical trials have been rare and non-life threatening. MDMA produces sympathomimetic effects that include significant transient, self limited increases in heart rate and blood pressure that were likely to be well tolerated by healthy

individuals [2, 4-6, 9-12]. Most people do not experience elevations that exceed those seen after moderate exercise. In the first MAPS Phase 1 safety study, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Risks posed by elevated blood pressure are addressed in clinical trials by excluding people with pre-existing uncontrolled hypertension and by frequently monitoring blood pressure and pulse. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the next 24 hours. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, impaired gait or balance, dry mouth, ruminations, muscle tension and thirst. Less common reactions include restlessness, parasthesias, impaired judgment, perspiration, drowsiness, and nystagmus. While anxiety, headache, fatigue, insomnia and lack of appetite were reported by 40% to 80% of subjects in both placebo and MDMA conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition. MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. MDMA was administered to thousands of people prior to scheduling and millions continue to use ecstasy around the world in various non-medical settings [14-18]. While a number of serious adverse events, including fatalities, have been reported after non-medical ecstasy and poly-drug use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use [19, 20]. The common effects in ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity, and hyponatremia. Currently MDMA has been administered to over 850 individuals for research purposes without the occurrence of unexpected drug-related Serious Adverse Events.

To date in the MAPS clinical research program there have been 79 people exposed to MDMA and a total of 210 exposures. MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 subjects treated in their first pilot study (MP-1 and MP-1 extension) in the United States (U.S.) [21]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [22]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 subjects suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [23]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that treated five subjects, with no drug-related Serious Adverse Events (SAEs). A dose-response study of MDMA-assisted psychotherapy for PTSD enrolled six subjects, with four receiving MDMA [24] without producing any safety concerns and observing some symptom reduction.

MAPS current program consists of one Phase 1 study of MDMA-assisted psychotherapy in the U.S. and four Phase 2 MDMA/PTSD studies in the U.S., Canada and Israel that are actively recruiting. Ongoing and planned Phase 2 studies of MDMA-assisted psychotherapy for PTSD treatment are laying the groundwork for an End-of-Phase 2 meeting with FDA and Phase 3 multi-site MDMA/PTSD research studies. Based on the experience in chronic, treatment-refractory PTSD, MAPS is exploring new indications for this treatment. Due to similarities in

symptom profiles and to reports from anecdotal research, MAPS is conducting a protocol investigating changes in social anxiety experienced by autistic adults when using two sessions of MDMA-assisted therapy, interspersed with biweekly non-drug integration sessions.

4. Introduction

MDMA:3,4-methylenedioxy-N-methylamphetamine, is not a novel compound, the history of its use in humans predates controlled studies in healthy volunteers and clinical trials. MDMA was first synthesized and patented by Merck in 1912 [25], but is currently not covered by a patent. MAPS currently holds the Drug Master File and an IND for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin [26], he and his colleagues provided initial reports of its pharmacology and effects in humans [27, 28]. MDMA was found to robustly influence human emotional status in a unique way [28] without adversely effecting physiological functions or perception, such as visual perception or cognition [3, 5, 7; Vollenweider, 1998 #880].

In the Merck Manual, MDMA is in the entactogen class. Entactogens contain a ring-substituted amphetamine core, and belong to the phenethylamine class of psychoactive drugs. Entactogens as a class of drugs are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions and increased interpersonal closeness. In comparison to anxiolytics, antidepressants and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy. A limited number of exposures to MDMA, spaced approximately a month apart at moderate doses, are sufficient to obtain comparable or better results than other medications that require daily dosing. This infrequent dosing mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing.

Shulgin and Nichols were the first to report the effects of MDMA in humans [28]. MDMA-assisted psychotherapy first occurred during the mid to late 1970s after Shulgin introduced MDMA to a psychotherapist. Reported effects of MDMA include enhanced feelings of closeness to others, wellbeing, and insightfulness [29-31]. Prior to scheduling in 1985, MDMA was used in individual, couple, and group therapy to treat diverse psychological disorders, including moderate depression and anxiety [30, 32] [33, 34]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [33]. No formal controlled clinical trials of safety and efficacy were conducted at the time [30, 35].

During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [14]. The first wave of non-medical use occurred not only in dance clubs but also in groups of people who used the drug in a self-exploratory or spiritual context. Non-medical use continues today in the same contexts [17, 36].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, indicating that it has a high potential for abuse and no accepted medical use [37, 38]. Shortly after it was scheduled, animal studies described long term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [39] that were not relevant to doses in clinical trials. A recently published meta-analysis took careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [40]. Reports of

adverse events seen following ecstasy use [41-43] and cognitive, physiological, and imaging findings in humans raised concerns regarding the safety of MDMA administration [44-48]. Preclinical studies have often employed inappropriately high doses of MDMA and their findings are open to several interpretations [49, 50], and the vast majority of studies of ecstasy users are retrospective reports in polydrug-using ecstasy users [40, 51]. Classification to schedule 1 combined with the early research in animals and recreational users hampered clinical research into the medical uses of MDMA until the 1990's.

While the initial studies in the 1990s examined the physiological effects of MDMA narrowly from a safety perspective, recent studies have examined the effects of this compound on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial report indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic treatment resistant PTSD[52]. In addition placebo-controlled Phase 1 clinical trials confirmed that MDMA produces an easily controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion, transient increases in anxiety and minor alterations in perception [3, 5-7, 53-57]. In MAPS first Phase 2 study, MP-1, no difference was seen in cognitive function between placebo and MDMA groups after MDMA was given on 2 occasions a month apart in the therapeutic dose range. In addition, published results from the first two Phase 2 studies (MP-1, MP-2) showed significant durable improvements in PTSD symptoms. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, it appears favorable to pursue the research of MDMA as a medicine used as an adjunct to psychotherapy.

5. Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is structurally similar to amphetamines and mescaline. MDMA, also known as 3,4-methylenedioxy-n-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. It was first synthesized as a precursor of a haemostatic drug called methylhydrastinine as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [1].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [1, 58]. All research in humans to date and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. Studies of drug discrimination in rodents [59, 60] and studies of self-administered and experimenter-administered MDMA enantiomers in primates [59, 61-64] suggest that MDMA enantiomers may produce different physiological and rewarding effects, but that there may be some synergy between the two when administered as a racemate. It seems that R(-)-MDMA may have hallucinogen-like effects, compared to S(+)-MDMA, which exhibits psychomotor stimulant-like effects. Findings comparing the effects of the enantiomers of the related compound methylenedioxyethylamphetamine (MDE) suggest that these different effects of MDMA enantiomers may occur in humans [65]. According to an *in vivo* microdialysis study, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [66]. A recent study in monkeys found that S(+)-MDMA, but not R(-)-MDMA, significantly increased extracellular dopamine levels in the dorsal striatum, whereas S(+)-MDMA significantly increased serotonin levels [63]. MDMA available for human in clinical trials is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the

enantiomers remain untested in humans.

For clinical trials, the Sponsor used racemic MDMA from two sources. Studies in the United States use MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA supply for the Sponsor was manufactured as a single lot for use in federally approved clinical research and has been utilized by a number of investigators in the U.S. A stability analysis conducted in 2006 indicates that the compound remains highly stable and pure after 21 years of storage [67]. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland and maintained by Prof.

The most recent analysis of drug stability and purity conducted on February 2, 2010 confirmed that this MDMA is 99.9% pure with no detectable decomposition. For Sponsor-supported studies, MDMA in the form of white crystalline powder is compounded with inert material into capsules. The capsules are stored in sealable containers placed within a dark safe at ambient temperature. Capsules are administered orally with a glass of water. Details of manufacturing are available from the manufacturers upon request.

MDMA doses in sponsor-supported studies are fixed, rather than based on body weight due to evidence of non-linear metabolism. Full dose is 125 mg, which is equivalent to 1.25 mg/kg (100kg) to 2.6 mg/kg (48kg) for the initial dose. The optional supplemental dose of 62.5 mg is equivalent to 1.3 mg/kg (100kg) to 2.6 mg/kg (48kg). Various comparator doses of less than 125mg of MDMA are also used in the clinical trials.

6. Nonclinical Studies

6.1. Nonclinical Pharmacology

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. MDMA prevents the uptake of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) and is involved in the release of these three neurotransmitters, with the greatest effects on serotonin release. Receptor binding studies of MDMA employing to very large amounts of MDMA relative to human plasma C_{max} found some affinity for specific serotonin, norepinephrine, acetylcholine, and histamine receptors, reporting that strength of activity on these receptors is low in comparison to monoamine transporters [68-71]. *In vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake [72, 73] and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine [74]. MDMA appears to alter the conformation of the serotonin transporter, enabling serotonin to diffuse out of the neuron rather than actively transporting extracellular serotonin into these neurons [75-77]. A recent microdialysis study of a therapeutically relevant dose of MDMA in rats confirms elevated brain serotonin [78]. In combination with other drugs, or at high doses, MDMA may provoke serotonin syndrome, a suite of specific signs and symptoms that can require intervention [79-81]. Participants in sponsor-supported studies are tapered off psychiatric medications that would increase this risk.

6.2. Pharmacology and Product Metabolism in Animals

6.2.1. Pharmacology in Animals

Research into the pharmacological, physiological, or psychological effects of MDMA began in the 1950s, when the U.S. Army administered MDMA to guinea pigs, monkeys, mice, rats, and dogs as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation [82]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA in an attempt to produce human-equivalent doses [83]. Recent reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology [49, 84, 85]. A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner and that MDMA had a shorter half-life in monkeys than in humans. Both species exhibited nonlinear pharmacokinetics, and it appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA [86, 87]. An investigation in rats also demonstrated nonlinear pharmacokinetics in that species as well, finding that human-equivalent doses of MDMA in rats are close to or identical to those in humans and drug half-life is rapid [49]. Doses of 10 mg/kg but not 2 mg/kg produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain two weeks after drug administration. These discoveries suggest that toxicological and behavioral studies of MDMA used doses exceeding human equivalent doses. As a consequence, it is difficult to interpret the relevance of findings in nonclinical studies employing these dosing regimes.

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release and activating 5HT₄ receptors [88, 89]. MDMA probably stimulates 5HT_{1A} receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial 5HT_{1A} antagonist in some brain areas [90]. Findings from other studies suggest that it shares qualities with 5HT_{1A} agonists. Early studies in rodents suggest that 5HT_{1A} receptors reduce anxiety and aggression [91, 92], and some drug discrimination studies suggest that the 5HT_{1A} agonist 8-OH-DPAT partially or fully substitutes for MDMA [93-95]. Administering a 5HT_{1A} antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly because it prevents elevation in oxytocin [96, 97]. At least some direct or indirect effects of MDMA on serotonin receptors may cause changes in GABA uptake in the ventral tegmental area of rats [98].

6.2.2. Gene Transcription in Animals

A number of research teams have studied the effects of MDMA on gene expression in rodents [99-102]. However, many of these reports used 10 to 20 mg/kg MDMA, and it is unlikely that these changes can be generalized to humans given lower doses. These studies report an increase in expression of genes that regulate the GABA transporter [99, 102]. Some of the increases in transcription are in genes associated with monoamine release [99]. Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release [99]. Examining rat brains two weeks after repeated MDMA detected a sharp drop in serotonin gene transporter expression [103], offering an alternative to axonal

damage as an explanation for alteration in serotonergic function after repeated doses of MDMA. A recent publication found that repeated administration of MDMA at 1 or 5 mg/kg weekly for four weeks increased transcripts for 5HT_{1B} receptors in various brain regions and 5HT_{2C} receptors in the cortex and hypothalamus [104]. Increases in transcripts of genes regulating extracellular signaling in mice were also reported [105]. It appears that serotonin may play more of a significant role than dopamine in transcription-level changes [104]. Transcripts were assessed ten hours after the last of repeated MDMA administrations and it is not clear whether these changes reflect residual acute effects of the MDMA or changes related to repeated MDMA administration. In addition, changes in transcription do not always correlate with changes in proteins produced from the genes. Future studies will need to separate direct and indirect effects of MDMA on gene expression.

6.2.3. Endocrine Effects in Animals

In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin [106-108], with elevation lasting up to four hours after dosing, and with hormone levels attenuated by a 5HT₂ receptor antagonist. Given the large dosage used, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. A study of isolated rat hypothalamus reported arginine vasopressin (AVP) and oxytocin release after administration of MDMA and its metabolite HMMA [109]. A recent study using 1-3 mg/kg doses found that R(-)-MDMA, but not S(+)-MDMA, significantly increased prolactin levels in rhesus monkey plasma, suggesting that at least the R(-) enantiomer of MDMA can influence endocrine signaling at doses relevant for studies in humans [63]. Fluoxetine attenuated prolactin release after administration of racemic MDMA, and fluoxetine and a 5HT_{2A} antagonist attenuated prolactin release after R(-)-MDMA, indicating that prolactin release is associated with serotonin release and action on 5HT_{2A} receptors by R(-)-MDMA.[64].

6.2.4. Thermoregulatory Effects in Animals

Rodents have generally been used to study the hyperthermic effects of MDMA. Given that rodents have a much smaller body mass and do not perspire, it is unlikely that thermoregulation occurs in the same way in rodents and humans [110]. Moderate and high doses of MDMA elevate body temperature and disrupt thermoregulation in rodents [76], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [111]. MDMA causes susceptibility to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures producing hypothermia [112-114]. High doses of MDMA also produce significant elevations in body temperature in primates [84, 115, 116]. At doses closer to those humans ingest [117], monkeys exhibit only slight to moderate elevation in body temperature [118, 119]. In contrast to findings in rodents, primates are not susceptible to changes in ambient temperature when they receive MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [117-119], though at least one study found that the ambient temperature influenced the effects of 1.5 mg/kg i. v. MDMA on body temperature in monkeys, with lower body temperatures seen in after MDMA and cool temperatures and higher body temperatures in another group given MDMA in a warm temperature [120]. It appears that findings in rodents do not extrapolate well to primates,

and studies in humans supported by the Sponsor will address the effects of moderate doses of MDMA on thermoregulation.

6.2.5. Cardiovascular Effects in Animals

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathetic activity, as seen in humans [76]. Injections of 20 mg/kg MDMA in conscious rodents assessed by radiotelemetry found that MDMA caused a prolonged increase in blood pressure [121]. In the same study, MDMA was found to produce mild isotonic contractions of rat aorta and vas deferens vascular tissue in anesthetized rodents, but could also inhibit prejunctional contractions evoked by stimulation [121]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [122]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [121, 123, 124]. A study in rodents suggests that norepinephrine may play a role in cardiovascular effects [125]. Given the affinity of MDMA for the norepinephrine transporter, it is possible that the cardiovascular effects of MDMA could be attributed to norepinephrine signaling in the peripheral nervous system.

6.2.6. Behavioral Effects in Animals

In rodents, doses of MDMA equivalent to human doses produce either few or no behavioral effects. However, doses of 5 mg/kg or greater have several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses, and decreased anxiety at higher doses [76, 126]. Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze [127], while rats given higher doses exhibited reduced anxiety on the maze. Rats given higher doses also reduced aggressive behavior as well as social investigation. Rodents responded to very high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail"), all signs of rodent serotonin syndrome [126]. MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. MDMA leads rats to walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [76]. However, it is notable that a recent publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [128]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [119].

To date, no empirical investigations have been conducted on the effects of MDMA on primate social interactions. Morley and colleagues observed rat behavior after receiving 5 mg/kg MDMA, noting that this dose correlated with prosocial behavior, such as lying next to each other [96]. Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through 5HT1A receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on 5HT1A receptors [97, 129]. To date, there have been no human pharmacological challenge studies combining MDMA with 5HT1A agonists, while 5HT1A antagonists have negligible effects on subjective or physiological effects of MDMA in humans [57, 130-132]. As a result, it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA [8, 15, 133, 134].

6.3. Toxicology

6.3.1. Neurotoxicity in Animals

Repeated high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psychobehavioral changes such as increased anxiety [76, 126, 135-137]. Studies in rodents and primates suggest that MDMA could damage serotonin axons and cause neurotoxicity [76, 138-141]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, an issue that remains true even in recent investigations [see for example 50, 142, 143]. It now appears that lower doses of MDMA do not reduce brain serotonin [84, 85]. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin, and no chemical markers of neuronal injury [144]. Rats receiving lower doses of MDMA also fail to exhibit signs of neurotoxicity [85]. A recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days [145]. Relying on previous *in vitro* and *in vivo* research and on their own current work, the same researchers present a case that MDMA is altering regulation of brain serotonin without producing damage to serotonin axons. They reach this conclusion through comparing findings of reduced brain serotonin and SERT with failure to detect other indicators of neuronal injury and findings of decreased expression of the SERT gene in rat brain [50].

6.3.2. LD50 in Animals

Intravenous MDMA doses that cause lethality in 50% of the cases, known as the LD50, are 97 mg/kg in mice, 49 mg/kg in rats, 14 to 18 mg/kg in dogs, and 22 mg/kg in monkeys [82]. The LD50 in mice housed together is 20 mg/kg, considerably lower than values in isolated animals [113, 146]. MDMA lethality also varies between the sexes and different strains in rats.[147-149].

6.3.3. Developmental Toxicity in Animals

15 mg/kg MDMA administered s.c. to pregnant rats was detected in amniotic fluid [150]. Several teams of researchers have performed studies of developmental toxicity in rodents. None of the studies found gross structural abnormalities in rats exposed to high doses of MDMA *in utero*. In an initial study, pregnant rats were administered twice-daily injections of high doses of MDMA (15 mg/kg) or saline from embryonic days (E) 14-20. Rat pups that had received MDMA showed reductions in the dopamine metabolite homovanillic acid, along with reductions in the serotonin (5-HT) metabolite 5-HIAA. Prenatally exposed MDMA animals also had reduced dopamine and serotonin turnover in the nucleus accumbens [151]. The same team reported postnatal exposure to MDMA correlated with reductions in serotonin and its metabolite, as well as significant increases in dopamine turnover and the prevalence of a dopamine metabolite in multiple forebrain structures and the brainstem. Brain-derived neurotrophic factor (BDNF), which controls neuronal growth in the brain, was significantly increased (19-38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates [152]. The researchers proposed that BDNF was compensating to minimize MDMA effects. However, later studies found that neonatal MDMA exposure did not affect hippocampal concentrations of serotonin or dopamine [153] and that a region-specific enhancement in BDNF expression did not mediate the abnormal

serotonergic signaling observed following neonatal MDMA exposure [154]. Postnatal days 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [152], so it is possible that exposure to high doses of MDMA *in utero* could have developmental effects, but these do not appear to be related to BDNF levels.

Prenatal MDMA exposure at high doses significantly increased locomotor activity of pups in a 20-min novel cage environment [151]. Rodents treated with MDMA during development were not significantly different than rodents who received MDMA as adults. The results of several behavioral tests did indicate that developmental MDMA exposure combined with adult exposure may interfere with some aspects of learning [153]. Neonatal MDMA administration did not alter working memory in the object-recognition test in young adulthood (PD 68-73) and there were no differences in binding of the radiolabeled SSRI citalopram to the serotonin transporter at this age. However, the pretreated animals showed increased thermal dysregulation and serotonin syndrome responses following MDMA challenge, especially with respect to head-weaving stereotypy [155]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose of MDMA [156]. A study in neonatal rats suggests two distinct critical periods wherein repeated doses affected learning versus acoustic startle [157]. Given differences between human and rodent development and thermoregulation, it is not clear whether such findings can be generalized to humans (see Section 6.2.4). Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

6.3.4. Self-Administration in Animals

Mice, rats, and monkeys will self-administer MDMA, indicating that MDMA has rewarding properties in animals [158-160]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [158], but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine [161, 162]. Taken together, these results suggest that the abuse liability of MDMA is moderate.

7. Effects in Humans

Evidence exists for intentional human use of MDMA as early as the late 1960s [26], and there are records of a police seizure of MDMA in the early 1970s [163]. Shulgin and Nichols were the first to report on the effects of MDMA in humans [28]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [30]. Legal therapeutic use continued until its placement in US Schedule 1 in 1985 [29, 33, 164]. Estimates indicate that 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [26, 164]. A few uncontrolled human studies of MDMA occurred in the 1980s [9, 165], including Greer and Tolbert's study of MDMA in a psychotherapeutic context. Recreational use of MDMA, known as "ecstasy," has been ongoing since the early 1970s, but controlled human studies of MDMA did not commence until the early to mid-1990s, with the publication of a Phase 1 dose-response safety study supported by the Sponsor and conducted by Grob and colleagues [13]. The Sponsor has completed two

investigations of MDMA-assisted psychotherapy for PTSD, one in the U.S. and one in Switzerland [21, 166, 167] with additional phase 2 studies underway.

7.1. Pharmacology and Product Metabolism in Humans

7.1.1. Pharmacology in Humans

Estimates from animal data suggest the LD50 in humans is probably between 10 - 20 mg/kg [1]. Typically, human trials have used doses between 1 and 2 mg/kg, with therapeutic studies using fixed dosing rather than adjusting dosing on a mg/kg basis, in order to achieve a more consistent subjective response between subjects. The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA.

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the entactogens [8, 31], defined as substances that produce changes in mood and social interaction, as well as feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens [3, 6, 7, 168], as well as a small number of pharmacologically related compounds, such as methylenedioxyethylamphetamine (MDE) [168]. Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy [15, 133, 134, 169]. Initial studies measured self-reported empathy or closeness to others in healthy volunteers [2, 5, 55], and recent controlled studies measured effects of MDMA on social cognition or emotion [53, 54, 56]. Although researchers have offered several models and explanations for the effects of entactogens, it appears that serotonin release plays a significant role in producing at least some of these effects, and norepinephrine release may play a lesser role. Indirect action on 5HT_{1A} or 5HT_{2A} receptors and neuroendocrine responses such as increases in the hormones oxytocin, vasopressin, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

Preventing serotonin release through administration of selective serotonin reuptake inhibitors (SSRIs) appears to attenuate or eliminate most subjective, physiological and immunological effects of MDMA [170-174]. Pre-treatment or co-administration with SSRIs attenuates the effects of MDMA on mood and perception without influencing specific effects such as nervousness or excitability [170]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [171, 174] while others report that SSRIs only attenuate elevated heart rate [173]. All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but that this combination prevents or significantly reduces the subjective effects of MDMA. These subjective effects are predominately mediated by direct or indirect action on 5HT_{2A} receptors [57, 132, 175], with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to 5HT_{2A} receptor activation [57]. In contrast, the 5HT_{1A} receptor appears to be minimally involved in producing the subjective effects of MDMA [57, 130-132]. Co-administration of the beta-blocker and 5HT_{1A} antagonist pindolol along with 1.5 mg/kg MDMA to 15 men attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA without actually attenuating MDMA-related reduction in performance on a task requiring visual attention, and coadministration of pindolol to 9 men and 8 women failed to alter the acute effects of 75 mg MDMA on self-reported mood [57, 130].

Recent human MDMA studies suggest that norepinephrine (NE) release may also contribute to the pharmacodynamic, physiological and psychological effects of MDMA [176-179]. Studies with NE uptake inhibitor reboxetine suggests that norepinephrine plays a role in the cardiovascular effects of MDMA and on subjective effects on positive mood and excitement [177]. Most of the psychostimulant-like and psychological effects of MDMA are blocked after administration of the dual SSSR/NRI duloxetine [178, 179], and there is evidence that norepinephrine and serotonin may play a role in elevated copeptin, a neuroendocrine hormone, in women after MDMA [179]. Preclinical and *in vitro* findings reports indicate that MDMA displays a higher affinity for the norepinephrine transporter than the serotonin transporter [73], which could possibly explain these results (Hysek/2012).

At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D₂ receptors, as administering the D₂ antagonist haloperidol diminished positive mood and increased anxiety in humans [180]. As of November, 2012, there have been no studies in healthy volunteers examining the role of dopamine release or uptake inhibition.

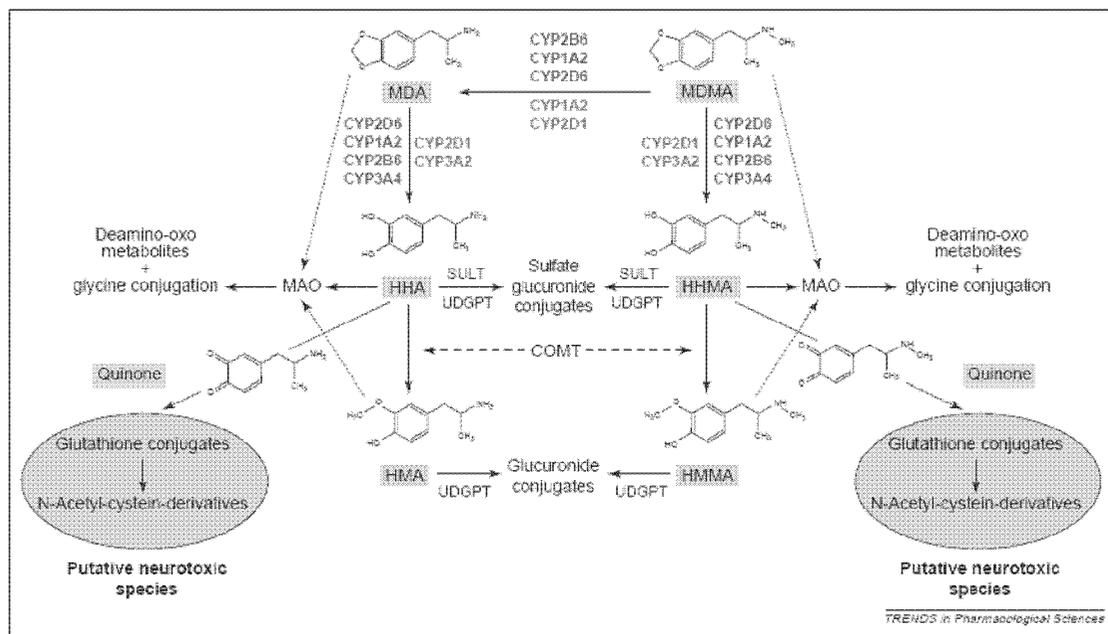


Figure 1. Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [181].

7.1.2. Metabolism in Humans

Metabolites of MDMA are summarized in Figure 1 [182-186]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [183]. Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [187-191]. Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery [191]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [192]. As was the case for maximal plasma values, urinary

recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA [187]. In one study, urinary excretion of the metabolite HMMA exceeded that of MDMA by 33 hours after a dose of 1.6 mg/kg MDMA [193], suggesting that secondary metabolism of MDMA continues during this period. A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed 2 hours later by 100 mg reported higher peak plasma MDMA than might be expected, and lower levels of the MDMA metabolites HMMA and HMA [194]. Findings support the enantioselective metabolism of MDMA and its metabolites measured in blood and urine [195, 196].

Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Self-reported duration of effects may increase with as the dose of MDMA increases [2]. Orally administered MDMA has a half-life of seven to nine hours in humans, with one report listing a half-life of 11 hours [188]). It is metabolized in the liver by several cytochrome P450 CYP enzymes, including CYP1A2, CYP3A4, and CYP2D6. It is likely that active doses of MDMA inhibit CYP2D6 function as measured by examining the effects of MDMA on dextromethorphan metabolism. Because O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until ten days after MDMA [197, 198]. After reviewing their data and the literature on MDMA pharmacokinetics, de la Torre and colleagues concluded variation in CYP2D6 genotype is not clinically significant, due in part to the fact that the enzyme is inhibited in most people after administration of an active dose [199]. In contrast, MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [200]. The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [192]. At least one variation in COMT genotype may affect MDMA elimination rate (K_e) and systolic blood pressure (SBP) after MDMA [201].

7.2. Physiological Effects in Humans

7.2.1. Endocrine Effects in Humans

MDMA acutely increases cortisol, prolactin, and adrenocorticotrophic hormone concentrations in a dose dependent manner [4, 5, 13, 56, 187, 202], whereas growth hormone is unchanged by up to 125 mg MDMA [4]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [4, 13]. A second dose of 100 mg MDMA, given four hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [203], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [187]. A naturalistic study in clubgoers found a much greater elevation in cortisol after ecstasy use [204]. In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug [5]. MDMA produces a robust increase in the neurohormone oxytocin [54], a finding first seen in a naturalistic study [205]. The naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without any detectable levels of MDMA. It is likely that all neuroendocrine changes result from monoamine release, and it is currently

unknown what role, if any, they play in producing the effects of MDMA. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol, in some circumstances, may serve as a signal to seek affiliation or to increase positive mood [206-209].

The significance of elevated oxytocin in producing changes in social cognition are discussed in section 7.1, and include potentially therapeutic effects, such as increased feelings of closeness to others or greater ability to detect expressions of positive mood in others. The significance of elevated cortisol after MDMA is unclear. It is possible that cortisol elevation could be tied to specific acute effects on mood or memory. However, pre-treatment with the cortisol synthesis inhibitor Metyrapone blocked MDMA-induced increase in cortisol levels in blood without preventing impaired performance on verbal memory tasks and without altering the effects of MDMA on mood, [210]. It is unclear what contributions, if any, elevated cortisol make to the subjective or physiological effects of MDMA.

7.2.1.1. *Endocrine Effects and Homeostasis in ecstasy users*

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use [83, 211-213]. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressin and oxytocin, likely all contribute to this very rare but serious adverse event in ecstasy users [205]. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

7.2.2. Thermoregulatory Effects in Humans

In the first Phase 1 safety study funded by the Sponsor, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Doses between 1.5 and 2 mg/kg MDMA produced only a slight elevation in body temperature that was not clinically significant [6, 171, 175] and this elevation was unaffected by ambient temperature [117]. Studies in MDMA-experienced volunteers given 2 mg/kg MDMA produced slight but statistically significant increases in core body temperature, at mean elevation of 0.6 ° C [117]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. A second dose of MDMA elevates body temperature, but not beyond what would be expected after the cumulative dose [194]. While MDMA did not increase or decrease perspiration overall, it was associated with a higher core temperature when people began perspiring. Ambient temperature neither attenuated nor amplified the subjective effects of MDMA, with people reporting similar drug effects in the warm and the cool environment. As expected, people felt warm when the room was warm and cold when the ambient temperature was cool, and MDMA did not distort perceptions of warmth or cold in either case. Unlike rodents given MDMA at higher mg/kg doses, humans do not exhibit reduced temperature when MDMA is given in a cold environment, and they do not exhibit significant hyperthermia in a warm environment. When compared with placebo, findings from 74 participants given MDMA found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram [6]. Subsequent studies have not confirmed this gender difference [11], and a report in a sample of 17

men and women reported higher oral temperatures in women [201]. It is notable that participants in studies in a clinical setting have not engaged in vigorous exercise and have remained either sitting or lying down throughout most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings. However, one out of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while two others failed to find any significant differences in ecstasy-user body temperature at a club [204, 214, 215].

Hyperthermia has occurred in people using ecstasy in unsupervised and non-medical conditions, and though rare, it is one of the most frequently reported serious adverse events occurring in ecstasy users [212, 216]. The exact conditions preceding hyperthermia are unknown. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. At least one case series of individuals seen on the same night and near or in the same nightclub suggest a relationship between ecstasy dose and likelihood of hyperthermia [217]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [218, 219]. No cases of hyperthermia have been reported in clinical trials with MDMA.

7.2.3. Cardiovascular Effects in Humans

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [9] and replicated by other research teams in the US and Europe [4, 6, 10]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [2, 5, 11, 12]. Most people do not experience elevations that are greater than those seen after moderate exercise. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration [9] and peak between 1 and 2 hours post-drug [7, 10], with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure and greater elevation in heart rate in a study summarizing and pooling data from a series of human MDMA studies [6]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/110 or higher occurred in approximately 5% of research participants receiving a single dose of at least 100 mg MDMA in research studies [4, 8]. Peiro and colleagues observed elevation in blood pressure above 150/90 as well in all ten participants given 50 mg followed two hours later by 100 mg MDMA [194]. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [4, 8, 194].

The alpha(1) – and beta-adrenergic receptor antagonist carvedilol reduced MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 h before MDMA without affecting the subjective effects of MDMA. Hence carvedilol could be useful in the treatment of cardiovascular and hyperthermic complications associated with ecstasy use [220]. Other antihypertensive medications either alter some of the effects of MDMA [221] or do not significantly reduce blood pressure [176].

As described above, administering 50 mg MDMA followed two hours later by 100 mg produces elevated HR and BP, but the elevations are no greater than those expected with plasma MDMA levels [194]. The study used a different dosing regimen than the one used in sponsor-supported studies.

The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional risks and complications [222-224], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [225] and cerebral or subarachnoid hemorrhage [41, 226-229]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [226, 228]. Increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [230, 231]. Although the presence of MDMA was rarely confirmed in reported cases, these types of events are all well established complications of hypertension and can occur after use of amphetamines. There have been no such events to date in any clinical trial of MDMA.

Some researchers expressed concern that MDMA activity at 5HT_{2B} receptors might be indicative of increasing risk of valvular heart disease with repeated use [69]. Studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease [232], and a case of valvular heart disease has occurred in a man reporting approximately 16 years of ecstasy use [233]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Previous to this, ECGs in eight ecstasy users also failed to find any cardiac abnormalities [10]. Since VHD-associated changes and VHD only occurred after extremely heavy ecstasy use, they are unlikely to be a risk within the research or therapeutic context.

7.2.4. Liver Effects in Humans

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from non-medical, uncontrolled ecstasy users collected from the mid-1990s to 2001, making it the third most common serious adverse event in reported in the literature [83]. There appears to be more than one pattern of ecstasy-related hepatotoxicity, and a number of factors, including polydrug use and setting of use may be involved [234]. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet [235-237]. In other cases, hepatotoxicity has occurred after months of regular ecstasy use [238]. Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure [239], nor have any cases of liver disease arisen during controlled studies. Examinations of case reports and a number of *in vitro* studies suggests an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, with it appearing after continued use and resolving after abstinence. In these cases, it appeared after continued use and resolved after a period of abstinence. These reports suggest a potential immunological response. Because hepatotoxicity has been noted in ecstasy users, *in vitro* and *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that high doses of MDMA can impair liver cell viability [240], increase profibrogenic activity in cultured stellate cells [241], and slightly reduce cell viability without producing lipid peroxidation [242]. However, peak liver exposure to MDMA in Sponsor studies should be

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

7.2.5. Immunological Effects in Humans

Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [172, 203, 243, 244]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma, and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [244, 245]. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [203, 246]. A second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [203]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.2.5.1. *Immunological Effects in Ecstasy Users*

A longitudinal study of regular ecstasy and cannabis users found a sustained reduction in interleukin 2 (IL-2), increased levels of transforming growth factor-Beta (TGF-B) and reduced CD4 cells, and regular ecstasy and cannabis users reported experiencing a greater number of mild infections than occasional ecstasy and cannabis users on a structured questionnaire [247].

7.2.6. Effects on Sleep in Humans

Serotonin and catecholamine neurotransmitters are known to modulate sleep architecture and alertness. To date, there is only a single study examining the acute effects of MDMA on sleep [248] while all other investigations have looked at sleep in ecstasy users. In a trial with 2 mg/kg MDMA given six hours prior to preparing for sleep, MDMA was found to increase Stage 1 sleep and reduce rapid eye movement (REM) sleep without producing an increase in daytime sleepiness [248].

7.2.6.1. *Effects on sleep in ecstasy users*

Examining sleep architecture in ecstasy users, the same investigators found less total sleep time and less stage 3 and 4 sleep on the adaptation night, but no overall differences in sleep architecture [248]. Another study comparing heavy ecstasy users with non-drug using controls

found no differences in baseline sleep using electroencephalography (EEG) [249]. Early studies in mostly heavy ecstasy users reported significant decreases in total sleep as well as stage 2 sleep [250], while recent studies found ecstasy users were able to fall asleep more easily upon depletion of catecholamine neurotransmitters suggesting an underlying difference in serotonergic control of sleep architecture [251, 252]. Findings of sleep disruption in ecstasy users are not likely applicable to the exposures seen in research or therapeutic settings.

A study of breathing during sleep in 71 ecstasy users and 62 polydrug users did not find overall differences in disrupted breathing, assessed via nasal cannula, but found that all moderate and severe breathing disruptions occurred in the ecstasy using sample [253]. McCann and colleagues reported a relationship between cumulative (lifetime) ecstasy exposures and instances of disrupted breathing during non-REM sleep and suggested ecstasy users could be vulnerable to potentially fatal sleep apnea. In contrast, other researchers failed to find greater night-time awakenings indicative of sleep apnea in ecstasy users [248, 249], and the high rate of disrupted breathing McCann and colleagues detected even in the controls suggest that this measure may not provide clinically significant assessments. Taken together, it appears that MDMA acutely produces lighter sleep with fewer REM periods.

7.3. Reproductive and Developmental Risks in Humans

Previous research supported a possible link between ecstasy use and birth defects [254], while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed to support this link, at least in respect to a specific cardiac defect [255]. However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant [256]. A 2012 survey of 96 women in the UK interviewed about their drug use during pregnancy found a link between self-reported extent of prenatal MDMA exposure and delays in infant development at 12 months, with heavily exposed infants delayed in mental and motor development but not language or emotional development [257].

There are no plans to include pregnant women in research studies with MDMA.

7.4. Abuse Potential in Humans

Studies in humans and animals suggest MDMA possesses some abuse potential. Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence [258], though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence [259], and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency [260]. When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that “none of the participants expressed any interest in taking MDMA as a recreational drug” after receiving MDMA in a controlled research setting [6]. Only one of 32 participants enrolled in sponsor-supported studies of MDMA-assisted psychotherapy for PTSD reported taking ecstasy outside the confines of the study and failed to reproduce the experience [166]. Several participants volunteered that they would not seek out ecstasy outside of therapy. All 12 participants enrolled in the study of MDMA-assisted psychotherapy in Switzerland did not test positive for stimulants or MDMA

[167]. It also appears that MDMA has fewer or less intensely rewarding effects than stimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than that for serotonergic hallucinogens but less than that for stimulants.

7.5. Neuropsychological Effects in Humans

7.5.1. Subjective Effects in Humans

MDMA alters mood, perception, and cognition. At doses of at least 1 mg/kg (or approximately 70 mg) and higher, active doses of MDMA alter mood and cognition and produce slight alterations in perception [6, 261]. Effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later [8, 262, 263]. Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later [5, 264, 265]. Most of the therapeutic effects of MDMA result from changes in affect, cognition, and social interaction. When combined with psychotherapy that supports one or more of these effects, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increases empathy and compassion for others and the self [24, 165, 266]. Though a naturalistic study reported that ecstasy increased accuracy of assessing at least some emotional expressions [267], a controlled study with 0.75 and 1.5 mg/kg MDMA failed to replicate this finding [11].

7.5.2. Emotional Effects in Humans

MDMA increases positive mood and anxiety [3, 5-7]. MDMA users report feeling more talkative and friendly after receiving MDMA, Self-reported interpersonal closeness was noted during a study in healthy volunteers [8]. Subsequent research confirmed the occurrence of increases in interpersonal closeness after MDMA [53-56, 173]. Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA [5], possibly due to the low sensitivity of this measure. However, a recent investigation into the effects of pretreatment with the SSRI paroxetine on MDMA effects in humans reported that MDMA increased feelings of being social and closeness to others, and that paroxetine reduced these effects [174]. People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [3, 6, 8].

People receiving active doses of MDMA experienced euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension, and dysphoria, as concern over losing control over the self [3, 5-7]. More surprisingly, participants report increased positive mood even after a dose of 25 mg [268]. It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects; there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood [7, 180]. MDMA may have a greater impact on mood in women than in men. Women report greater elevation in negative mood. A second dose of MDMA does not increase subjective effects beyond effects reported after an initial dose, results which Peiro and colleagues interpreted as

indications of tolerance to these effects [194]. It is notable that the second dose in this study was double that of the first dose, in contrast to sponsor-supported studies, wherein the second dose is half the size of the initial dose.

Positron emission tomography (PET) brain scans 75 minutes after administration of 1.7 mg/kg MDMA found increased regional cerebral blood flow (rCBF) in ventromedial prefrontal, inferior temporal, and cerebellar areas and decreased rCBF in the left amygdala [269]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [270]. An fMRI study conducted by Bedi and colleagues found that 1.5 and 0.75 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo, though without changing the response to faces showing fear [11]. These researchers also detected increased activity in the ventral striatum in response to happy faces. Taken together, these findings suggest that MDMA changes the way emotional facial expressions are processed or the response to them. Complimenting these findings are results from Hysek and colleagues demonstrating that MDMA enhanced the accuracy of recognizing faces exhibition expressions of positive mood, impaired mind reading for facial expressions of negative mood, and had no effect on mind reading for neutral stimuli [56]. Hysek suggests that the enhanced mind reading of positive emotions may facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings. There is also some evidence for MDMA producing selective difficulty in recognizing faces expressing fear Baggott, 2008 #1606}.

7.5.2.1. *Emotional effects in ecstasy users*

Retrospective surveys of people who have used MDMA or ecstasy offer similar accounts of MDMA effects to those reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents report experiencing stimulant-like effects, such as greater energy or talkativeness, and hallucinogen-like effects, including as perceptual changes or poor concentration. They also report that ecstasy increased feelings of closeness, compassion, or empathy toward the self or others [15, 133, 134, 271]. The disparity in detection of entactogenic effects in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness.

Psychiatric problems after uncontrolled, non-medical ecstasy use were reported in 22.1% of 199 case reports from the early 1990s to 2001, and are the most common reason for appearance at an emergency department [83]. Psychiatric symptoms included affective responses, such as dysphoria, anxiety, panic, and psychotic response, as well as cases with mixed psychotic and affective features. The most common problem reported as psychotic response, as seen in [272]. The mechanisms behind ecstasy-associated psychiatric problems remain unclear but are likely the result of an interaction between pharmacology and individual susceptibility. The difficulty of assessing the frequency of these events is increased given that that pre-existing psychiatric problems occur in people who choose to use ecstasy [273] and findings of an association between use of ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after ecstasy use resolved after supportive care [216, 274]. Anxiety responses associated with MDMA administration reported in

controlled trials have resolved over time, usually either during the period of acute drug effect or with the waning of drug effects.

Previous reports have found an association between ecstasy use and increases in symptoms of depression or anxiety, (see for example [275, 276]). A meta-analysis of self-reported depressive symptoms detected an association between ecstasy use and scores on the Beck Depression Inventory (BDI), a popular self-report measure of depression symptoms [277]. However, the association was strongest in studies with small samples, and drug use variables were often incompletely reported and not verified through any methods save self-report in the studies analyzed. Many studies found that increases in self-reported anxiety or depression were more strongly related to polydrug use rather than to use of any one substance [278-281]. One found an equal or stronger association between regular use of cannabis, and not ecstasy, and anxiety, depression or other psychological problems [282].

7.5.3. Effects on Perception in Humans

Study participants receiving MDMA experienced slight changes in visual or auditory perception, including changes in the brightness of the room or colors, sounds seeming closer or farther away, and simple visual distortions [2, 3, 5, 6]. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA [8]. People maintained insight as to their experience, and there was little indication that MDMA produced any strong alterations to the sense of self or control over the experience [5, 7]. Healthy volunteers reporting unusual beliefs retained a degree of insight [5]. Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes [6]. The perceptual effects of MDMA appear to be the result of direct or indirect action on 5HT_{2A} receptors, as coadministration of the 5HT_{2A} antagonist ketanserin reduced reported perceptual alterations as well as eliminating slight elevations in body temperature after 1.5 mg/kg MDMA [175], while co-administration with the 5HT_{1A} antagonist pindolol did not [130].

7.5.4. Cognitive Effects in Humans

MDMA does not affect responses on tasks requiring attention and response to visual stimuli or visually presented words [8, 269], but interferes with performance on digit-symbol substitution, a measure of attention, psychomotor speed and visual memory [3]. A dose of 75 mg improved visual tracking speed but impaired estimating the position of a blocked (occluded) object in a study of acute effects on skills used in driving cars [262]. A recent series of studies conducted in the Netherlands that examined the effects of MDMA on skills needed for automobile driving reported transient and selective changes in verbal and visual attention and memory after 75 or 100 mg MDMA [283-286]. MDMA caused difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects. MDMA did not cause impairment in spotting scene changes and reduced weaving in a driving simulation. MDMA was associated with an excessively cautious response to the actions of another car in an assessment of actual driving [287]. MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [284]. The causes of these changes are unclear but may relate to changes in attention, salience of visual objects, and altered time perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug

methylphenidate (Ritalin) did not produce similar changes [283, 286, 287]. Administering a 5HT_{2A} receptor antagonist but not a 5HT_{1A} antagonist reduced impaired performance on a word learning and recall task after MDMA, suggesting that interference is due in part to direct or indirect activation of these receptors [132]. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

In the sponsor-supported study of MDMA-assisted psychotherapy in people with PTSD, Mithoefer and colleagues did not detect significant differences in cognitive function between participants who received two doses of MDMA and participants who received placebo [21]. These findings suggest that MDMA given within a clinical trial does not produce impaired cognition.

7.5.4.1. Long-term cognitive effects in ecstasy users

Many investigations have examined cognitive function in ecstasy users. Rogers and colleagues performed a meta-analysis on a large number of retrospective studies of ecstasy users and various cognitive functions. Given methodological flaws in this type of analysis, the investigators cautiously concluded that there may be a significant effect of ecstasy use on verbal memory, and a lesser effect on visual memory [40]. Two meta-analyses of memory in ecstasy users arrived at somewhat contradictory conclusions [288, 289]. Both detected an association between ecstasy use and impaired performance on at least some measures of memory. However, one reported that this association had a medium to large effect size with no effect of ecstasy dose [288], while the other reported that the association had a small to medium effect size with an ecstasy dose effect, and that polydrug use itself contributed to impaired cognitive function [289]. A meta-analysis comparing current ecstasy users and drug-using controls on visuospatial skills reported that current users performed less well on measures of visual recall, recognition and item production than controls [290], but found no significant relationship between lifetime ecstasy use and visuospatial task performance.

The only study attempting to address effects of ecstasy use on cognitive function in middle aged versus younger users and did not find a greater degree of impairment. Schilt and colleagues reported impaired verbal memory in people who began using ecstasy in their 30s compared with age-matched drug-naïve and polydrug using controls reporting some lifetime ecstasy use, but did not find a greater effect size for ecstasy use in this sample than in samples of younger ecstasy users, leading them to conclude that ecstasy use does not have a greater impact on cognitive function in older users [291].

In a prospective study comparing cognitive function in people before and up to 18 months after reported initiation of ecstasy use, Schilt and colleagues found an association between ecstasy use and performance on measures of verbal memory, but not attention or working memory [292]. All scores were within normal range; people who did not use ecstasy showed greater improvement in performance at the second time of assessment than people reporting some use. A second prospective study examined working memory in people reporting ecstasy use similar to subjects in Schilt's study with controls, and failed to find any significant differences in working memory and selective attention [293].

The nature and strength of the association between regular ecstasy use and impaired executive function remains inconclusive, with some reports finding impaired executive function in ecstasy users [18, 294, 295], and others finding no association [296], or finding executive function impairments only in male ecstasy users [297]. A meta-analysis comparing executive function in ecstasy users and non-ecstasy using controls found a significant effect of ecstasy use on one component of executive function (updating), no effect on another (shifting) and mixed results when looking at other components (response inhibition and access to long-term memory) [298]. Polydrug use likely contributes to findings of impaired executive function seen in ecstasy users [280, 299]. Current research has not settled the question.

Investigations of the interaction between genotype and regular ecstasy use have supported differential effects upon reward-based attention or visual or verbal memory [300-302]. Given the small samples and uneven numbers with different genotypes, any conclusions await further support.

The relationship between ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in ecstasy users and others failing to find any differences, as seen in [45, 303]. Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [304-306]. Two recent studies using the same measure of behavioral impulsivity in samples of heavy ecstasy users yet obtained different findings [304, 306]. It is possible that people who self-administer ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility, and studies published in the last two years suggest that polydrug use may be equally or more strongly related to impulsivity in ecstasy users [265, 307, 308]. The relationship between drug use, including ecstasy use, and impulsivity, is complex.

Not all studies report that ecstasy users fare worse on measures of cognitive function than controls. A number of recent reports detected little or no significant differences between ecstasy users and polydrug user controls in performance on tasks of cognitive function [293, 306, 309-313] though other studies continue to find consistent differences, particularly in verbal memory [252, 314-317]. Regular use of many substances, including alcohol, may affect cognitive function, with ecstasy being only one of those substances [318]. Several reports have found relationships between cognitive function and use of other drugs as well as or instead of ecstasy [301, 309, 311, 314, 319, 320].

7.5.5. Brain Activity In Humans

Brain imaging recorded during a task requiring keeping a target cue in mind, attention, and response inhibition also found changes in parietal activity when comparing performance under placebo or 75 mg MDMA [321]. MDMA increased activity in frontal areas and decreased activity in occipital sites as measured via fMRI [322]. Subjects given MDMA exhibited similar brain activity when reading or encoding a word list, suggesting that they were investing similar effort into both tasks. Ten ecstasy user participants receiving a minimum dose of two doses of 1-1.25 mg/kg or 2.25-2.5 mg/kg MDMA exhibited signal decreases in bilateral visual cortex, caudate, superior parietal, and dorsolateral frontal regions 10 to 21 days later, with increased rCBF measured in two participants at a later time point [323]. However, a comparison between

heavy ecstasy users and non-user controls failed to find differences in baseline rCBF [269], and a report assessing changes before and after initial use found increased rCBF in only one area of the prefrontal cortex [324], suggesting that the changes seen by Chang and colleagues are a transient effect. Electroencephalography (EEG) recorded two hours after MDMA administration showed the following changes in EEG activity: overall increase in beta activity, reduction in alpha activity, and specific decreases in alpha and delta in frontal areas and increased frontotemporal beta signal [325]. The authors reported these EEG patterns as being similar to those seen with serotonergic and noradrenergic drugs, as well as, to a lesser extent, with dopaminergic drugs.

7.5.5.1. *Changes in brain activity in ecstasy users*

Studies comparing brain activity in ecstasy users and non-ecstasy using controls reported some but not many differences in brain activity. These included greater brain activation in the occipital cortex, with concomitant methamphetamine use contributing to increased activation to a visual stimulus [326]. The same group of researchers detected less within-region coherence in the thalamus in ecstasy users who averaged 29 episodes of use when compared with non-ecstasy-using controls [327]. A prospective study comparing brain activity before and after use of ecstasy failed to detect differences in working memory, attention or brain activity [293], suggesting a relationship between repeated, regular use of ecstasy and other drugs and changes in brain activation.

Researchers using slightly different methods have reported differing results. These include finding no differences between ecstasy user and polydrug user control in SERT sites [328], modest reductions in estimated SERT sites in ecstasy users versus non-drug using or cannabis-using controls [329], and an association between decreased SERT sites and lifetime ecstasy use [330]. This study also reported finding slightly fewer 5HT_{2A} sites in both “ecstasy preferring” and “hallucinogen preferring” groups. Studies in very moderate ecstasy did not report an increase in this marker [324], and only one of three studies heavy users detected a change in 5HT_{2A} receptor density. [331-333]. A prospective study in moderate ecstasy users also failed to find any chemical markers of neuronal injury, and only found decreased cerebral blood volume in the dorsolateral frontal cortex [324, 334]. A re-examination of brain imaging using the less specific SERT marker Beta-CIT indicate an inverse relationship between age of first use of ecstasy and mid-number of midbrain serotonin sites without detecting any relationship between age of first use and frontal SERT sites [335].

7.6. Long Term Effects in Ecstasy Users

Spurred on by nonhuman animal studies that found that repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of ecstasy in humans [44-46, 336], and as described in the sections above. Early investigations possessed a number of methodological flaws, including retrospective design and poor matching of ecstasy users with appropriate controls [51, 83, 337]. Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactives, including alcohol [294, 296, 338, 339]. Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points [340-342]. Most studies suggested that heavy but not moderate ecstasy users had impaired verbal memory

and lower numbers of estimated SERT sites, with heavy use often defined as being at or greater than 50 times or tablets. Taken together, there is some risk of long-term effects with respect to number of estimated SERT sites in specific brain areas and performance on measures of memory. However, findings of changes in serotonin receptors or cognitive function after repeated ecstasy use are complicated by the possible impact of polydrug use and other potential pre-existing factors in retrospective reports, and the findings are not readily transferrable to use of MDMA in a therapeutic or research context.

7.7. Adverse Events Outside of Sponsor-Supported Studies

MDMA was administered to thousands of people prior to scheduling and many continue to use ecstasy around the world in various non-medical settings [14-18]. While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use [19, 20]. These include hyperthermia, including hyperthermia arising from "serotonin syndrome," psychiatric problems, hepatotoxicity, including acute liver failure arising from hyperthermia and liver disease and hyponatremia [19, 40, 213, 216, 343]. Unexpected drug-related serious adverse events have not occurred in any of the human MDMA research studies so far. Set and setting may play a role in the development of some ecstasy-related adverse events, such as rigorous exercise, lack of attention to somatic cues, and too little or too much hydration resulting in hyperthermia or hyponatremia [212]. Hall and Henry address medical emergencies related to ecstasy use [344]. While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only [216, 274, 345]. A very extensive and systematic review reached similar conclusions concerning the frequency and nature of emergency department admissions, though also noting that owing to complexities of nonmedical and recreational use, the researchers found it hard to establish a lethal dose [40]. As is the case with fatalities, medical emergencies after ecstasy use are more likely to occur in men [216].

Other infrequently reported serious adverse events reported in ecstasy users and reported in case reports or series, include cardiac problems (as arrhythmias) [230, 231, 346], cerebrovascular events (such as cerebral hemorrhage or infarction [222, 223, 347], dermatological (dermatitis, guttate rash [348]), dental (tooth erosion, likely from frequent bruxism) [349-351], hematological, including aplastic anemia [352, 353], respiratory (pneumomediastinum and subcutaneous emphysema) [354-357], ophthalmic (sixth nerve palsy, chorioretinopathy (a condition associated with sympathomimetic use), corneal epitheliopathy (resulting from corneal exposure produced by consuming CNS depressants) [358, 359], urological (as urinary retention) events [360-362].

A large number of the case reports published between 2008 and 2012 described conditions and emergencies that have previously appeared in the literature. They included 12 cardiac events [363-368], three hepatic events (including a cardiac and hepatic event) [369-371], five cerebrovascular events [347, 372, 373], four psychiatric events [374-376], three instances of hyponatremia [377-379], three cases of rhabdomyolysis and/or hyperthermia [380-382], three neurological cases [383-385], and single reports of facial rash (eruption) [386], urinary retention

[360], rhabdomyolysis of masseter muscle [387], aplastic anemia [388] and fatal allergic reaction [389]. The cases reported 13 deaths [365, 367-369, 377, 379, 382, 388, 389] (7 after cardiac events, two after hyponatremia, one after liver disease, one after hyperthermia and rhabdomyolysis, one after aplastic anemia and one after apparent allergic reaction. The death after aplastic anemia occurred from complications of treatment 17 months after the first admission from complications arising from immunosuppressant therapy given after bone marrow transplant. Detectable levels of MDMA in blood or urine are reported in seven of the 31 case reports, and range from 50 ng/mL (reported as less than 0.05 mg/L) in the allergic reaction [389] to 1500 ng/mL (reported as 1.5 mg/L) in a fatal case of hyperthermia and rhabdomyolysis [382]. Only one of three neurological events provided information on MDMA levels, 0.83 ng/mL detected in the hair of a girl who developed encephalopathy [384], with a course and symptoms that are similar to those seen after central nervous system herpes infection. It is more difficult to associate event with MDMA when the compound is not detected or when detection is for amphetamines in general. Some events, such as valvular heart disease, acute hepatitis with gallbladder inflammation, or urinary retention self-reported daily use for months to years prior to the event, The case of valvular heart disease occurred in an individual who indicated that he had taken ecstasy daily for approximately 16 years, from age 17 to 33 years old.

The report of possible anaphylactic shock occurred in a 13-year old girl who had at least one previous exposure to ecstasy. Her friends reported that she experienced swelling lips after the first exposure. After approximately 1.5 tablets, the girl experienced nausea and vomited, and later had difficulty breathing. On admission she was hypothermic and hypotensive. None of the other individuals consuming tablets from the same batch underwent similar experiences. Autopsy found a massive brain edema as well as laryngeal edema and lung congestion. Chemical analyses ruled out hyponatremia. The reaction may have been to MDMA or to an adulterant in the tablet.

None of these events have occurred within the context of Phase 1 or Phase 2 human studies with MDMA.

7.8. Related Expected Adverse Events From Studies in Healthy Volunteers

Common expected adverse events of MDMA reported in Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [3-6]. Some reports indicated decreased rather than increased alertness [3]. Other common adverse events reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall [8], and unusual thoughts or ideas [5]. Other less commonly reported events include paresthesias (unusual body sensations) such as tingling or feeling hot or cold. MDMA produces anxiety in healthy volunteers [5, 6, 8]. These effects are transient and recede with the waning of drug effects. One study found that women were more likely than men to experience the most commonly reported adverse effects of MDMA, though men were more likely than women to experience the specific adverse events of nausea and sweating [6]. Adverse effects in women undergoing a single session of MDMA-assisted psychotherapy for PTSD were mild and appear to be similar to those in healthy controls [24].

Table 1: Acute Adverse events of MDMA Compiled from Literature of Human Trials with MDMA.

Data Source	Prevalence Across Literature		Downing 1986	Greer & Tolbert 1986	Vollenweider et al. 1998	Gamma et al. 2000	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Harris et. al. 2002	Bouso et. al. 2008	Hysek 2011	Hysek et. al. 2012a	Hysek et. al. 2012b
	Placebo	MDMA												
N:	10-57	6-174	10	29	13	16	14	14	16	8	4	16	16	16
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	75-150, 200 mg	1.7 mg/kg	1.7 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	0.5, 1.5 mg/kg	50, 75 mg	125 mg	125 mg	125 mg
Time post-drug	-	-	2-5 hr	N/A	0-3 hr	N/A	N/A	N/A	N/A	0-24 hr	24 hr	0, 3, 24 hr	3, 24 hr	3, 24 hr
Lack of Appetite	2%	68%	100%	97%	62%	63%	50%	50%	50%	63%	N/A	75%	56%	69%
Dry Mouth	N/A	64%	N/A	N/A	N/A	N/A	57%	57%	N/A	88%	N/A	N/A	63%	N/A
Jaw Clenching	0%	60%	60%	76%	62%	64%	57%	71%	44%	N/A	N/A	N/A	44%	50%
Concentration Issues	16%	53%	30%	3%	62%	50%	71%	50%	63%	88%	25%	75%	N/A	N/A
Thirst	4%	48%	N/A	N/A	38%	50%	57%	57%	38%	N/A	N/A	N/A	N/A	63%
Restlessness	0%	46%	N/A	N/A	31%	N/A	50%	29%	44%	N/A	N/A	50%	44%	69%
Restless Legs	0%	45%	N/A	N/A	46%	N/A	N/A	N/A	44%	N/A	N/A	N/A	N/A	N/A
Impaired Balance/Gait	0%	44%	70%	10%	62%	N/A	71%	43%	50%	N/A	N/A	N/A	N/A	N/A
Dizziness	2%	43%	N/A	N/A	31%	N/A	57%	21%	50%	75%	N/A	38%	N/A	N/A
Feeling Cold	4%	43%	N/A	N/A	23%	N/A	43%	N/A	N/A	75%	N/A	N/A	N/A	N/A

Perspiration	0%	40%	N/A	N/A	0%	50%	36%	N/A	N/A	50%	N/A	N/A	50%	50%
Sensitivity to Cold	7%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Private Worries	23%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Heavy Legs	0%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Palpitations	0%	37%	N/A	N/A	31%	38%	43%	21%	N/A	63%	N/A	N/A	N/A	N/A
Drowsiness	50%	26%	N/A	14%	N/A	N/A	43%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Data Source	Prevalence Across Literature		Downing 1986	Greer & Tolbert 1986	Vollenweider et al. 1998	Gamma et al. 2000	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Harris et al. 2002	Bouso et al. 2008	Hysek 2011	Hysek et al. 2012a	Hysek et al. 2012b
	Placebo	MDMA												
N:	10-57	6-174	10	29	13	16	14	14	16	8	4	16	16	16
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	75-150, 200 mg	1.7 mg/kg	1.7 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	0.5, 1.5 mg/kg	50, 75 mg	125 mg	125 mg	125 mg
Nystagmus	N/A	23%	80%	3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hot Flashes	0%	23%	N/A	N/A	23%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea	4%	21%	10%	24%	8%	N/A	36%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trismus	N/A	21%	N/A	3%	N/A	N/A	57%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anxiety	0%	19%	N/A	17%	N/A	N/A	14%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Inner Tension	0%	18%	N/A	3%	23%	N/A	43%	14%	19%	N/A	50%	N/A	N/A	N/A

Insomnia	0%	17%	0%	N/A	31%	N/A								
Weakness	0%	16%	N/A	3%	23%	N/A	36%	N/A						
Urge to Urinate	8%	15%	N/A	N/A	15%	N/A								
Tremor	0%	22%	N/A	3%	31%	N/A	21%	14%	N/A	N/A	N/A	56%	N/A	N/A
Muscle Ache/ Tension	N/A	20%	N/A	21%	0%	N/A	N/A	N/A	N/A	50%	N/A	N/A	N/A	N/A
Forgetfulness	0%	15%	N/A	3%	38%	N/A	N/A	N/A	N/A	N/A	25%	N/A	N/A	N/A
Fatigue	26%	15%	N/A	7%	8%	N/A	N/A	29%	N/A	N/A	50%	N/A	N/A	N/A
Parasthesias	0%	22%	N/A	3%	31%	N/A	N/A	N/A	N/A	75%	N/A	N/A	N/A	N/A
Lack of Energy	14%	14%	N/A	3%	N/A	N/A	29%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Brooding	0%	12%	N/A	3%	N/A	N/A	29%	N/A						
Fainting	N/A	3%	N/A	3%	N/A									
Blurred Vision	N/A	3%	N/A	3%	N/A									
Lip Swelling	N/A	2%	N/A	3%	0%	N/A								
Headaches	N/A	11%	0%	3%	N/A	N/A	N/A	0%	N/A	50%	50%	N/A	N/A	N/A

8. Safety and Efficacy in Humans

In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible [390, 391]. The first double blind, placebo controlled, ascending dose U.S. Phase 1 study sanctioned by the FDA and supported by the Sponsor was conducted in 1994 [13, 202, 323]. In this study, MDMA was found to be generally tolerable in a clinical setting. These results lead to the first Phase 2 safety and efficacy study of low doses of MDMA-assisted psychotherapy in Spain on a small sample of women with chronic PTSD [24]. The study was originally approved for 29 subjects, but media and political pressure caused discontinuation of the study after only 6 subjects had been treated. The small sample size precluded statistical analysis for efficacy, yet the safety profile in the PTSD subject sample appeared promising as neither 50 nor 75 mg MDMA were found to increase psychopathological symptoms in this patient population. In July 2010, the Sponsor completed the first U.S. Phase 2 pilot study investigating the safety and efficacy of MDMA-assisted psychotherapy for patients with chronic treatment-resistant PTSD, protocol MP-1 [266]. Analysis of the results from this small pilot study from 21 subjects randomized to 125mg MDMA (N=13) or inactive placebo (N=8) suggest that MDMA-assisted psychotherapy can significantly decrease PTSD symptoms compared to placebo-assisted psychotherapy and appears to be safe when administered in a controlled therapeutic setting [266]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [22]. The Sponsor completed a second study in Switzerland, MP-2, with a randomized, active placebo controlled, double blind design. In this study, 12 subjects were randomized to receive 25mg or 125mg MDMA during three psychotherapy sessions (Oehen 2012). Results suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [23]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. Additional phase studies are currently underway.

8.1. Safety of MDMA-assisted psychotherapy for PTSD

MP-1 enrolled 22 adult participants with PTSD with symptoms that failed to respond to at least one course of psychotherapy and at least one course of pharmacotherapy. An additional participant, a male veteran who refused prior treatment, was also enrolled after approval of an amendment by the FDA. The study enrolled eight women and five men, all were European-American, average age 40.6 years. Subjects enrolled had no history of major medical conditions, psychotic disorders, dissociative identity disorder, or personality disorders. Safety data obtained from this study included: scores from tests of cognitive function performed before and after study participation, vital signs and a measure of psychological distress during experimental sessions, expected adverse events for three experimental sessions, and adverse events that occurred during the study.

Two subjects (1 woman, 1 man) withdrew from the study after a single experimental session. The male subject withdrew from the study due to financial constraints on travel reimbursements, and the female subject withdrew from the study after experiencing a relapse of depression that required medication occurring 42 days after MDMA administration. Prior to relapse, the same subject had been hospitalized for benzodiazepine withdrawal while tapering medication. This subject reported reduction in PTSD symptoms even though the depression required medication.

There were no deaths during this study and no drug-related serious adverse events. Two unrelated, non-life threatening, serious adverse events occurred during the study. The first was a fractured clavicle from a vehicular accident in which the subject was a passenger, resulting in temporary disability and resolving with complete recovery. The second was an episode of vasovagal syncope, occurring 41 days after the second administration of MDMA and resolving with recovery to baseline. This subject had a medical history of fainting spells, and follow-up reports filed 15 months after the event indicate that it was not recurrent.

MP-2 enrolled fourteen adult participants (11 women, three men, average age 41.8 years) with PTSD with symptoms that failed to respond to at least one course of psychotherapy or pharmacotherapy. Most were of European ethnicity, but one woman was African and one man was Middle Eastern. Subjects enrolled had no psychotic disorders, dissociative identity disorder, or personality disorders. One subject had a previous history of breast cancer, but had been in remission for over 10 years and was not symptomatic at screening. Safety data obtained from this study included: vital signs and a measure of psychological distress during experimental sessions, expected adverse events for three to five experimental sessions, and adverse events that occurred during the study.

There were no serious drug-related adverse events in the MP-2 study. There was one death during the post-treatment follow-up period of the study from the metastasis of a brain tumor. The subject's death was the result of a previous condition and was determined to be unrelated to the study drug. There was one non-fatal, drug-unrelated serious adverse event that occurred during the study. A subject allegedly was hospitalized two weeks prior to administration of the study drug after exhibiting suicidal behavior following a conflict with her ex-husband. The subject was discharged from the hospital the next day, and did not exhibit suicidal or violent tendencies or any mental state requiring hospitalization prior to or after this event.

Two subjects (1 man, 1 woman) withdrew from the study as a result of adverse events occurring during the first experimental session. The first participant, who had received 125 mg MDMA experienced severe exacerbation of anxiety during the first experimental session. This event interrupted the experimental session and was treated with additional support during therapy until the drug effects dissipated. The anxiety was a part of PTSD symptoms present at baseline and its exacerbation was deemed to be probably related to drug administration. The second participant, who received 25 + 12.5 mg MDMA, experienced severe anxiety in reaction to being confronted with traumatic memories during the first experimental session, with the anxiety deemed possibly related to drug administration. The anxiety was treated with additional support in the form of therapy after the drug effects dissipated.

8.1.1. Vital signs

As expected, vital signs during experimental sessions indicate that MDMA elevates blood pressure and heart rate, but elevations return to baseline or near-baseline seven to eight hours after drug administration. Repeated measures analyses of variance using MP-1 average pre-drug, peak and final post-drug measurements of SBP, DBP, heart rate and body temperature after placebo versus MDMA detected significant interactions between measurement and dose for SBP ($F(1, 130) = 12.24, p < 0.000$) and heart rate ($F(2, 130) = 13.01, p < 0.000$), and not for DBP

or body temperature. As expected, MDMA significantly elevated SBP and HR when compared with inactive placebo. By the end of the experimental session, SBP after MDM was 33 mm Hg lower than peak values, and HR was 20.47 BPM lower, indicating the return to pre-drug or near pre-drug levels. Analyses of MP-2 Stage 1 cardiovascular and body temperature measures found a main effect of condition for peak and post-drug average SBP, but one-way ANOVA failed to detect any main effect of condition for DBP, heart rate, or body temperature. Because MP-2 did not collect final measurement, the degree to which peak values returned to normal post-drug cannot be assessed in this sample. The addition of a supplemental dose of MDMA did not increase peak values for vital signs measured during experimental sessions.

Table 2a. : Pre-Drug, Peak, and Final SBP and DBP Values Measured During MP-1

Dose administered within session		SBP: Pre-Drug	SBP: Peak	SBP: Final	DBP: Pre-drug	DBP: Peak	DBP: Final
0 mg 16 sessions 8 subjects	Mean (SD)	112.3 (10.8)	127.7 (15.3)	108.8 (13.1)	73.5 (8.4)	84.6 (10.4)	69.4 (10.4)
	Peak	136.5	157.0	133.0	87.5	102.0	89.0
125 mg 25 sessions 14 subjects	Mean (SD)	111.9 (11.7)	144.7 (18.3)	112.5 (9.3)	72.2 (8.8)	88.6 (11.0)	71.1 (6.7)
	Peak	145.5	189.0	126.0	93.5	113.0	87.0
187.5 mg 26 sessions 10 subjects	Mean (SD)	122.6 (9.9)	151.0 (15.9)	116.7 (10.8)	79.7 (6.4)	93.7 (7.8)	76.2 (6.8)
	Peak	143.5	181.0	141.0	94.0	103.0	88.0

Table 2b. Pre-Drug, Peak, and Final HR and BT (C°) Values Measured During MP-1

Dose administered within session		HR: Pre-drug	HR: Peak	HR: Final	BT: Pre-drug	BT: Peak	BT: Final
0 mg 16 sessions 8 subjects	Mean (SD)	68.2 (10.2)	82.5 (9.6)	71.4 (8.4)	97.5 (0.9)	98.4 (0.6)	97.8 (0.6)
	Peak	91.0	107.0	89.0	99.0	99.6	98.6
125 mg 25 sessions 14 subjects	Mean (SD)	73.3 (11.5)	102.8 (15.0)	82.7 (10.0)	97.6 (0.7)	98.9 (0.5)	98.0 (0.7)
	Peak	99.5	135.0	104.0	99.6	100.0	99.4
187.5 mg 26 sessions 10 subjects	Mean (SD)	74.2 (13.0)	103.7 (19.1)	82.9 (15.7)	97.4 (0.9)	98.6 (0.9)	98.0 (0.7)
	Peak	95.0	140.0	119.0	99.1	100.1	99.3

Table 2c. Pre-Drug, Peak, and Final SBP and DBP Values Measured During MP-2

Dose administered within session		SBP: Pre-drug	SBP: Peak	SBP: Final	DBP: Pre-drug	DBP: Peak	DBP: Final
37.5 mg 13 sessions 5 subjects	Mean (SD)	119.5 (4.6)	131.3 (7.3)	115.9 (7.0)	76.3 (4.0)	84.8 (4.8)	74.5 (3.8)
	Peak	126	144	127	84	92	81
125 mg 3 sessions 2 subjects	Mean (SD)	142.0 (12.3)	181.3 (15.3)	155.3 (11.7)	90.3 (6.6)	110.3 (10.1)	95.7 (7.8)
	Peak	151	193	164	98	121	102
187.5 mg 36 sessions 12 subjects	Mean (SD)	129.9 (16.1)	154.4 (19.4)	135.4 (16.3)	80.0 (8.8)	92.8 (10.2)	81.4 (9.3)
	Peak	177	200	168	101	114	100
212.5 mg 2 sessions 2 subjects	Mean (SD)	132.0 (17.0)	170.5 (20.5)	148.5 (17.7)	83.0 (9.9)	103.5 (6.4)	87.5 (12.0)
	Peak	144	185	161	90	108	96
225 mg 2 sessions 2 subjects	Mean (SD)	124.0 (31.1)	142.5 (20.5)	133.5 (23.3)	74.5 (20.5)	87.0 (12.7)	76.5 (13.4)
	Peak	146	157	150	89	96	86

Table 2d. Pre-Drug, Peak, and Final HR and BT (C°) Values Measured During MP-2

Dose administered within session		HR: Pre-Drug	HR: Peak	HR: Final	BT: Pre-Drug	BT: Peak	BT: Final
37.5 mg 13 sessions 5 subjects	Mean (SD)	76.1 (9.8)	90.8 (18.1)	76.0 (10.9)	36.6 (0.2)	37.6 (0.5)	37.2 (0.4)
	Peak	94	124	90	37.1	38.5	38.00
125 mg 3 sessions 2 subjects	Mean (SD)	79.3 (2.9)	88.7 (15.3)	78.3 (10.6)	36.7 (0.5)	37.3 (0.2)	37.1 (0.2)
	Peak	81	98	88	37.1	37.5	37.30
187.5 mg 36 sessions 12 subjects	Mean (SD)	80.8 (10.4)	105.3 (15.3)	89.0 (12.2)	36.5 (0.4)	37.6 (0.6)	37.2 (0.4)
	Peak	109	144	116	37.6	38.7	38.40
212.5 mg 2 sessions 2 subjects	Mean (SD)	76.0 (1.4)	107.5 (0.7)	96.0 (4.2)	36.7 (0.1)	37.6 (0.4)	37.3 (0.6)
	Peak	77	108	99	36.7	37.9	37.68
225 mg 2 sessions 2 subjects	Mean (SD)	82.5 (19.1)	104.0 (29.7)	93.0 (26.9)	36.7 (0.1)	37.9 (0.5)	37.4 (0.2)
	Peak	96	125	112	36.7	38.2	37.54

8.1.2. Psychological Effects

Psychological distress of participants was assessed periodically throughout experimental sessions in both studies with the single-item, seven-point Subjective Units of Distress (SUD). In both studies, there was no significant difference in SUD scores between MDMA and placebo conditions. In MP-1, an analysis comparing pre-drug average, peak and final post-drug SUD ratings made by participants receiving MDMA versus placebo across Stage 1 and Stage 2 failed to find statistically significant differences in SUD scores. The interaction between dose given (placebo, MDMA) and pre-drug, peak and post-drug SUD was $F(2, 130) = 1.84, p = 0.164$, and there was no main effect of dose (MDMA or placebo), $F(1, 65) = 1.16, p > 0.05 (p = 0.29)$. MDMA did not elevate psychological distress in participants with PTSD to a greater degree than for participants given placebo.

Table 3: Table : Subjective Units of Distress Measured in MP-1

	Dose given	Mean	Std. Dev.	N
Pre-drug	Placebo	3.72	1.97	16
	MDMA	3.05	1.81	51
	Total	3.21	1.85	67
Peak	Placebo	5.19	1.56	16
	MDMA	4.55	1.88	51
	Total	4.70	1.82	67
Final	Placebo	1.69	0.60	16
	MDMA	1.82	1.01	51
	Total	1.79	0.93	67

8.1.3. Expected Adverse Events

Spontaneously reported expected adverse events were collected during the day of each experimental session and for seven days after each session. The list of commonly expected adverse events was derived from the literature (see Table 1). Severity of spontaneously reported reactions were collected on the day of each experimental session and for up to seven days after the session through telephone or face to face contact, with severity rated on a three-point scale. The investigators collected information on duration of reaction for any reaction reported on the day of an experimental session. Anxiety, fatigue, tight jaw, headache, insomnia and lack of appetite were commonly listed during experimental sessions. Anxiety and fatigue were reported at near equal levels by participants given inactive or active placebo and MDMA, while reports of tight jaw were far more frequent in people who received a full dose of MDMA than people who received placebo. Feeling cold, while reported in only 38% of 35 people given a full dose of MDMA, was reported markedly less often in people given inactive or active placebo (19% and 15% respectively). Other less frequently reported reactions that appeared to occur more often in people given at least 125 mg MDMA included impaired gait or balance, impaired concentration and restlessness.

Table 4: Expected Adverse Events Reported for Studies MP-1 and MP-2

Study	MP1		MP2			Total			
	0	125	25	125	150	0	25	125	150
MDMA Initial Dose (mg)	0	125	25	125	150	0	25	125	150
Number of Subjects	8	22	5	13	3	8	5	35	3
Number of Sessions	16	51	13	39	4	16	13	90	4
Psychiatric									
Anxiety	14(88%)	48(94%)	4(31%)	20(51%)	1(25%)	14(88%)	4(31%)	67(74%)	1(25%)
Low mood	8(50%)	16(31%)	7(54%)	20(51%)	1(25%)	8(50%)	7(54%)	35(39%)	1(25%)
Insomnia	12(75%)	32(63%)	9(69%)	24(62%)	3(75%)	12(75%)	9(69%)	55(61%)	3(75%)
Restlessness	2(13%)	10(20%)	0	17(44%)	1(25%)	2(13%)	0	24(27%)	1(25%)
Disturbance in attention	2(13%)	12(24%)	0	13(33%)	0	2(13%)	0	25(28%)	0
Drowsiness	3(19%)	4(8%)	1(8%)	3(8%)	0	3(19%)	1(8%)	7(8%)	0
Private Worries	2(13%)	6(12%)	3(23%)	10(26%)	0	2(13%)	3(23%)	15(17%)	0
Nervous System									
Headache	10(63%)	29(57%)	5(38%)	15(38%)	1(25%)	10(63%)	5(38%)	46(51%)	1(25%)
Dizziness	2(13%)	21(41%)	4(31%)	12(31%)	3(75%)	2(13%)	4(31%)	33(37%)	3(75%)
Gastrointestinal									
Nausea	4(25%)	25(49%)	3(23%)	11(28%)	1(25%)	4(25%)	3(23%)	35(39%)	1(25%)
General									
Fatigue	14(88%)	44(86%)	7(54%)	27(69%)	3(75%)	14(88%)	7(54%)	69(77%)	3(75%)
Dry Mouth	0	13(25%)	0	7(18%)	1(25%)	0	0	20(22%)	1(25%)
Heavy Legs	0	2(4%)	1(8%)	1(3%)	1(25%)	0	1(8%)	3(3%)	1(25%)
Impaired Balance	1(6%)	15(29%)	3(23%)	16(41%)	2(50%)	1(6%)	3(23%)	29(32%)	2(50%)
Irritability	8(50%)	18(35%)	1(8%)	9(23%)	0	8(50%)	1(8%)	26(29%)	0
Needs More Sleep	2(13%)	11(22%)	2(15%)	4(10%)	2(50%)	2(13%)	2(15%)	15(17%)	2(50%)
Nystagmus	0	8(16%)	0	4(10%)	1(25%)	0	0	12(13%)	1(25%)
Parasthesia	0	4(8%)	0	2(5%)	1(25%)	0	0	6(7%)	1(25%)
Perspiration	2(13%)	13(25%)	0	6(15%)	1(25%)	2(13%)	0	18(20%)	1(25%)
Feeling Cold	3(19%)	24(47%)	2(15%)	10(26%)	0	3(19%)	2(15%)	34(38%)	0
Thirstiness	1(6%)	7(14%)	0	10(26%)	0	1(6%)	0	17(19%)	0
Feeling Weak	1(6%)	10(20%)	0	5(13%)	1(25%)	1(6%)	0	15(17%)	1(25%)
Musculoskeletal & Connective Tissue									
Muscle tension	3(19%)	42(82%)	1(8%)	16(41%)	1(25%)	3(19%)	1(8%)	56(62%)	1(25%)
Metabolism and Nutrition									
Lack of appetite	1(6%)	33(65%)	6(46%)	17(44%)	1(25%)	1(6%)	6(46%)	43(48%)	1(25%)

8.1.4. Unexpected Adverse Events

One hundred eighty-six adverse events were reported as occurring during studies MP-1 and MP-2. A hundred and twenty-five unexpected adverse events were reported during study MP-1 and 61 unexpected AEs were reported during study MP2. This includes events that occurred prior to administration of medication but after study enrollment. The majority of these events were deemed unrelated (44% of 186 reported, or 81 events) and 34% (63%) were deemed to be possibly related. Twenty-three per cent (42 of 186) were rated as probably related. Since relationship was assessed when the investigator was blinded during Study MP1, some unexpected AEs that were deemed related to the study drug occurred in people given inactive placebo. The greatest number of AEs was reported in 29 of 35 people receiving a full dose (125 mg, with or without supplemental dose) (139 of 186). Fourteen AEs occurred in three of five people given 25 mg MDMA and 33 occurred in all eight people given placebo. Information on the number of unexpected AEs, relatedness, severity and AE outcome can be found in Tables 5a to 5c, below.

Table 5a. Presence and Frequency of Unexpected AEs in Studies MP-1 and MP-2

	Placebo	25 mg	125 mg	Total
Number of Subjects given dose	8	5 [#]	35 ^{#**}	
Any AEs	33	14	139	186
% of Unexpected AEs	18%	8%	75%	100%
At Least Possibly Related AEs	24 [*]	4	77	105
% of all AEs within Dose	73%	29%	55%	100%
% of all Unexpected AEs	13%	2%	41%	56%
Serious AEs	0	0	4	4
% of all AEs within dose	0%	0%	3%	2%
% of all Unexpected AEs	0%	0%	2%	2%
At Least Possibly Related SAEs	0	0	0	0

*Relatedness rated while blinded

#Subjects withdrew prior to all three sessions, including 1 at 25 mg and three at 125 mg.

** Includes 24 at Stage 1 and 11 placebo or active placebo subjects at Stage 2

Combined table for MP1 and MP2

The intensity of most unexpected adverse events across both studies was rated as moderate. This was true for events in participants who received placebo and 125 mg MDMA. The equal percentage of moderate and severe AEs in participants given active placebo likely reflects the small number of events. Most subjects reported full recovery from these AEs, with 91% of AEs across placebo, 25 and 125 mg MDMA dose.

Table 5b. Severity of unexpected AEs from studies MP1 and MP2 listed by dose

AE Severity	Placebo	%/all Placebo AEs	25 mg MDMA	%/all 25 mg MDMA AEs	125 mg MDMA	%/all 125 mg MDMA AEs	Total	%/all AEs
Mild	5	15%	4	29%	43	31%	52	28%
Moderate	25	76%	5	36%	87	63%	117	63%
Severe	3	9%	5	36%	9	06%	17	9%
Total	33		14		139		186	

Table 5c. All Studies Cumulative Severe Adverse Events
(Based on data received from the sites)

Study	Dose	Subject Number	Adverse Event Diagnosis	Date Last MDMA Admin.	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-1	Placebo	0204	Re-experiencing episode	27-Aug-04	28-Aug-04	29-Aug-04	N	Single/ Intermittent	None	Other	Phone contact	Full recovery/ return to baseline	Possibly related
MP-1	Before dosing	0208	Agoraphobia	none	4-Apr-05	9-May-05	N	Continuous	Delayed experimental session	Hospitalization	None	Full recovery/ return to baseline	Not related
MP-1	125mg MDMA	0208	Relapse of major depression	17-Jun-05	29-Jul-05	Ongoing at time of discontinuation	N	Continuous	Discontinued experimental session	Prescription med	Per her doctor	Persists, diminishing	Not related
MP-1	Before dosing	0208	Benzodiazepine withdrawal	none	4-Apr-05	9-May-05	N	Continuous	Delayed experimental session	Hospitalization	None	Full recovery/ return to baseline	Not related
MP-1	125mg MDMA	0209	Sinusitis	22-Jul-05	12-Sep-05	22-Sep-05	N	Single/ Intermittent	None	Prescription med	None	Full recovery/ return to baseline	Not related
MP-1	Placebo	0212	Musculoskeletal chest pain	10-Mar-06	10-Mar-06	10-Mar-06	N	Single/ Intermittent	None	None	None	Full recovery/ return to baseline	Probably related

Unexpected adverse events across both studies were distributed across 19 of the 26 highest-level groups of MedDRA (System Organ Classes, or SOCs), and one that was not placed within any SOC (being the passenger in an automobile accident without reported injury). Most AEs fell under Psychiatric Disorders or General Disorders. From 24 to 43% all AEs fell within the Psychiatric Disorders SOC and included increased anxiety, panic attack, derealization and insomnia. AEs listed under general disorders included fatigue, feeling hot or cold, or body tension. Amount of psychiatric complaints were relatively equal throughout all conditions. It is interesting that increased reports of pain or tightness appeared with relatively greater frequency in people given placebo (30% of people given placebo versus 13% of people given full-dose MDMA; none in people given 25 mg MDMA).

Table 6a. Unexpected AEs by MedDRA System Organ Class listed by dose

MDMA Dose	0 mg			25 mg			125 mg			Total	
	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	SOC/ AEs
No AE (N/subjects)	0			2	14%	25%	6	4%	75%	8	4%
Cardiac disorders	0			0			2	1%	100%	2	1%
Ear and Labyrinth Disorders	0			1	7%	100%	0			1	1%
Eye disorder	0			0			4	3%	100%	4	2%
Gastrointestinal Disorders	2	6%	10%	0			18	13%	90%	20	11%
General Disorders and Administration Site Conditions	4	12%	14%	4	29%	14%	21	15%	72%	29	16%
Infections and Infestations	3	9%	23%	0			10	7%	77%	13	7%
Injury, Poisonings and Procedural Complications	0			0			1	1%	100%	1	1%
Investigations	0			0			2	1%	100%	2	1%
Metabolism and Nutrition Disorders	0			0			4	3%	100%	4	2%
Musculoskeletal and Connective Tissue Disorders	10	30%	36%	0			18	13%	64%	28	15%
Neoplasms: Benign, Malignant and Unspecified	0			0			1	1%	100%	1	1%

MAPS

Investigator's Brochure
 MDMA

MDMA Dose	0 mg			25 mg			125 mg			Total	
	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	SOC/ AEs
Nervous System Disorders	2	6%	13%	2	14%	13%	12	9%	75%	16	9%
Psychiatric Disorders	8	24%	16%	6	43%	12%	35	25%	71%	49	26%
Renal and urinary disorders	0			0			2			2	1%
Reproductive system and breast disorders	0			0			1	1	100%	1	1%
Respiratory, Thoracic, and Mediastinal Disorders	1	3%	14%	1	7%	14%	5	4%	71%	7	4%
Skin and Subcutaneous Tissue Disorders	2	6%	67%	0			1	1%	33%	3	2%
Surgical and medical procedures	0			0			1	1	100%	1	1%
Vascular Disorders	0			0			1	1	100%	1	1%
Not in established SOC*	1	3%	100%	0			0			1	1%
Total of all AEs	33			14			139			186	

Full dose includes full dose administered in Stage 1 and Stage 2. A count of “No AEs” could occur in one or both stages.

Seven severe unexpected AEs rated as either possibly or probably related to the study drug occurred during Study MP-1 and Study MP-2. Four of seven events represented a psychiatric complaint or experience, such as a panic attack or an episode of re-experiencing. Full recovery followed all seven events. Upon unblinding it transpired that two of these events had occurred in subjects given inactive placebo; an episode of re-experiencing and musculoskeletal chest pain. The other events were a panic attack after 125 and 62.5 mg in Study MP1, distress after confronting traumatic memories after 25 mg, headache after 25 mg, anxiety and increase in PTSD symptoms after 125 mg and a panic attack after 125 mg. Onset of these events ranged from the day of an experimental session in four cases to seven days after an experimental session in one case. Two of the events from Study MP-2 led to withdrawal from the study for one participant in the active placebo condition and one in the full dose condition. More details about these events can be seen in Table 5c.

Table 6b. Cumulative Frequency of Severe Adverse Events by Relatedness for Studies MP-1 and MP-2

Adverse Event	MP-1		MP-2		Total	
	PR	NR	PR	NR	PR*	NR*
Number of Subjects	23		14		37**	
Number of Experimental Sessions	67		52		119	
Relatedness	PR	NR	PR	NR	PR*	NR*
Psychiatric						
Re-experiencing episode	1				1(2%)	0
Panic Attack	1		1		2(4%)	0
Relapse of major depression		1			0	1(2%)
Anxiety, distress			2		2(4%)	0
Insomnia				2	0	2(4%)
Agoraphobia		1			0	1(2%)
Nervous System						
Headache			1		1(2%)	0
Sciatica		1			0	1(2%)
Gastrointestinal						
Abdominal Cramps/Pain				1	0	1(2%)
General						
Benzodiazepine withdrawal		1			0	1(2%)
Body Pain				1	0	1(2%)
Musculoskeletal & Connective Tissue						
Musculoskeletal chest pain	1				1(2%)	0
Infections and Infestations						
Sinusitis		1			0	1(2%)
Neoplasms						
Brain metastasis				1	0	1(2%)

* Note: PR = Possibly or Probably Related to drug, NR = Not Related to drug, in the opinion of the investigator prior to breaking blind.

** Note: Percentages were calculated based on number of subjects experiencing the AE. Each subject receives between 2 and 6 experimental sessions, depending on the study protocol and their condition assignment

** Based on final data analyzed from the sponsor database listings for completed studies, and preliminary data for ongoing studies

Table 6c. Frequency of Unexpected Adverse Events by Relatedness and by Dosage

Relatedness	Placebo	25 mg MDMA	125 mg MDMA	Total	Relatedness /All AEs
Unrelated	9	10	62	81	44%
% out of all Unrelated AEs	11%	12%	77%	100%	
% of AEs at listed dose	27%	71%	45%	44%	
Possibly Related	21*	4	38	63	34%
% of all Possibly Related AEs	33%	6%	60%	100%	
% of all at listed dose	64%	29%	27%	34%	
Probably Related	3*	0	39	42	23%
% of all Probably Related AEs	7%	0	93%	100%	
% of all at listed dose	9%	0	28%	23%	
Total	33	14	139	186	100%

*Assessment made while blinded

Table 6d. Frequency of Unexpected Adverse Events by Outcome and Condition

Outcome	0 mg	%/ Out come	25 mg	%/ Out Come	125 mg	% Out Come	Total	%/All Unexpec ted AEs
Full Recovery	30	18%	12	7%	127	75%	169	91%
Persists, Diminishing	1	8%	2	17%	9	75%	12	6%
Persists, the Same	2	67%	0	0%	1	33%	3	2%
Persists, Worsening	0	0%	0	0%	1	100%	1	0.05%
Death	0	0%	0	0%	1	100%	1	0.05%

* Lists number of events and percentage of each dose category that makes up each outcome and for outcome totals, percentage of each outcome within all unexpected adverse events

Four serious adverse events occurred, two in study MP1 and two in study MP2. None of them were drug related. These included broken clavicle, syncope, frontal lobe syndrome, later discerned to be the result of tumor metastasis, and psychiatric hospitalization after self-harm. See table 6e for details of SAEs.

Table 6e. All Studies Cumulative Serious Adverse Events Occurring in Studies MP-1 and MP-2

Study	Dose	Subject Number	Adverse Event Diagnosis	Date Last MDMA Admin.	Onset Date	Resolution Date	Severity	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-1	125mg MDMA	0203	Fractured Clavicle (Auto Accident)	20-Aug-04	31-Aug-04	Continuing	Moderate	Single/ Intermittent	None	Other	Treated in ER	Persists, diminishing	Not related
MP-1	125mg MDMA	0209	Vasovagal Syncope	22-Jul-05	1-Sep-05	1-Sep-05	Moderate	Single/ Intermittent	None	Other	Evaluated in the ER	Full recovery/ return to baseline	Not related
MP-2	125mg MDMA	0101	Brain metastasis (Frontal brain syndrome)	4-Jan-07	31-May-07	18-Jul-07	Severe	Continuous	Removed from study	Hospitalization	None	Death	Not related
MP-2	Before dosing	0103	Psychiatric hospitalization	none	20-Feb-07	21-Feb-07	Moderate	Single/ Intermittent	None	None	None	Full recovery/ return to baseline	Not related

One death occurred in study MP2. A participant with a previous history of breast cancer assigned to the MDMA condition had a tumor that had metastasized to the brain.

Table 6f. Other significant unexpected adverse events reported during Studies MP-1 and MP-2, including events that led to participant withdrawal

Study	Dose (mg)	Subject	Date of Last Drug Admin	MedDRA Lower Level term	Onset date	Resolution date	Action taken-treatment	Severity	Outcome	Relatedness
MP1	125 mg MDMA	208	17-Jun-2005	Major depression	29-July-2005	None listed	Prescription medication	Severe	Persists, diminishing	Unrelated
MP2	125 mg MDMA	101	24-Nov-06	Panic Attack	26-Nov-06	26-Nov-06	Prescription Medication	Moderate	Full Recovery	Possibly Related
MP2	125 mg MDMA	101	4-Jan-07	Panic Attack	6-Jan-07	6-Jan-07	Prescription Medication	Severe	Full Recovery	Possibly Related
MP2	125 mg MDMA	105	6-Sep-07	Exacerbation of anxiety	6-Sep-07	19-Sep-07	Withdrawn from study due to AE, Prescription Med	Severe	Persists, Diminishing	Probably Related
MP2	37.5 mg MDMA	105	13-Mar-08	Anxiety reaction	13-Mar-08	UNK-Apr-08	Prescription Medication, therapy	Severe	Full Recovery	Possibly Related

8.1.5. Cognitive Effects

An independent rater blind to study condition assessed cognitive performance in all participants at baseline and two months after the second experimental session, using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [392], the Paced Auditory Serial Addition and Subtraction Task (PASAT) [393, 394], and the Rey Osterreith figure [395]. The RBANS is a relatively short series of tests used to examine cognitive function. It yields a total score and five sub-scales, including memory, visual spatial, language, attention, and delayed memory, and the PASAT requires participants to add or subtract whole numbers (integers) as they are spoken by a recorded voice. Analyses examined RBANS total scores, percentile scores for PASAT Trial 1 and Trial 2, and X score for the Rey-Osterreith Figure. After establishing that participants in the MDMA and the placebo group performed similarly at baseline using an independent t-test, analyses comparing performance two months after the second experimental session also failed to find either improved or impaired cognitive function participants in the MDMA condition compared with participants in the placebo condition, suggesting that MDMA given during psychotherapy did not adversely affect cognitive function. There was no statistically significant difference between total RBANS scores obtained by participants given MDMA versus those given placebo at two-month follow up, as shown in a comparison of the difference between two-month follow up and baseline total RBANS score $t(1, 19) = 1.32, p > 0.05$ ($p = 0.2$). A comparison of the difference between two-month follow up and baseline PASAT scores for both trials failed to find significant differences in performance between participants in the MDMA and the placebo condition, including performance on trial one ($t(1, 19) = -0.211, p > 0.05$ [$p = 0.83$] and trial 2 ($t(1, 18) = 1.2, p > 0.05$ [$p = 0.244$]). The difference between two-month follow up and baseline performance on 30-second delay component of the Rey-Osterreith figure, a measure of delayed visual recall and design reproduction, was compared after MDMA and placebo. The analysis did not detect significant differences between MDMA and placebo participants on 30-second delay performance; 30-second delay raw score $t(1, 18) = 1.024, p > 0.05$ [$p = 0.319$], 30-second delay T score, $t(1, 17)$

= 1.115, $p > 0.05$ [$p = 0.281$], and Centile score $t(1, 16) = 0.543$, $p > 0.05$ [$p = 0.595$]. Taken together, these tests indicate a lack of effect of MDMA upon cognitive function in this study.

Table 8a. Neurocognitive Function - RBANS Total Scores at Baseline and Two Months after the Second Experimental Session

Condition	RBANS Total Score*: Baseline		RBANS Total Score*: 2-month follow up	
	Mean	SD	Mean	SD
Placebo (N = 8)	97.50	12.66	104.88	12.10
MDMA (N = 13)	107.85	13.48	109.00	10.80

*Higher scores indicate greater cognitive function

Table 8b. Cognitive Function - PASAT Trial 1 and Trial 2 Percentile Scores Baseline and Two months Post Follow Up

Condition	PASAT Trial 1 Baseline		PASAT Trial 1 2 month follow up		PASAT Trial 2 Baseline		PASAT Trial 2 2-month follow up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo (N = 8)	30.50	34.45	34.25	32.92	38.24	36.02	46.25	34.01
MDMA (N = 13)*	46.85	29.12	34.46	26.72	59.54	27.56	44.33	24.89

*N = 12 for Trial 2 at two-month follow up, as one person did not complete task.

Table 8c. Table 7c: Cognitive Function Rey Osterreith Completion at Thirty Seconds Delay at Baseline and Two Month Follow-Up

Condition	30 Second Delay: Baseline		30 Second Delay: 2-month follow up	
	Mean	SD	Mean	SD
Placebo (N = 8)	39.50	9.15	42.88	6.22
MDMA (N = 13*)	40.75	12.97	48.17	11.04

*Data for one subject is missing at Baseline

8.2. Efficacy of MDMA-assisted psychotherapy for PTSD

8.2.1. MP-1 Efficacy Results

Analyses of the Clinician Administered PTSD Scale (CAPS) [396, 397] prior to and after two experimental sessions found lower global scores, reflecting fewer or less intense PTSD symptoms, after undergoing experimental psychotherapy sessions with MDMA or placebo. In addition, participants in the MDMA condition experienced a greater decline in PTSD symptoms after undergoing experimental sessions than did participants in the placebo condition. Global CAPS scores declined for all participants over time (overall baseline mean Global CAPS = 79.1 +/- 21.7, and two months after the second experimental session, mean Global CAPS = 38.2 +/-

30.3), indicating a drop of 40.9 points, and a 52% reduction in symptoms. People in the MDMA and placebo conditions began the study with similar CAPS scores, while CAPS scores after experimental sessions were lower for people in the MDMA condition up through two months after the second experimental session (Placebo = 59.1 +/-28.9 versus MDMA, 25.4 +/- 23.95). Placebo participant scores dropped 20.5 points two months after the second experimental session while MDMA participant CAPS scores dropped 53.3 points, or a 26% drop in PTSD symptoms for controls versus a 68% drop in PTSD symptoms for MDMA participants.

Table 8a. Global CAPS Scores for Placebo and MDMA Subjects for MP-1 at T0 (baseline), T1 (post-Session 1), T2 (post-Session 2), and T3 (2 months post-Session 2)

Condition	T0*	T1	T2	T3
Placebo (n = 8)				
Mean (SD)	79.6 (22.0)	74.1 (28.5)	66.8 (27.0)	59.1 (28.9)
Range	54-111	21-105	22-103	14-86
MDMA (n = 13)				
Mean (SD)	79.7 (21.0)	36.4 (28.6)	29.2 (18.6)	25.39 (24.0)
Range	43-113	6-107	2-59	0-79
Total (n = 21)				
Mean (SD)	79.7 (20.8)	50.8 (33.6)	43.5 (28.5)	38.2 (30.3)
Range	43-113	6-107	2-103	0-86

*Dropout baseline scores excluded

At baseline, overall Impact of Events Scale scores were similar across both conditions (45.12 +/- 11.84 for placebo, 45 +/- 16.1 for MDMA). As with the CAPS, there was an overall decline in IES scores in participants in both groups two months after a second experimental session (from 45.05 +/- 14.3 at baseline to 212.625 +/- 18.4), or a 232.458-point decline in PTSD symptoms (520% decline). Participants who received MDMA had scores of 15.31 +/- 15.2, representing a 64% decline in PTSD symptoms (28.92 point decline) at two month follow up and participants that received placebo had 32.0 +/- 20.8, representing a 30% decline in symptoms (13.62 point drop). Two months after two sessions of MDMA-assisted psychotherapy, participants who received MDMA had scores of 16.08 +/- 15.6, representing a 64% decline in PTSD symptoms (28.92 point decline) and participants that received placebo had 31.5 +/- 19.3, representing a 30% decline in symptoms (13.62 point drop).

Five participants in the MDMA condition who received an additional session of MDMA-assisted psychotherapy experienced an additional decline in PTSD symptoms, with a global CAPS score of 17, (an 8.5 point decline) below the score seen two months after two sessions of MDMA-assisted psychotherapy under blinded conditions. For participants in the placebo condition, taking part in the open-label study continuation ("Stage 2") produced a Global CAPS of 33.86 (N = 7), a 31.7 point drop in global CAPS (43% decline in PTSD symptoms).

Table 8b. Table 8b: CAPS Scores for Stage 2 (Open-Label) at T3 (Post-Stage 1 Session 3), T4 (2 months post-Stage 2 Session 2), and T5 (2 months post-Stage 3 Session 3)

	T3	T4	T5
N	5	7	4
Mean (SD)	17.0 (15.8)	33.9 (12.8)	25.75 (7.0)
Range	0-36	15-49	19-34

At baseline, overall Impact of Events Scale scores were similar across both conditions (45.12 +/- 11.84 for placebo, 45 +/- 16.1 for MDMA). As with the CAPS, there was an overall decline in IES scores in participants in both groups two months after two experimental sessions (from 45.05 +/- 14.3 at baseline to 22.25 +/- 18.4), or a 22.8-point decline in PTSD symptoms (50% decline). Two months after two sessions of MDMA-assisted psychotherapy, participants who received MDMA had scores of 16.08 +/- 15.6, representing a 64% decline in PTSD symptoms (28.92 point decline) and participants that received placebo had 31.5 +/- 19.3, representing a 30% decline in symptoms (13.62 point drop).

Long-term follow-up data was collected for 20 participants of MP-1 [398]247, which was not statistically different from the mean CAPS score obtained two months after the second stage 1 or stage 2 experimental session (23.924.6; only includes the 17 participants who completed CAPS at LTFU) reported at the 2-month final outcome. The mean IES score at LTFU was 212.194, which was also not statistically different from the mean IES score (13.1919.8) reported at the 2-month final outcome. On the LTFU questionnaire, all subjects reported a benefit from participating in the study, with at least some benefit persisting.

Table 8c. Table 8c: CAPS Scores at LTFU

	Originally MDMA	Originally Placebo	MDMA and Placebo
N	11	6	17
Mean (SD)	25.7 (27.1)	18.7 (7.6)	23.2 (22.1)
Range	0-91	10-31	0-91

At the time of enrollment, 16 of 19 participants reached at LTFU (84%) of subjects were in active psychotherapy, with 12 of 19 (58%) taking psychiatric medications. At LTFU, only 9 of 19 (42%) were in psychotherapy, five of whom were receiving a different type of psychotherapy or psychotherapy from a different therapist. Only one participant not in psychotherapy just prior to the study was attending psychotherapy at LTFU. The percentage of subjects taking psychiatric medication did not change (12/19; 58%), but the mean number of medicines taken fell from 1.7 to 1.3. In addition, none of the medications taken at time of LTFU were for treatment of PTSD.

Table 8d. Table 8d: Medication and Psychotherapy Data Reported at LTFU

	Entry (n=19)	LTFU (n=19)
# taking meds	12	12
% taking meds	58%	58%
# taking meds for PTSD	7	0
Total # meds	32	23
Avg # meds	1.7	1.3
	Entry (n=20)	LTFU (n=20)
In therapy	17	9

These findings are suggestive of an effect of MDMA in combination with psychotherapy in reducing PTSD symptoms. The long-term follow-up findings further suggest that the benefits of MDMA-assisted psychotherapy for PTSD are enduring. The greatest problem in study interpretation is that the blind was not very effective, with most participants correctly guessing condition assignment and the investigators correctly guessing in all cases. However, the blind was effective for the independent rater, who was not present during therapy sessions and did not know people's guesses concerning their condition.

8.2.2. MP-2 Efficacy Results

The MP-2 study found results similar to the MP-1 study, but results were less marked. Analyses of global CAPS scores prior to and after three experimental sessions found lower global scores after undergoing experimental psychotherapy sessions with 125 mg MDMA, but not with a 25 mg MDMA active placebo. Global CAPS scores declined over time for the eight participants given a full dose of MDMA (overall baseline mean Global CAPS = 66.4 +/- 13.6, and three weeks after the third experimental session, mean Global CAPS = 50.7 +/- 19.7), indicating a drop of 15.7 points, or a 23.5% decrease in scores. On the other hand, global CAPS scores increased slightly over time for the four participants given an active placebo (overall baseline mean Global CAPS = 63.2 +/- 7.9, and three weeks after the third experimental session, mean Global CAPS = 66.5 +/- 7.5), indicating an increase of 2.3 points, or a 5.2% increase in CAPS scores.

Table 8e. MP-2 Stage 1 Mean CAPS Scores at T0 (Baseline), T1 (3 weeks post-Session 2), and T2 (3 weeks post-Session 3)

Condition assignment		T0	T1	T2
25 mg MDMA	N	5	4	4
	Mean (SD)	64.8 (7.7)	60.0 (6.8)	66.5 (7.6)
	Range	54-72	50-65	57-75
125 mg MDMA	N	9	8	8
	Mean (SD)	68.6 (14.3)	63.0 (17.8)	50.8 (19.7)
	Range	48-86	30-85	14-74
Total	N	14	12	12
	Mean (SD)	67.2 (12.1)	62.0 (14.7)	56.0 (17.9)
	Range	48-86	30-85	14-75

All four active placebo subjects continued to Stage 2 of the study and received open-label full dose MDMA. These subjects experienced a distinct decrease in PTSD symptom severity (at end of Stage 1, mean global CAPS = 66.5 +/- 7.5, and at end of Stage 2, mean global CAPS = 43.7 +/- 14.1).

Table 8f. MP-2 Stage 2 Mean CAPS Scores at T3 (3 weeks post-Session 2), T4 (3 weeks post-Session 3), and T5 (2 months post-Session 3)

Condition assignment		T3	T4	T5
25 mg MDMA (receiving 125 mg in Stage 2)	N	4	4	4
	Mean (SD)	42.5 (25.3)	43.8 (14.1)	36.8 (13.6)
	Range	11-64	25-56	21-50

Twelve participants were assessed 2 months after their final Stage 1 or Stage 2 experimental session, three participants were assessed 6 months after their final Stage 1 or Stage 2 experimental session, and ten participants were assessed 12 months after their final Stage 1 or Stage 2 session. From the 2-month follow-up, after receiving full dose MDMA in either Stage 1 or Stage 2, CAPS Global scores had dropped from an average of 45.0 +/- 16.4 (N=12) to 33.9 +/- 16.8 (N=10) at 12 months after final session. These data suggest that subjects may retain the benefits they experienced three weeks after their third full dose MDMA session, and they may continue to improve after finishing the treatment portion of the study. However, caution should be used in interpreting these results, as many subjects resumed concomitant therapy during the follow-up.

Table 8g. MP-2 Mean CAPS Scores at T6 (2 months follow-up post-Stage 1 or Stage 2), T7 (6 months follow-up), and T8 (12 months follow-up)

Condition assignment		T6	T7	T8
25 mg MDMA	N	4	1	4
	Mean (SD)	36.8 (13.6)	21.0	31.5 (19.2)
	Range	21-50	21	11-54
125 mg MDMA	N	8	2	6
	Mean (SD)	49.1 (16.8)	62.5 (3.5)	35.5 (16.8)
	Range	27-75	61-66	8-54
Total	N	12	3	10
	Mean (SD)	45.0 (16.4)	49.3 (24.7)	33.9 (16.8)
	Range	21-75	21-66	8-54

Though they do not represent as strong an effect of MDMA-assisted psychotherapy upon PTSD symptoms as findings from the MP-1 study, findings from the MP-2 study suggest that MDMA in combination with psychotherapy can reduce PTSD symptoms. The two studies differed with respect to sample size and location and placebo comparator, with MP-1 employing an inactive placebo while MP-2 employed 25 mg MDMA as an active placebo, resulting in somewhat greater success in maintaining the study blind.

Efficacy findings from both studies suggest that people with PTSD could benefit from a course of two or three sessions of MDMA-assisted psychotherapy.

8.3. Marketing Experience

MDMA is currently not approved for marketing anywhere in the world and is a Schedule 1 controlled substance in the U.S.

9. Summary of Data and Guidance for the Investigator

MDMA is a psychoactive compound that some researchers refer to as an entactogen, a compound that affects mood and perception and increasing prosocial feelings. On the basis of narrative reports and several initial studies of MDMA in psychotherapy, the sponsor is investigating use of this compound in combination with psychotherapy for people with PTSD.

Researchers have conducted *in vitro* and *in vivo* studies with MDMA, and clinical trials have been conducted in humans. MDMA is listed in the most restrictive drug schedule in the U.S. (Schedule 1) and is not permitted for use outside of research settings.

9.1. Pharmacology

The pharmacology of MDMA is complex and the chief mechanism behind its therapeutic effects is currently under investigation. Studies in rodents and cell cultures find that MDMA primarily releases serotonin, along with some norepinephrine and even less dopamine. This activity is probably through direct interaction with the transporters for each neurotransmitter. It also acts as an uptake inhibitor of serotonin, norepinephrine, and dopamine. MDMA has very little direct activity on postsynaptic neurotransmitter receptors, and most effects of MDMA are likely due to the direct and indirect effects of monoamine release. Indirect but potentially significant effects of MDMA include the release of the hormones oxytocin and prolactin and transient immunosuppressive and anti-inflammatory effects. Potentially therapeutic effects, such as increased feelings of closeness to others and specific changes in ability to detect facial emotion expression, may be tied to elevated oxytocin after MDMA. One study reported that blocking activation of 5HT_{2A} receptors, but blockage of 5HT_{1A} receptors, attenuated the mood-boosting effects of MDMA. Increased sociability and preclinical studies suggest that the MDMA enantiomers R-(-)-MDMA and S-(+)-MDMA produce different physiological and apparent subjective effects, but comparisons of MDMA enantiomers have not yet occurred in humans.

MDMA shares some effects with psychostimulants, such as increased energy, positive mood, increased blood pressure, heart rate, and it shares other effects with hallucinogenic (psychedelic) compounds, such as changes in perception and thinking, including perceived changes in meaning given to perception, facilitated imagination, and recall. Most previous research in rodents and primates used doses that are higher than those used in humans, and reported increased locomotor activity and signs of serotonin syndrome including flat body posture, an erect tail, forepaw treading and hyperactivity. Studies using approximately human equivalent doses do not report great increases in locomotion.

In humans, MDMA elevates positive mood, and may produce positively or negatively experienced derealization, increased vigor, and anxiety, and slight changes in perception. Recent reports suggest that it may also cause increased feelings of friendliness and sociability. Acutely, MDMA transiently and selectively affects performance on tasks requiring attention and memory. Studies investigating the impact of MDMA on driving suggest that the drug does not strongly alter driving, but impairs some driving-related skills.

MDMA is administered orally in all investigations in humans to date. In humans, onset of effects occurs approximately 30 to 60 minutes after administration, and peak effects occur 75 to 120 minutes after oral administration. Duration of effects lasts three to six hours. Orally administered MDMA has a half-life of seven to nine hours in humans and approximately three hours in monkeys. MDMA is metabolized in the liver by several enzymes. It is likely that active doses of MDMA saturate CYP2D6 function for an extended period, with function normalizing up to ten days post-MDMA. The enzymes CYP1A2, COMT and monoamine oxidase (MAO) may also be involved in the metabolism of MDMA.

Because of its activity as a monoamine releaser, MDMA administration is contraindicated in participants requiring medication with MAO inhibitors. Fatalities have been reported after the combination of MAOIs and MDMA in ecstasy users. Co-administration with an SSRI may eliminate or greatly attenuate the effects of MDMA.

9.2. Risks

Psychotherapists in the US began to use MDMA as an adjunct to psychotherapy in the mid to late 1970s, and a number of narrative accounts exist of therapeutic use prior to its scheduling. MDMA was administered to thousands of people prior to scheduling, and as of November, 2012, it has been administered to approximately 811 people. MDMA has been administered in early open-label studies as well as blinded, placebo controlled Phase 1 studies conducted in the US, Switzerland, Spain, the Netherlands, and the UK, and sponsor-supported studies of MDMA-assisted psychotherapy in the US, Switzerland and Israel. Two sponsor-supported studies have completed investigations of MDMA-assisted psychotherapy in people with PTSD, and another study was designed to investigate MDMA-assisted psychotherapy in people with advanced stage cancer. These studies have demonstrated that MDMA can be safely administered to people with PTSD in a clinical setting.

9.2.1. Risks Associated with Eligibility Screening

Investigators must establish participant eligibility prior to enrollment in trials with MDMA, with eligibility established through medical history, physical examination, vital signs, clinical laboratory tests, stress ECG (if indicated), psychiatric interview, and assessment of relevant psychiatric symptoms. Additional procedures may be used as required, such as exercise tests and ultrasound imaging. If the study is investigating use of MDMA in people with a specific psychiatric condition, then the investigators must also determine whether an individual has the condition. Submitting to a full medical examination may be time consuming and may be distressing or uncomfortable for some.

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

Studies of subjective effects of MDMA will employ measures of self-reported mood, experience, and emotional closeness to others. History, presence, and severity of psychiatric disorders are assessed via psychiatric interview and validated instruments such as the Structured Clinical Interview for Diagnosis (SCID) and the CAPS, to assess specific conditions. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. These measures are expected to produce minimal discomfort. Investigators should be experienced in treating the condition under investigation and they should seek to minimize anxiety and distress during these interviews.

9.2.2. Risks Associated with Psychotherapy

Participants enrolled in studies of MDMA-assisted psychotherapy will have a moderate course of psychotherapy sessions with a pair of investigators, one male and one female. During both non-drug and MDMA-assisted psychotherapy sessions, participants will be asked to think about and discuss their experiences, thoughts, and emotions relating to their condition. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing traumatic experiences, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy and experimental sessions. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from the therapists. Discontinuing PTSD medications and the acute and sub-acute effects of MDMA-assisted psychotherapy can produce shifts in mood and activation, which may increase likelihood of suicidal ideation or behavior.

The sponsor will record all psychotherapy sessions to audio and video, and participants may have access to recordings if they request them. The recordings will be used for further development of a manualized form of MDMA-assisted psychotherapy to be used in future research and to assess investigator adherence to any standardized treatment. Participants will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by investigators, trainees, or regulatory agencies. Permission for the recording is part of the informed consent.

9.2.3. Risks of MDMA

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Serious MDMA toxicity is rare even in uncontrolled settings, where people take material of unknown identity, potency, and purity, and the many users consuming estimated MDMA doses that are several times higher than those used in the proposed program, without apparent toxicity. Hyperthermia is the most frequently reported adverse effect to occur in this population. In addition to hyperthermic syndromes, other rare adverse events include dysphoria, panic or psychotic response, hepatotoxicity, and hyponatremia. The majority of ecstasy users visiting emergency departments do so because of anxiety or panic. In human clinical trials using MDMA, restrictions in study eligibility are intended to reduce the likelihood of serious adverse events.

Most clinical trials of MDMA employ doses between 75 and 140 mg (1 to 2 mg/kg), comparing these doses with inactive placebo, lower doses of MDMA, or other compounds, such as methylphenidate (Ritalin). Sponsor-supported studies employ a standard full dose of 125 mg, possibly followed by a dose of 62.5 mg 1.5 to 2.5 hours later. A few studies have investigated repeated doses, with doses ranging from 75 and 50 mg to two doses of 100 mg MDMA. Earlier investigations administered the supplemental dose at 2 to 2.5 hours later. This dose has been

compared with doses of 25 mg and 12.5 mg MDMA, with more recent planned studies also employing 30 mg, 40 mg and 75 mg MDMA as comparison doses. All doses are orally administered in opaque capsules. Lactose or a similar inactive material will be used to ensure that all capsules are of equivalent weight and appearance.

Adverse events of MDMA are modest and generally have not been associated with serious discomfort by healthy volunteers in previous studies. Commonly reported adverse events of MDMA include tight jaw, loss of appetite, difficulty concentrating, and impaired gait or balance. Sub-acute effects, including fatigue, feeling anxious or weak, or experiencing low mood are reported up to three days after MDMA administration.

9.2.4. Neurological Risks

Extensive studies in animals suggest that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nuclei, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site densities. While these findings are consistent across studies, these studies generally overestimated the human equivalence of the doses. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials. However, studies in very moderate ecstasy users do not report an increase in a biological marker of neuronal injury, and only one of three studies of this marker in humans detected it in heavy users. Three recent retrospective studies found changes in 5HT_{2A} receptors in moderate to heavy ecstasy users. Many retrospective studies have found that ecstasy users have fewer estimated serotonin transporter sites when compared with non-ecstasy users, though some have failed to detect differences. Retrospective studies have also found impaired performance of measures of verbal memory, planning and making decisions, and visual memory. However, some retrospective studies have found little or no differences in cognitive function. A team in the Netherlands has conducted a prospective study of people prior to and after moderate use of ecstasy (in most cases 1-6 tablets). They failed to find changes in serotonin transporter sites or signs of neuronal injury. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else. They did find that ecstasy users showed less improvement on a memory task than non-users. It is notable that the study examining SERT sites and regional cerebral blood flow did not employ non-ecstasy user controls, that all participants in the study of cognitive function performed within the normal range, and that one individual examined in the study of cognitive function had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other subjects. Data from MP-1, described previously, failed to find differences in neurocognitive performance between people given MDMA and people given inactive placebo. Taken together, these findings fail to confirm serotonergic neurotoxicity after low ecstasy use, but do suggest possible indications of impaired memory.

9.2.5. Cardiovascular Risks

The full dose of 125 mg, alone or followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hours later, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. Participants enrolled in controlled trials with a single dose of MDMA (approximately 5% per trial) have had elevations above a cut-off of at least 140/90 mmHg, while all participants given a regimen of 100 mg followed by 50 mg two hours later had elevations above 140/90.

Systolic blood pressure above 160 mmHg was detected in approximately 20% to 30% of participants with PTSD, and diastolic blood pressure greater than 110 mmHg occurred in approximately 7% to 10% of participants with PTSD. No medical intervention was needed in studies of healthy humans or people with PTSD. Tables XX to YY show the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. While maximum peak blood pressure during a given session in some cases rose above the cut-off for making more frequent measures (160 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP)), no subjects in MP-1 or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure or pulse, and all values returned to normal as the effects of MDMA diminished. The degree of additional blood pressure and pulse elevation is minimal after a second dose of MDMA half the original dose given 1.5 to 2.5 hours after the first dose.

Data from MP-1 demonstrates that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose. Lower doses of MDMA (e.g., 30 or 75 mg) are expected to have lesser effects on blood pressure and heart rate than 125 mg.

Potential complications of elevated blood pressure or heart rate include stroke or myocardial ischemia. These events have not occurred in clinical trials of MDMA. Excluding people with cerebrovascular or cardiovascular disease will reduce the likelihood of risks arising from the cardiovascular effects of MDMA. Investigators conducting trials of MDMA should be prepared to treat elevated blood pressure with medications if necessary and either to provide appropriate care related to these effects or to transport individuals to an emergency department if necessary.

Because of its activity at 5HT_{2B} receptors, it is possible that MDMA could stimulate valvular heart disease (VHD). However, studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease, and echocardiograms of a small sample of ecstasy users appear normal.

9.2.6. Psychological Risks

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. Psychological distress from MDMA could arise at any time from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the effects of MDMA have subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from the investigator, with occasional use of benzodiazepines for anxiety more than 24 hours after the experimental session. In clinical trials of PTSD treatment, participants are informed that experimental sessions have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, anxiety, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. In Phase I trials

with normal volunteers, mild anxiety and depressed mood are reported by some subjects 1 to 3 days after MDMA administration.

The potential for destabilizing psychological distress will be minimized by:

- excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder - 1 or with psychotic disorders)
- preparatory non-drug psychotherapy sessions before the experimental session
- creating an atmosphere of trust during the experimental session
- close monitoring
- daily contact with subjects for the period of a week after the experimental session
- providing non-drug integrative psychotherapy sessions
- having subjects remain at the study site for the night of each experimental session to further reduce psychological distress, and having qualified personnel, such as a trained attendant, available during the overnight stay to respond to the needs of the subject.

Attendants will be instructed to contact the investigator upon request or at the appearance of signs of a potential adverse event. Every effort will be made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session. Such efforts will include empathic listening on the part of the investigators and affect management techniques such as diaphragmatic breathing by subjects.

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

1. If the subject is anxious, agitated, and/or in danger of any self-harm or is suicidal at the end of the MDMA session, the investigators will remain with the subject for at least two more hours. During this time, the investigators will employ affect management techniques reviewed during the introductory sessions and will talk with the subject to help him or her gain cognitive perspective of their experience. If this situation should occur during an integrative therapy session, the same approach will be used, and at least one of the investigators will be available to stay with the subject for at least two additional hours.
2. If a subject remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the clinical investigator will decide between the following options:
 - a. A psychiatric nurse, therapeutic assistant, or therapist will stay with the subject until the time of his or her appointment with investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed.
 - b. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." Investigators should not prescribe an SSRI, SNRI, MAOI, or any other psychotropic medication in this context. Residual symptoms will be addressed during the frequent follow-

- up psychotherapy visits with the investigators.
- c. Hospitalization for stabilization. If a subject should become psychotic, arrangements will be made to stabilize and transfer him or her to the study site inpatient unit or the nearest appropriate inpatient psychiatric facility.

Subjects hospitalized after a severe panic reaction will be suspended from further participation in the trial until after recovery or stabilization, at which time the investigator will carefully evaluate the subject's emotional status and decide whether or not the subject may continue the study. For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject's outside therapists will be involved in the management of any psychiatric complications.

9.2.7. Risks Related to Body Temperature

Findings from previous Phase 1 trials indicate that MDMA administered in a controlled setting produces only a slight increase in body temperature, and ambient temperature neither increases nor attenuates this slight elevation in humans. Approximately 30% of people with PTSD exhibited an elevation in BT greater than 1 C, but no medical intervention was required in any of these cases. However, hyperthermia has occurred in ecstasy users. Maximum body temperature could rise above normal temperature, as with the maximum peak of 100° Fahrenheit (F), or 37.7 Celsius (C), during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, MDMA and placebo conditions combined). In this study, body temperature returned to normal without treatment other than simply lowering the ambient temperature, which may or may not have been necessary. Investigators should assess body temperature periodically. Sponsor-supported studies have assessed it every 60 to 90 minutes. The investigators must be able to cool body temperature if necessary through removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. Further cooling with ice packs or, if available, a cooling blanket, can be used if these steps do not reduce body temperature. Subjects with signs or symptoms of heat stroke will be transferred to the nearest hospital for treatment.

9.2.8. Immunological Risks

Humans exhibit transient immunological changes after a dose of 100 mg, including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. In several respects, these effects are similar to those that occur with other psychoactive substances and are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release. The significance of these immunological effects remains unclear. Previous reports did not show increases in infections after MDMA and data from the study of MDMA-assisted psychotherapy has reported only instances of infection (upper respiratory) within seven days of MDMA administration. Based on results from trials conducted by the Sponsor, the impact of these effects is expected to be modest. The investigators may exclude participants that might face additional risks from immunosuppression.

9.2.9. Reproductive and Developmental Risks

Risks posed to pregnant women by MDMA are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, and a third study detected a link between degree of self-reported prenatal exposure to ecstasy and delays in infant development. All sponsor-supported trials of MDMA exclude pregnant and lactating women, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control during the period of the protocol. If any participant becomes pregnant during study participation, the sponsor and clinical investigator will follow the pregnancy to outcome.

9.2.10. Risk of Abuse

Despite its classification as a Schedule 1 drug, an examination of findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine. Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic ecstasy use or dependence. In two studies of MDMA-assisted psychotherapy for people with PTSD, only one of 32 participants reported using ecstasy subsequent to study participation, and several subjects volunteered that they would not seek out ecstasy outside of a psychotherapeutic setting. Diversion is not an issue for sponsor-supported studies because MDMA will only be administered under the supervision of the clinical investigator and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

10. Conclusion

Based on the current state of scientific knowledge, the risk for subjects meeting inclusion and exclusion criteria who are exposed to MDMA at doses used in sponsor-supported studies in a clinical setting appear to be manageable. Future studies conducted by the Sponsor are intended to further develop the safety profile of MDMA in the PTSD subject population. MDMA-assisted psychotherapy appears to be a promising treatment method for chronic PTSD, and more clinical trials in larger subject populations are warranted.

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MAPS Study MP4
Canada

Summary of Changes Amendment 1 Version 2
June 20, 2013

PROTOCOL MP-4

Summary of Changes

IND #63,384

Original: March 17, 2009
Amendment 1 Version 1: October 27, 2010
Amendment 1 Version 2: June 20, 2013

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

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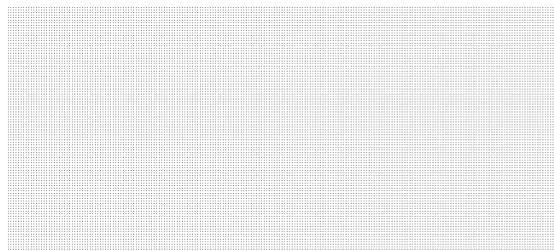
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1.0 MP4 Amendment 1 Version 2 Rationale

This amendment is being submitted prior to study start and is necessary due to the amount of time that passed between the original protocol approval to the time MAPS was allowed to import study drug. During the four years since the original approval the overall MDMA/PTSD development plan has progressed as studies have been completed, this amendment brings the protocol inline with the current Phase 2 program. This amendment reflects the most up to date study design, timing of treatment and selection of doses that MAPS is now investigating as part of the overall dose response investigation across multiple Phase 2 studies. The primary changes in Amendment 1 Version 2 effect the study design, cross over time point, timing of the primary endpoint, Stage 2 dosing and the addition of obfuscation to the informed consent. The primary changes are discussed below as well as in section 2.0. There are additional changes throughout the protocol that do not effect design but provide additional detail to procedures, provide clarifications or are administrative changes based on our new protocol template. A protocol in track changes is being provided as well as the summary of changes to document all changes in detail.

1.1 Summary of Design Changes

The protocol design has been amended to move the primary endpoint assessment of PTSD symptoms and unblinding from after the third experimental session to one-month after the second blinded experimental session. This change and the alignment of all study visit time points brings the study design into accordance with the timing of the primary endpoint and visits of other MDMA/PTSD Phase 2 studies in the clinical development plan.

Full dose subjects will still have three full dose experimental sessions as in the original approved protocol. The first two experimental sessions will be blinded. After unblinding, only full dose subjects will continue onto the 3rd experimental session and associated integrative sessions in Stage 1. Upon unblinding at the primary endpoint, subjects in the comparator dose group will cross over from Stage 1 to Stage 2 after two instead of three experimental sessions. Previously, unblinding was after the third experimental session at the two-month follow-up. Subjects who received the comparator dose during the blinded portion of the study will continue to have the opportunity to cross over to Stage 2 and receive three experimental sessions. Stage 2 procedures and schedule will be similar to Stage 1 but will be open label. The doses in Stage 2 have been amended from full dose MDMA to explore the optimal therapeutic dose of MDMA. Subjects in Stage 2 will receive an initial dose of 100 mg at the first experimental session, either an initial dose of 100 mg or 125 mg MDMA at the second and third experimental sessions based on the opinion of the therapist team. The supplemental doses for each session will be half of the initial dose, respectively.

The crossover is three months earlier than the previous protocol version that required three experimental sessions for all subjects in Stage 1. This was done to decrease the

amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether the treatment method will involve two rather than three experimental sessions. Based on our experience in previous studies, in those who have received a low or active placebo dose, we believe it is safe to administer three low dose sessions, but it may create an unnecessary hardship for subjects by extending their treatment at low and medium doses. We believe that only two sessions prior to unblinding are likely to demonstrate significant separation between the comparator dose group and the full dose group based on completed MDMA/PTSD studies sponsored by MAPS.

As a part of MAPS' ongoing efforts to optimize the double-blind of MDMA-assisted psychotherapy studies, subjects will be informed of the two groups that they may be randomly assigned to, but a level of obfuscation will be added to the informed consent process during the blinded portion of the study. The sponsor is currently exploring two approaches to successful maintenance of the double blind. One of these approaches is a dose-response design, which is already being tested in an ongoing MAPS-sponsored Phase 2 study in veterans and first responders in the USA. One complication of this approach is that confusion about the condition assignment is based on the subjective effects of the drug, which are likely to be proportional to the dose the subjects receive. If the subjective effects of the lower dose are large enough to confuse a subject about the dose they receive, the dose may also have some level of efficacy. One potential approach to this issue is to add obfuscation to the informed consent process in which subjects would be told they would receive either an inactive placebo or one of several doses of MDMA. Then subjects would be asked to guess if they received active MDMA or placebo to enable assessment of the double blind. In order for the lower dose to be confused with a full dose of MDMA, the informed consent form states that the comparator may or may not have MDMA. The obfuscation is for a limited period during treatment until subjects are fully debriefed upon unblinding after only two blinded drug-assisted sessions. The research cannot be practically conducted without this alteration to the protocol because obfuscation will make it possible for subjects to be less certain of the identity of the comparator.

A long-term follow up assessment has been added to the study, with symptoms assessed 1 year after a participant has had a final MDMA-assisted psychotherapy session. A number of secondary changes occurred in this amendment as a result of the addition of the long-term follow-up, including changes in wording and instructions concerning collection of adverse events and the use of a memory aid card for use between the final study visit and the long-term follow up assessment.

Finally, the protocol has been restructured. Some sections appear earlier in the Amendment than in the original protocol, and the section containing Pharmacology included in the original study protocol is omitted from the Amendment. Most of the information within the omitted section can be found in the 6th edition of the Investigator's Brochure. Changes were made to sections that are associated with the major changes discussed above these include updates to the protocol objectives, visit descriptions, time and events and analysis sections.

Obfuscation here

Grammatical changes were made throughout in order to accommodate the changes to the protocol. In addition, corrections to spelling and sentence structure have been updated for readability. These types of changes are not included in the change list below.

Due to the amount of changes in this protocol, a red-line version of the protocol will be provided to view exact changes.

2.0 Systematic Changes Effecting Multiple Sections

1. The PI has established Research Affiliate status with the Center for Addiction Research in British Columbia (CARBC) as a part of the University of Victoria in order to support qualifications for the study.
2. The study synopsis has been revised to match the Sponsor's new synopsis template, which no longer includes the inclusion/exclusion criteria and now includes protocol objectives, measures, procedures for recruitment and statistical analysis as well as an abbreviated study flowchart.
3. The Time and Events Table has been revised to match updated study procedures, and a new Summary of Events flowchart has been added to graphically depict study procedures.
4. Updated language throughout to match new template wording. Section numbers have been added to each section with numbers alongside headers, with the List of Abbreviations given the first number of 1.0, to provide a clear way to reference portions of the protocol. Rationale: This was done to make it easier to read and follow the protocol and to locate and reference specific sections of the protocol.
5. The protocol title has changed to reflect the study design. It is now titled "A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada"
6. A list of abbreviations now appears prior to the text of the protocol to provide clarity while reading the protocol.
7. "Principal investigator" and PI have been replaced by the terms "clinical investigator" and "CI" throughout the document.
8. Updated all sub-sections in 3.0 Background information with most recent scientific literature and results of clinical trials with MDMA-assisted psychotherapy for PTSD. Updated the purpose to be consistent with the new design.

9. A level of obfuscation was added to the informed consent process to better mask the blind. The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of 50 mg of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive full dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint assessments when unblinding occurs. Section 5.0 on Informed Consent has been revised to include this information as well as procedures for withdrawal of consent. The informed consent quiz has been removed in line with current procedures in MAPS-sponsored studies. Subjects will complete the informed consent process with the PI to ensure that accurate and thorough information is provided about the study in verbal and written form.
10. The plan for subject recruitment has been updated to reflect how this will be conducted for the subject population. Recruitment will now include the use of advertisements and announcements on internet sites, including the sponsor site.
11. Clarity was added to the overall study objective in light of completed studies of MDMA-assisted psychotherapy and the development of a Treatment Manual. Study Objectives have been rewritten so that there is a single primary study objective and so that secondary objectives address newly added measures.
12. The Primary Objective has been updated to reflect the unblinding at the primary endpoint after the second experimental session.

Previously: "Assess changes in PTSD symptoms as measured via Clinician-Administered PTSD Scale (CAPS) scores in Stage 1 in participants receiving the active placebo vs. full dose of MDMA-assisted psychotherapy."

Now: "Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session. This update was to reflect the unblinding at the primary endpoint after the second experimental session."

13. The Secondary Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session. Additional secondary objectives describing process measures were added regarding adherence to the Treatment manual, belief of condition assignment, testing the two vs. three session treatment

model, and exploration of the role of non-ordinary states of consciousness immediately after experimental sessions.

14. The Safety Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session and the proper assessment timeline to support the updated primary endpoint, but also added the Visual Analog Scale to collect changes to pre-existing tinnitus and/or chronic pain symptoms, specifically in subjects with a medical history of tinnitus and/or chronic pain. Objectives related to the RBANS and PASAT were moved from outcome measures to safety measures to appropriately reflect the goal of assessing neurocognitive function after MDMA-assisted psychotherapy. The safety objective concerning measures of cognitive function has been revised with the study design.
15. The RBANS and PASAT will be administered at a third visit two months after the third Stage 1 or Stage 2 session to assess the safety effects of MDMA in people who have all received full dose MDMA during the course of the study. The measures of cognitive function will be assessed via RBANS and PASAT again two months after the third Stage 1/Stage 2 experimental sessions in addition to baseline and primary endpoint assessments. The administration of a repeatable test battery will confirm and extend data concerning any potential effects of MDMA on cognitive function. At the secondary endpoint, most participants will have had received the maximum cumulative exposure of MDMA for the study.
16. The addition of the following assessments:
 - DES-II: Dissociation Experiences Scale II- The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory. It is an established measure of dissociative symptoms. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms. Subjects will complete the DES-II at the same time as the CAPS is administered according to the Time and Events Table. Dissociation and depersonalization are likely to be added to symptoms of PTSD with the upcoming revision of the DSM, DSM-V. In order to compare the prevalence of these symptoms to future studies that may use the DSM-V, this secondary measure will be used.
 - The NEO-PI (Neuroticism-Extroversion-Openness Personality Inventory-Revised) will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with

sound properties of reliability and validity that operationally define personality structure according to a five-factor model.

- **PSQI: Pittsburgh Sleep Quality Index-** The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers.
- **SOCQ: States of Consciousness Questionnaire-** The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues. It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day, and results will inform comparison of MDMA to the subjective effects other psychoactive drugs that have been studied with this measure.
- **Changes in Tinnitus or Pain using the Visual Analog Scale:** A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain. The changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from “None” to “Worst Case Imaginable”. This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response. Changes will be collected in subjects presenting with a history of either. PTSD, chronic pain, and tinnitus are frequently co-morbid. In order to track the prevalence and variation in symptom severity of chronic pain and tinnitus symptoms for accurate collection of any exacerbations as Adverse Events, or any improvements in the symptoms as a result of study participation, this new measure has been added.
- **Perceptions of experimental sessions:** Perceptions of the experimental sessions will be collected from each full dose subject during the primary endpoint visit after unblinding and from Stage 2 subjects during the secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage 2. Perceptions will be collected again at the end of Stage 1/Stage 2. These perceptions are collected as a part of the sponsor’s ongoing initiative to assess the therapeutic value of the third experimental session and information on the optimal therapeutic dose of MDMA.

- The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [133, 134]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions.
- Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.
- The revised Beck Depression Inventory, or BDI-II, will be used in place of the BDI.
- The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the self or others.
- The NEO-PI will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.
- The suicidality assessment Adult Suicide Ideation Questionnaire (ASIQ) will be replaced with the Columbia Suicide Severity Rating Scale (C-SSRS), and it will be administered more frequently than in the original study design, according to U.S. FDA requirements for psychiatric clinical trials. The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial. The C-SSRS will be performed by the PI at baseline, and repeated throughout the protocol to assess suicidality.
- The long-term follow-up assessment will include a questionnaire concerning perceived benefits and harms of study participation and views concerning study participation.

12. Changed the comparator dose from 25 mg with an optional 12.5mg supplemental dose to 50 mg with an optional 25mg supplemental dose. Changed wording describing the lower dose from “Active Placebo” to “Comparator Dose” for consistency amongst protocols in describing the slightly higher 50mg dose. This change was made in line with the sponsor’s progression through the clinical development plan and completion of a study with the 25mg active placebo dose in the interim of the approval process for this study. Section 12.1 Statistical Power was updated to reflect the estimated effect size based on completed studies.
13. Defined and clarified treatment resistant subjects as those who “were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to either:
 - a. Inability to tolerate psychotherapy for PTSD (e.g. persistent “over-engagement” when attempting Prolonged Exposure Therapy).
 - b. Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;”
11. Addition of five new inclusion criteria of subjects who “Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by Clinical Investigators in the event of a subject becoming suicidal; those who “Agree to inform the Clinical Investigators within 48 hours of any planned medical interventions;” those who “Agree to have all clinic visit sessions recorded to audio and video;” those who “Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.” and those who “Are at least 21 years old.” These criteria were added to ensure that the results of the study are clearly attributed to the investigational treatment, that the recruitment population is clearly captured in the criteria, and that subjects are willing to share personal and medical information with the investigators.
14. Revision of the inclusion criterion for subjects who “Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control” to also allow for subjects “on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.” Instructions for medication tapering were added to Section 14.4 in the form of a table and additional wording describing the timing of preparatory sessions with medication tapering was added to Section 7.3 Study Duration and Visit Windows.
15. Addition of one exclusion criterion #12, those who “Have any current problem, which in the opinion of the Principal Clinical Investigator or Medical Monitor,

- might interfere with participation in the study.” The sponsor is continuing to refine exclusion criteria for the treatment in preparation for Phase 3 studies, and will collect information on problems that may interfere with treatment through this criterion.
16. Moved unblinding to after the second experimental session, rather than the third. This was done to decrease the amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether our treatment method will involve two rather than three experimental sessions.
 17. CAPS score was raised to 60 from 50. The CAPS score cutoff was raised to 60 in order to work with more severe PTSD cases and to avoid floor effects.
 18. The Amendment clarifies that a single consent form will cover Stage 1 and Stage 2. The revision was made so that enrollment includes the possibility of entering stage 2. Subjects who are eligible for stage 2 and do not wish to enroll can withdraw from the study.
 19. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.
 20. The amounts of MDMA encapsulated for Stage 1 has been updated to: 125 mg, 62.5 mg, 50 mg, and 12.5 mg. Previously, 125 mg, 62.5 mg, 50 mg, and 25 mg, were to be created. Section 8.0 has been revised to accommodate changes in dosing strategy for Stage 1 and Stage 2. New tables and text were provided for clarity to describe the various doses of study drug to be employed, and drug labels were revised in accordance with Health Canada regulations.
 21. Section 9.1 and 9.2 were revised to match the Sponsor’s new web-based randomization program requirements that will enable real-time drug accountability and randomization tracking.
 22. Reference to Emergency Unblinding Envelopes has been removed, as the site should now contact the sponsor, if needed. If there is an emergency requiring knowledge of subject’s condition assignment, the blind may be broken for an individual subject. The investigator may be provided with the condition assignment in case of emergency through the web-based randomization system. At any time the unblinded Randomization Monitor can be contacted if assistance is needed.

23. Section 9.4 Visit Descriptions have been re-written for clarity and to align with the new study design and assessments.
24. Section 10.0 "Removal of Subjects from Therapy or Assessment" has been updated with language to provide clarification on study procedures relating to collecting follow-up data on subjects removed from the study. Subjects removed from the study may still be assessed at long-term follow up if possible for an intent-to-treat analysis. This analysis will address the potential that outcomes for the study will only be assessed in subjects who are likely to complete the study.
25. Section 12.0 Data Analysis has been updated to reflect the new study design and primary and secondary endpoints.
26. Section 12.1 Statistical Power has been revised to calculate power using comparator dose and full dose and information drawn from publications of data from sponsor-supported studies. The statistical power has been updated to reflect new information concerning sponsor-supported research and the comparator dose.
27. Section 13.0 is no longer titled "Monitoring for Toxicity". Plans for Risk Mitigation were moved from the Appendix to Section 13.0, and it is now titled "Risk Mitigation". The section was shortened to include only relevant information to the protocol. All other more specific and in-depth information is contained in the Investigator's Brochure. In line with recently completed and published MDMA/PTSD studies, the potential for toxicity during experimental sessions was found to be minimal and adequately covered under Section 16.0 "Risks of Participation." Likewise, Section 13.1 "Medical Emergencies" has been updated with information on number of experimental sessions and that adverse events during sponsor-supported studies generally resolved without requiring medical intervention.
28. Section 14.0 "Adverse Events" has updated contact information for medical monitors, describes the use of memory aid cards for the interval between final stage 1 or stage 2 visits and long-term follow up, and details the types of adverse events collected during the course of the study. The AE collection information was updated to provide information related to study staff and requirements for AE collection during the long term follow up. In addition, all AEs related to changes in psychiatric status will be collected throughout the study to provide for further capturing of psychiatric AEs.
29. Section 14.3, previously titled "Commonly Expected Side Effects" is now titled "Spontaneously Reported Reactions." These expected reactions were updated with the most recent information and MDMA program collection. They are referred to as reactions with the understanding that the side effect profile of MDMA-assisted psychotherapy will only be determined post-approval.
30. Concomitant Medication collection and tapering instructions have been updated. A table containing commonly prescribed psychiatric medications and their half-

- lives is provided. Memory aid card information is now provided. This section has been updated to match the amended AE collections, particularly during the interval after the final stage 1 or stage 2 site visit and long-term follow up, and to provide clarity and information on all medications and tapering of pre-study medications throughout the protocol. The table permits informed estimation of appropriate tapering procedures.
31. Section 14.5 Clinical Laboratory Assessments has been updated to reflect the full panel of tests to be performed for thorough medical evaluation prior to enrollment and accurate assessment of adverse events that could be related to treatment.
 32. Section 15.0 Study Monitoring, Auditing and Documentation has been updated with new template language. Language was added to this section to provide consistency across MAPS studies and compliance with GCP.
 33. Section 16 "Risks of Participation" has been revised for clarification, to include risk mitigation information previously under other sections and to encompass the literature and data from Sponsor-supported research. The risk section contains relevant information on the risks of receiving MDMA. Information originally in "Risk Mitigation" is contained within this section.
 34. The section "Risk/Benefit Analysis" is no longer present in the protocol. The section was removed in line with sponsor protocol template design. The risks and benefits of the research are detailed in the "Introduction" and "Risks" sections. A thorough Risk/Benefit Analysis is not possible in a single pilot study with this sample size, and would be influenced by findings from multiple studies. As such, the Risk/Benefit Analysis will be conducted on an ongoing basis across multiple Phase 2 studies supported by the sponsor and is likely to change across the duration of this study.
 35. Section 18.0 Confidentiality was revised to reflect the Sponsor's updated procedures and requirements for ensuring confidentiality of study data kept in digital media.
 36. Section 22.0 Record Retention describing the conditions of record storage and responsibilities of the investigator concerning length of record retention has been added in compliance with agency regulations.
 37. Section 21.0 "Publication Policy" was added to the protocol to include the Sponsor's updated publication policy in line with previous and future publications of Phase 2 pilot studies in the clinical development plan.
 38. The section that was previously Chemistry and Manufacturing and Control has been removed as it is contained in the Investigator's Brochure in line with the sponsor's new protocol template.

39. Appendices describing facilities and visit by visit descriptions have been removed from the protocol. Study procedures are now described in a visit by visit fashion to improve compliance with the protocol. Facilities are only listed in the title page and are no longer part of the protocol template.
40. Draft case report forms are no longer present as an appendix. Draft case report forms are no longer part of the protocol template as the sponsor plans on utilizing Electronic Data Capture (EDC) for this study.

MAPS Study MP-4
Canada

Amendment 1 Version 2
June 20, 2013

PROTOCOL MP-4
IND #63,384

Original Protocol: March 17, 2009
Amendment 1 Version 1: October 27, 2010
Amendment 1 Version 2: June 20, 2013

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

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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 (EMA) 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

1.0 List of Abbreviations

AE(s)	Adverse Event(s)
AED	Automated External Defibrillator
A:G	Albumin : Globulin ratio
ALT/SGPT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory II
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
C	Celsius
CAPS	Clinician Administered PTSD Scale
CI	Clinical Investigator(s) (e.g. therapists, co-Clinical Investigators)
CPK	Creatine phosphokinase
CPT	Cognitive Processing Therapy
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Administration
DES-II	Dissociation Experiences Scale II
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
ECG/EKG	Electrocardiogram
ED	Emergency Department
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPA	Health Information Protection Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
ISF	Clinical Investigator Site File
IV	Intra-venous
LSD	d-Lysergic acid diethylamide

MAPS Study MP-4
Canada

Amendment 1 Version 2
June 20, 2013

MAOI	<u>Monoamine oxidase Inhibitor</u>
MAPS	<u>Multidisciplinary Association for Psychedelic Studies</u>
MCH	<u>Mean Corpuscular Hemoglobin</u>
MCHC	<u>Mean Corpuscular Hemoglobin Concentration</u>
MCV	<u>Mean Corpuscular Volume</u>
MDMA	<u>3,4-Methylenedioxymethamphetamine</u>
MP-1	<u>MAPS' First Clinical Trial of MDMA-assisted Psychotherapy for PTSD</u>
MP-2	<u>MAPS' Second Clinical Trial of MDMA-assisted Psychotherapy for PTSD</u>
NEO-PI	<u>Neuroticism Extroversion Openness Personality Inventory</u>
OT	<u>Oxytocin</u>
PASAT	<u>Paced Auditory Serial Addition Test</u>
PDS	<u>PTSD Diagnostic Scale</u>
PI	<u>Principal Clinical Investigator</u>
PRN	<u>As Needed</u>
PSQI	<u>Pittsburgh Sleep Quality Index</u>
PTSD	<u>Posttraumatic Stress Disorder</u>
PTCA	<u>Percutaneous Transluminal Coronary Angioplasty</u>
PTGI	<u>Posttraumatic Growth Inventory</u>
PTSD	<u>Posttraumatic Stress Disorder</u>
PTT	<u>Partial Thromboplastin Time</u>
RBANS	<u>Repeatable Battery for the Assessment of Neuropsychological Status</u>
RBC	<u>Red Blood Cell Count</u>
RDW	<u>Red Cell Distribution Width</u>
RRPQ	<u>Reactions to Research Participation Questionnaire</u>
SAE(s)	<u>Serious Adverse Event(s)</u>
SBP	<u>Systolic Blood Pressure</u>
SCID-I-RV	<u>Structured Clinical Interview for Diagnoses Axis I Research Version</u>
SERT	<u>Serotonin Transporter</u>
SL	<u>Sublingual</u>
SNRI	<u>Serotonin Norepinephrine Reuptake Inhibitor</u>
SOP(s)	<u>Standard Operating Procedure(s)</u>
SSRI	<u>Selective Serotonin Reuptake Inhibitor</u>
SUD	<u>Subjective Units of Distress</u>
T3	<u>Triiodothyronine</u>
T4	<u>Thyroxine</u>
TSH	<u>Thyroid Stimulating Hormones</u>
U.S.	<u>United States of America</u>
WBC	<u>White Blood Cell Count</u>

2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with chronic treatment-resistant posttraumatic stress disorder (PTSD). This study, seeking to test MDMA-assisted psychotherapy in Canadian residents with chronic treatment-resistant PTSD, is part of an international series of Phase 2 clinical trials. Ongoing and planned Phase 2 studies are laying the groundwork for a possible End-of-Phase 2 meeting with FDA and Phase 3 multi-site studies.

MAPS has published results indicating sustained improvements in PTSD severity after MDMA-assisted psychotherapy [1-3]. MAPS is currently conducting a U.S.-based Phase 2 trial treating U.S. military veterans, firefighters, and police officers with service-related, chronic, treatment-resistant PTSD, a U.S. Phase 2 pilot study in 12 subjects in Boulder, Colorado, and an Israeli Phase 2 pilot study in 10 subjects. Taken together, these pilot studies will help to gather preliminary data about the safety and efficacy of MDMA-assisted psychotherapy that will inform the design of possible Phase 3 multi-site studies.

This Canadian pilot study is a randomized, double-blind, dose comparison evaluation of MDMA-assisted psychotherapy in 12 patients with chronic, treatment-resistant PTSD. PTSD must be of at least 6 months duration without remission from prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or where treatment was discontinued due to lack of tolerability. This study is designed to obtain estimates of effect size for safety and efficacy. The data will be combined with ongoing Phase 2 dose response studies in a meta-analysis.

This pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, seven of 12 people will receive a dose of MDMA expected to be fully therapeutic (full dose) and five of 12 will receive a comparator dose of MDMA during the blinded part of the study, referred to as Stage 1. PTSD and associated symptoms will be assessed at baseline and one month after the second double-blind MDMA-assisted (experimental) psychotherapy session. Cognitive function will also be assessed at baseline and again one month after the second experimental session. Study subjects will receive psychotherapy before and after each experimental session.

Unblinding will take place after the primary endpoint assessments. Full dose subjects will continue in Stage 1 and receive a third MDMA-assisted (experimental) psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose

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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.

may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.

3.0 Background

3.1 Posttraumatic Stress Disorder

PTSD is a debilitating psychiatric disorder arising after a traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. A complex biopsychosocial condition, PTSD is characterized by a combination of three types of symptoms:

1. Hyperarousal symptoms such as hypervigilance, anxiety, and sleep disturbance.
2. Intrusive re-experiencing of traumatic experiences, such as intrusive memories, nightmares, or flashbacks.
3. Avoidance symptoms, including emotional numbing and withdrawal [4, 5].

The DSM-IV criteria for PTSD include:

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

The lifetime prevalence of PTSD in the U.S. general population is between 6% and 10% [6-10], but it is common in other countries as well [11-14]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [13]. In U.S. military personnel returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [15]. It is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [16]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [14, 17, 18].

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 sub-threshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased

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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 ... [3]

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to 10.3% [19]. A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate [20]. 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 that were deployed more than once [21]. 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 is clearly a serious public health problem and contributes substantially to healthcare costs [5, 8, 9]. PTSD is typically a chronic illness [6, 22], associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [7-10, 23]. People suffering from PTSD face challenges in relationships and work productivity [24]. Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [25]. Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, which are known to affect the serotonergic components of PTSD, are currently marketed as PTSD medications in the U.S. [26, 27]. SSRIs must be used every day in order to be effective for PTSD symptoms [28]. However, SSRIs are associated with a high rate of discontinuation due to lack of tolerability caused by treatment-emergent side effects that may be under-reported [29, 30].

A wider array of effective treatments are needed for PTSD. At least a third of PTSD patients fail to respond to established PTSD psychotherapies or do not respond in a clinically significant manner [31-33]. In the U.S. National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In both subgroups, more than a third of the patients still had symptoms several times per week after 10 years [34]. Forty to 60% of PTSD patients were found to be resistant to treatment in this study. In a comparison of two types of psychotherapy for women with PTSD after sexual assault in 2002, 47% of each treatment group still satisfied diagnostic criteria for PTSD based on Clinician Administered PTSD Scale (CAPS) scores, an outcome which was considered highly efficacious [35]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [26] and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [36]. These findings suggest that there is still a substantial need for innovative treatments for PTSD.

Another treatment approach is to develop drugs and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies [37-39]. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [40, 41], although some patients may need more than one type of treatment to reduce or resolve those symptoms [28]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including those listed above, are similarly effective with PTSD [42]. In recent years, there has been a growing amount of research into drugs and other methods that may augment the effectiveness of

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psychotherapy for PTSD (see [43] for a review). Examples of this are virtual reality-assisted exposure therapy [44-47] and D-cycloserine-assisted psychotherapy [48]. MDMA-assisted psychotherapy is another such approach.

3.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative. Chemists at the Merck pharmaceutical company first synthesized it in 1912 [49, 50], though its clinical effects were not subject to formal investigation until the 1980s. MDMA is a potent monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [51-56].

MDMA acutely decreases activity in the left amygdala [57], a brain region involved in interpretation of negative cues, and attenuates amygdalar response to angry faces [58]. This action of MDMA is compatible with its reported reduction in fear of emotional injury or defensiveness [59]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [58]. A recent study in healthy volunteers found correlations between oxytocin (OT) levels, amygdalar volume, and extraverted personality [60].

OT is a neuropeptide associated with pair bonding and social affiliation in mammals that also attenuates amygdalar response to anxiogenic stimuli [61, 62]. OT administration is associated with increased interpersonal trust and changes in social perception, including attenuated reactivity to threatening faces [63-66]. MDMA elevates OT in peripheral blood [67-69], which is an imperfect but somewhat reliable indicator of elevated OT in the brain [62]. Findings of an association between elevated OT and detectable MDMA in peripheral blood were first reported in a naturalistic study of London nightclub attendees with and without detectable serum MDMA levels [67]. Dumont and colleagues reproduced these results in humans and found that MDMA significantly elevated peripheral plasma OT levels in a placebo-controlled study in healthy volunteers [68], in addition to a positive association between elevated levels of OT and prosocial feelings. Hysek and colleagues replicated these results and reported that administering a serotonin reuptake inhibitor, but not a norepinephrine uptake inhibitor nor several adrenergic antagonists, attenuated the effects of MDMA on OT levels, suggesting a serotonergic mechanism in producing elevated OT [69]. The effects of MDMA on OT may influence empathy or compassion for self and others, decrease defensiveness, and strengthen therapeutic alliance. The multi-level effects of MDMA on monoaminergic signaling and OT, combined with a therapeutic setting, are more likely to provide the opportunity for a corrective emotional experience than OT alone, and could be useful in the treatment of PTSD.

3.3 Previous Clinical Experience with MDMA

Classification as a Schedule I drug in the United States has hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible due to an open IND with

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 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 ... [46]

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the FDA [70]. The first double-blind, placebo-controlled U.S. Phase 1 study sanctioned by the FDA was conducted at Harbor-UCLA Medical Center in 1994, with findings that suggested MDMA may cause a statistically significant increase in body temperature, heart rate, and blood pressure in some healthy volunteers [71]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [68, 71-76]. The elevation in body temperature noted in healthy volunteers was not clinically significant in sponsor-supported studies at normal ambient temperatures [1, 77]. As of May 2013, MDMA has been administered to more than 845 research subjects, in both Phase 1 and Phase 2 studies, and the sponsor has not been informed of or seen published reports of any unexpected MDMA-related Serious Adverse Events (SAEs) in research studies [1, 51, 54, 58, 59, 68, 69, 71, 72, 74, 76-108].

The potentially therapeutic effects of MDMA were initially investigated in a dose response pilot study funded by MAPS in Spain, in six female survivors of sexual assault with treatment-resistant PTSD [78, 109]. In this study, doses ranging from 50 mg to 75 mg demonstrated mild signs of improvement without any adverse events (AEs) or signs of deteriorating mental health [109].

MAPS sponsored the first U.S. Phase 2 randomized, placebo-controlled study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, designated as MP-1. MP-1 demonstrated promising results in a sample of 20 subjects [77]. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded Independent Rater (IR) at baseline, three to five days after each experimental session, and at two-month follow-up. Data from this randomized, placebo-controlled pilot study suggests that MDMA is associated with significantly greater improvement in PTSD than placebo (N=20) [77]. Two months after treatment with MDMA-assisted psychotherapy, 83.3% (8 of 12) of the subjects no longer had a PTSD diagnosis and exhibited a 68% drop in CAPS global severity scores. Twenty five percent (two of eight) of the subjects in the placebo and psychotherapy group no longer had a PTSD diagnosis and exhibited a 26% drop in CAPS global severity scores. Seven of the eight subjects receiving placebo went through the treatment program again to receive full dose MDMA. The crossover subjects experienced a 48% drop in CAPS scores and none of these subjects qualified for a PTSD diagnosis at the end of the study, establishing that subjects receiving placebo were not more resistant to treatment. Evaluation of subjects on an average of 45.4 months after receiving MDMA-assisted psychotherapy indicates that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [3]. PTSD symptom severity in subjects who completed the CAPS at long-term follow-up (mean CAPS scores 23.7±22.8, N=16) were statistically equivalent on average to the end of the treatment program (mean CAPS scores 24.6±18.6, N=16) [3].

The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland with three experimental sessions,

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The ASIQ is 25-item self-report measure of suicidal ideation and behavior

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designated as MP-2. The study results suggested a trend toward significant improvement in subjects receiving full dose MDMA, when compared to a 25 mg active placebo MDMA at two-month follow-up [1]. The improvement continued to increase during the 12-month follow-up [1].

In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that enrolled five subjects, with no drug-related Serious Adverse Events (SAEs).

Overall, the results of these studies suggest that MDMA-assisted psychotherapy may be safe and effective in these subjects regardless of trauma etiology.

3.4 MDMA-assisted Psychotherapy for PTSD

MDMA-assisted psychotherapy is an innovative mode of treatment that combines therapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of therapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to therapy. MDMA is capable of inducing unique psychopharmacological effects, including:

- Decreased feelings of fear.
- Increased feelings of wellbeing.
- Increased sociability and extroversion.
- Increased interpersonal trust.
- Alert state of consciousness.

Early observers noted increased acceptance of self and others, increased tolerance of emotionally upsetting materials, and the ability to address these issues without extreme disorientation or ego loss [110-113]. In the U.S., MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists in the treatment of neuroses, relationship problems, and PTSD [110, 111, 114, 115] before it was placed in Schedule I in 1985, as a result of extensive non-medical use [59, 113, 116]. Placement in Schedule I prohibited it for use, except in a federally approved research setting in the U.S.

In contrast to daily administrations of SSRIs, MDMA-assisted psychotherapy consists of several drug-assisted sessions interspersed with a moderate course of non-drug psychotherapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [117, 118]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [119]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

Many psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in psychotherapy with an appropriate level of emotional engagement [5]. To be effective, exposure must be accompanied by a degree of emotional engagement or “fear activation” while avoiding dissociation or overwhelming emotion [120]. This has been referred to as working within the “optimal arousal zone” or “window of tolerance” [121-123]. When given in an appropriate setting, MDMA produces increased positive mood, facilitates recall and imagination, changes in emotion perception, and social affiliation [58, 68, 69, 103, 124]. These effects are thought to permit revisiting of trauma-associated memories, thoughts, and feelings while maintaining the window of tolerance.

In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [59]. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients, as it appears to stimulate spontaneous engagement in elements of conventional therapies, such as exposure therapy, psychodynamic therapy, and internal family systems therapy in the therapeutic context. Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms, interrupting and counteracting the stress-induced neurobiological abnormalities that may be associated with the condition. The biologic and therapeutic approaches are intended to overlap and reinforce each other.

A combined treatment of MDMA and psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [77, 109, 111, 113]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [110]. Subjects are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-assisted psychotherapy may enable the subjects to restructure their perspective and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

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 outweighed by the possibility that this treatment may offer significant

benefits. A comprehensive review of MDMA research is included in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

3.5 Purpose

This Phase 2 pilot study is a randomized, double-blind, dose comparison study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment.

After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.

A therapy team will conduct psychotherapy visits according to the treatment manual provided. The team will include two licensed therapists who will work together as co-therapists.

4.0 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. 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 U.S. 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 Harmonization (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 will be considered 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 will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

5.0 Informed Consent

The Clinical Investigator is responsible for overseeing informed consent is obtained in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. The informed consent discussion must be conducted by a person who is qualified according to regulations. Written information about the trial will be provided in an understandable Informed Consent Form (ICF). Written consent must be given by the subject. The ICF document must be explained and the subjects' questions must be answered. The subject should have the opportunity to inquire about details of the MDMA-assisted session and to consider participation.

The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive active dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint visit when unblinding occurs. Unblinding and debriefing at the primary endpoint will take place with the co-therapist team and the subject. During the debriefing, subjects will be informed of the contents of the investigational product they received during the blinded experimental sessions in Stage 1.

In addition to the explanation of study visits, the ICF should include that access to original medical records and processing of coded personal information must be authorized. Written consent to take part in the study includes giving the Clinical Investigators permission to view the subject's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible subjects may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol, including screening activities). The process of obtaining informed consent should be documented in the subject source records. The therapists will provide a copy of the signed ICF to the subject and will maintain the original in the ISF.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised ICF and written information should receive approval from an IRB before use. The subject should be informed in a timely manner if new information becomes available that might affect the decision to take part in the MDMA-assisted session. The communication of this information should be documented.

Subjects can withdraw consent at any time without prejudice. If a subject withdraws consent but does not revoke Health Information Protection Act (HIPA), the Clinical Investigators will have access to the subject's study related medical records and data will be used. If a subject revokes consent and HIPA, the Clinical Investigators will have access to the subject's medical records prior to the date and time of revocation but the data will not be used.

6.0 Study Objectives

The overall objective of this study is to examine whether the full dose of MDMA versus the comparator dose of MDMA used in conjunction with manualized psychotherapy will reduce or attenuate PTSD symptoms as evaluated by standard clinical measures and to collect safety data.

6.1 Primary Objective

- Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

6.2 Secondary Objectives

The following objectives will compare full dose subjects to comparator dose subjects in Stage 1:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.

- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint.

The following objectives will compare effects in specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

The following objectives will include exploratory analyses intended to inform protocol design:

- Explore the effects of each experimental session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effect of the third experimental session for full dose subjects in Stage 1 and Stage 2 using CAPS, PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, and DES-II.
- Assess the ability of the Clinical Investigators and subjects to accurately guess condition assignment in Stage 1.
- Correlate adherence to the treatment manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.

6.3 Safety Objectives

The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- Vital signs (blood pressure, heart rate, and temperature) and Subjective Units of Distress (SUD) will be measured during each experimental session. Comparisons will be made for SUD scores and vital signs between each condition.
- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.

- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

7.0 General Investigational Plan

7.1 Recruitment and Subject Population

Subjects may be men or women aged 21 or older with a confirmed diagnosis of chronic, treatment-resistant PTSD who have undergone psychotherapeutic or psychopharmacological treatment for PTSD of adequate dose/duration without achieving remission. Subjects who discontinued PTSD treatment due to inability to tolerate psychotherapy (e.g. due to persistent "over-engagement") or psychopharmacology due to treatment-emergent side effects would not be excluded. Subjects will also not be excluded for having more than one traumatic event. Subjects must have a CAPS score equal to or greater than 60 and meet all inclusion criteria and no exclusion criteria at baseline. They must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Seven of 12 subjects will be randomly assigned to receive the full dose and five subjects will be randomly assigned to receive the comparator dose.

Study subjects will be Canadian residents recruited by letters of referral sent to psychiatrists and psychotherapists, written advertisements, announcements placed on appropriate Internet sites and the sponsor site, and through word of mouth. Site staff will interview prospective subjects by telephone to learn if they meet basic eligibility criteria. If the prospective subject is interested in taking part in the study, the Clinical Investigators will provide the prospective subject with consent materials for review and consideration.

7.2 Enrollment Criteria

7.2.1 Inclusion Criteria

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

1. Meet DSM-IV criteria for current PTSD, with a CAPS score of 60 or higher, indicating moderate to severe PTSD symptoms;
2. Have chronic PTSD, defined as PTSD persisting for longer than 6 months; subjects may have experienced one or more traumatic event;
3. Have treatment-resistant PTSD, who were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to either:

- a. Inability to tolerate psychotherapy for PTSD (e.g. persistent “over-engagement” when attempting Prolonged Exposure Therapy).
 - b. Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;
4. Are at least 21 years old;
5. Are willing to commit to medication dosing, experimental sessions, follow-up session and completion of evaluation instruments;
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician;
7. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the Clinical Investigators to communicate directly with their therapist. Subjects may not change therapists, increase the frequency of therapy, or commence any new type of therapy until after the evaluation session at the end of Stage 1 or Stage 2, as applicable;
8. Agree to refrain from taking, for one week preceding each experimental session:
 - a. Any herbal supplement (except with prior approval of the research team).
 - b. Any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
 - c. Any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
Note: Must have physician’s approval;
9. Agree to take nothing by mouth except alcohol-free liquids after midnight the evening before the experimental session. Subjects must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each experimental session;
10. Are willing to remain overnight at the clinic after each experimental session until the integrative session occurring the next morning. An attendant with previous training in managing psychological distress will be present to assist with personal needs if requested and offer dinner and breakfast;
11. Are willing to locate an individual to drive them home the morning after the experimental sessions, after the integrative session. If a subject is unable to locate someone to transport them home, the Clinical Investigators will assist the subject in obtaining transport from the clinic to the subject’s home or any other location where he or she is staying temporarily;
12. Are willing to be contacted via telephone on a daily basis by one of the Clinical Investigators for a week after each experimental session;

13. Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by Clinical Investigators in the event of a subject becoming suicidal;
14. Agree to inform the Clinical Investigators within 48 hours of any planned medical interventions;
15. Have a negative pregnancy test and must agree to use an effective form of birth control, if the participant is a female of childbearing potential;
16. Are literate and proficient in reading documents written in English and speaking English;
17. Agree to have all clinic visit sessions recorded to audio and video;
18. Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.

7.2.2 Exclusion Criteria

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

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control;
2. Have a history of, or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder;
3. Have dissociative identity disorder or an eating disorder with active purging;
4. Have evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, cardiac, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, or any other medical disorder judged by the Principal Clinical Investigator to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);
5. Have hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia;
6. Weigh less than 48 kg;
7. Have used "Ecstasy" (illicit drug preparations purported to contain MDMA) more than five times in the last 10 years or at least once within six months of enrollment;
8. Would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, as determined through psychiatric interview, responses to C-SSRS and through clinical judgment of the Principal Clinical Investigator;
9. Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
10. Meet DSM-IV criteria for active substance abuse or dependence for any substance other than caffeine or nicotine in the past 6 months;
11. Are not able to give adequate informed consent;

12. Have any current problem, which in the opinion of the Principal Clinical Investigator or Medical Monitor, might interfere with participation in the study.

7.3 Planned Duration of Study and Visit Windows

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months
- Comparator dose subjects who complete Stage 2: 18 months

Screening may take up to two months, with the baseline CAPS being conducted no more than 8 weeks before the first experimental session, leaving room for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, and one additional week for stabilization. For example, the maximum washout would be 7 weeks for subjects tapering off of fluoxetine plus one week for stabilization. Preparatory sessions should be scheduled approximately one week apart, with the first experimental session taking place 3-5 weeks after enrollment, and at most 8 weeks after the baseline CAPS. The maximum window from the start of screening to the first experimental session is 13 weeks. The optimal timing for Stage 2 is one month after the primary endpoint visit in Stage 1, with a maximum allowable window of five months. Any delay between visits would result in a corresponding extension of study duration.

8.0 Drug Description and Dosage

Subjects assigned to the full dose condition will receive three experimental sessions with an initial dose of 125 mg possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 62.5 mg MDMA. Subjects in the comparator dose condition will be assigned to receive two experimental sessions with an initial dose of 50 mg MDMA possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 25 mg MDMA. Seven of 12 subjects, or 58%, will be assigned to the full dose condition, and five of 12, or 42%, will be assigned to the comparator dose condition.

Subjects in the comparator dose condition during Stage 1 will have the opportunity to cross over to Stage 2. Stage 2 will be used to explore the optimal therapeutic dose using a clinical titration dosing strategy using varied active doses of MDMA. In Stage 2 subjects will receive an initial dose of 100 mg followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg MDMA during the first experimental session. In the second and third session they will receive an initial dose of 100 mg or 125 mg MDMA followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg or 62.5mg as appropriate to the initial dose of MDMA. The decision to titrate the dose in the second and third session will be based on the experience of the first session, if 100mg MDMA does not seem to be the optimal therapeutic dose based on the first experimental session in Stage 2, the dosage may be increased by an increment of 25mg

in order to achieve the optimal therapeutic dose. The supplemental doses for each experimental session will be half of the initial dose, respectively.

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [71, 72, 74, 75, 124, 125]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [74, 75, 91, 126-128]. Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [59, 111, 113]. The initial full 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 drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions.

The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD. The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension [72, 109, 129]. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

8.1 MDMA Compounding, Doses, and Labeling

The investigational product (IP) for the study is MDMA. Bulk IP will be received at the pharmacy via a secure delivery system in accordance with all local regulations. A receipt will be kept on file at the pharmacy and at the site. Six strengths of IP will be created: 125 mg, 100 mg, 62.5 mg, 50 mg, 25 mg and 12.5 mg. Each of these batches will be created with the bulk MDMA and varied amounts of lactose during the compounding process. A "packing stat" will be created by filling 10 capsules with lactose to calibrate the amount of compounded IP per capsule. Once encapsulated, the total number of capsules will be recorded on the drug accountability log.

The encapsulation will be performed by a pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all capsules have similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging.

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

Figure 1. Examples of Drug Labels

Holding Box Labels

Holding Box Label
MAPS Study# MP-4
Investigational Product: MDMA
Dose: XXmg
Lot #: XXX
Restricted drug for clinical trial use by Qualified investigator only

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Amendment 1 Version 2
 June 20, 2013

Stage 1 Primary Container Labels

Blinded	Open Label Session 3
<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 1 Blinded Experimental Session # _____ Container # XXX Lot # XXX Expiry date: XXX Store at 22°C</p> <p>Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 1 Open Label Experimental Session #3 Container # XXX 125mg & 62.5mg MDMA Lot # XXX Expiry date: XXX Store at 22°C</p> <p>Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>

Stage 1 Inner Envelope Labels

Blinded	Blinded
<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4 Stage 1 Container # XXX Initial Dose Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4 Stage 1 Container # XXX Supplemental Dose Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>
Open Label Session 3	Open Label Session 3
<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4 Stage 1 Open Label Container # XXX Initial Dose 125mg MDMA Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4 Stage 1 Open Label Container # XXX Supplemental Dose 62.5mg MDMA Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>

Stage 2 Primary Container Labels

Open Label	Open Label	Open Label
<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 1 Container # XXX 100mg & 50mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C</p> <p>Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 2 Container # XXX 100+25mg & 50+12.5mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C</p> <p>Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060 Study # MP-4 Stage 2 Experimental Session # 3 Container # XXX 100+25mg & 50+12.5mg MDMA Lot #: XXX Expiry date: XXX Store at 22°C</p> <p>Subject # _____ Restricted drug for clinical trial use by Qualified investigator only</p>

Stage 2 Inner Envelope Labels

Unblinded Session 1

Inner Envelope
MAPS Study # MP-4
Stage 2 Open Label
Experimental Session # 1
Container # XXX
Initial Dose 100mg MDMA
Subject # _____
Restricted drug for clinical trial use by
Qualified investigator only

Unblinded Session 1

Inner Envelope
MAPS Study # MP-4
Stage 2 Open Label
Experimental Session # 1
Container # XXX
Supplemental Dose
50mg MDMA
Subject # _____
Restricted drug for clinical trial use by
Qualified investigator only

Unblinded Session 2 or 3

Inner Envelope
MAPS Study # MP-4
Stage 2 Open Label
Experimental Session # _____
Container # XXX
Initial Dose 100mg MDMA
Open Label
Subject # _____
Restricted drug for clinical trial use by
Qualified investigator only

Unblinded Session 2 or 3

Inner Envelope
MAPS Study # MP-4
Stage 2 Open Label
Experimental Session # _____
Container # XXX
Initial Dose increment
25mg MDMA
Subject # _____
Restricted drug for clinical trial use by
Qualified investigator only

8.2 MDMA Accountability

Forms will be provided to track drug accountability and administration throughout the study. Blinded drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all provincial and national regulations and forms pertaining to the use of controlled substances in Canada, and forms will be maintained by the pharmacist.

Each primary container label will contain a unique container number for the drug assigned to a single experimental session. The container numbers will be used to track drug administration in the Source Record and the drug administration log. The web-based randomization system will enable tracking of blinded primary containers for drug accountability purposes.

8.3 MDMA Storage and Handling

MDMA is a Schedule III compound in Canada and the pharmacist will store and handle it in compliance with relevant Federal and Province regulations. The pharmacist will be responsible for storing and dispensing the MDMA in accordance with all regulatory requirements. The IP will be stored at room temperature in a locked safe at the pharmacy and only the pharmacist will have access to it.

IP will only be removed for a single experimental session at a time and will be administered orally at the office of the Principal Clinical Investigator (PI). All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each experimental session. Supplemental doses are provided for each experimental session but are optional to use. In addition, the clinical titration doses with corresponding supplemental dose are provided in Stage 2 session 2 and 3 and are optional to use.

The pharmacist will dispense one primary container with the appropriate container number to the PI before each experimental session. If the PI decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the Pharmacist for return to the pharmacy safe. At the end of the study, the Sponsor will be consulted to determine the course of action if there is any unused IP remaining.

9.0 Method

This Phase 2 pilot study is a randomized, double-blind, dose-response study in 12 subjects comparing the effect size of comparator dose to full dose MDMA as an adjunct to manualized MDMA-assisted psychotherapy. A therapy team will conduct psychotherapy visits according to the treatment manual provided. The team will be two licensed therapists who will work together as co-therapists. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 of the study will consist of two blinded experimental sessions for all subjects and one open-label experimental session for full dose subjects, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. Each subject will be unblinded after completion of outcome measures at the primary endpoint, one month after the second experimental session in Stage 1. A blinded IR will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session as well as the equivalent time points in Stage 2. After unblinding, full dose subjects will have one more full dose session in Stage 1 and comparator dose subjects will have the opportunity to cross over to open-label Stage 2, which will be used to explore the optimal therapeutic dose for cross over subjects. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2. This study will provide an estimate of effect size based on a dose comparison of PTSD symptoms to MDMA-assisted psychotherapy.

9.1 Randomization

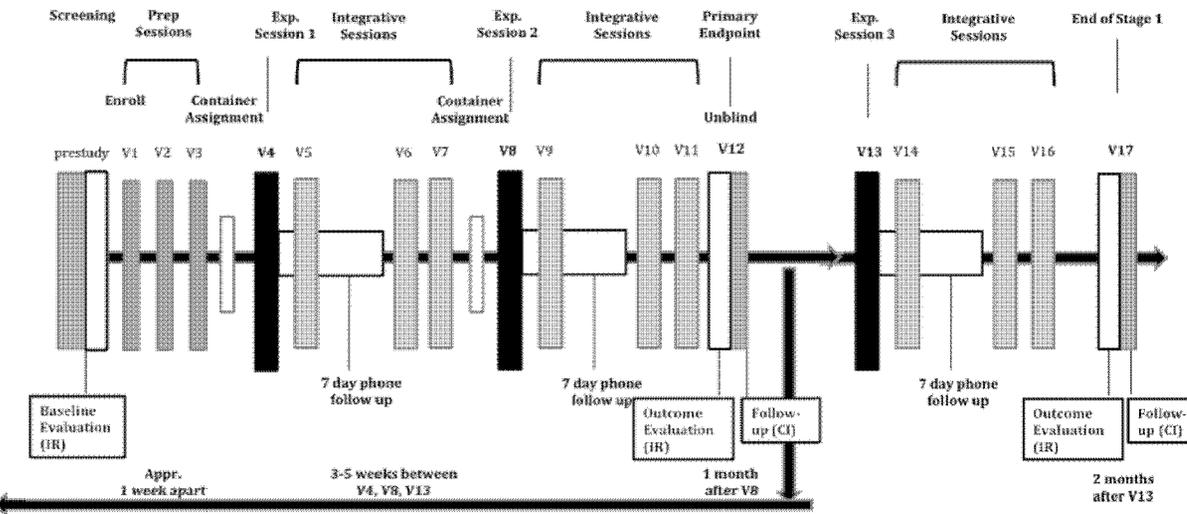
In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions. An unblinded randomization monitor will generate the randomization list prior to enrollment of subjects. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject's sequential subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. Blinded personnel will conduct all study evaluations in the randomized portion of the study until the blind is broken for each subject at the primary endpoint per protocol via the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

The therapists, the Independent Rater, and all site personnel except the pharmacist will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of the subject's condition assignment, the blind may be broken for an individual subject by contacting the Sponsor's Randomization Monitor. In most cases it should be sufficient to inform the treating physician for the emergency that the subject had received a minimum of 50mg MDMA and a maximum of 125mg MDMA with a supplemental dose of 62.5mg MDMA.

9.2 Subject Numbering

Prior to enrollment, subjects will be tracked with a secondary identifier number and a screening number assigned sequentially starting at "001". Subjects who meet the enrollment criteria will be enrolled in the study and assigned a 5-digit subject number. The first two digits identify the study site. The next three 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 04001, second 04002, etc.

Stage 1 Summary of Events



Stage 2 Summary of Events

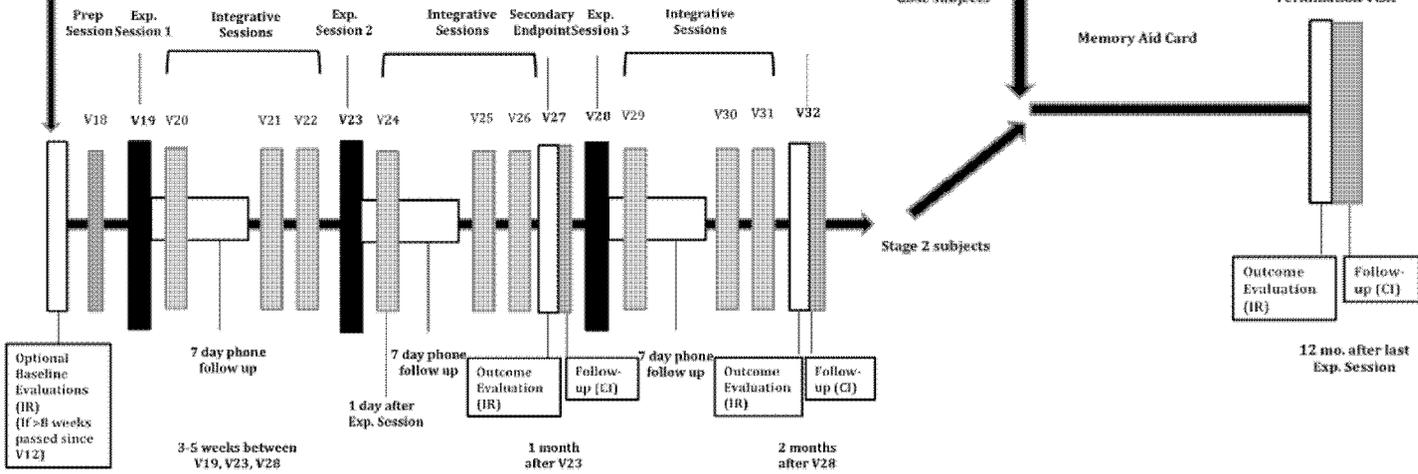


Table 3. Time & Events Stage 1

Study Phase	Screen/ Baseline	Preparatory Sessions	Experimental Session 1		Experimental Session 2		Primary Endpoint	Experimental Session 3		End of Stage 1
Visit #	V1	V1, V2, V3	V4	V5, V7	V8	V9, V11, V12	V13	V14, V15, V16	V17	
Type of Visit	Screening/Baseline	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Integrative	Outcome	
Visit Timing	Up to 2 months prior to V1	1 week apart	1-5 weeks post-baseline	Between V4 and V5	1-5 weeks post V4	Between V8 and V12	1 month post V8	Between V14 and V16	2 months post V16	
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID-IV (R)	✓									
Clinical Lab Tests with HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Medication Taper (if applicable)		✓								
Study Enrollment (if eligible)		✓								
Record to Audio/Video		✓	✓	✓	✓	✓	✓	✓	✓	
General Wellbeing	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Pregnancy Screen (if applicable)	✓						✓			
Obtain Container Assignment			✓		✓					
CAPS, GAF, BDI-II, NEO-PI, PSQI	✓						✓		✓	
PTGI, DES-II	✓						✓		✓	
RRANS/PASAT	✓						✓		✓	
PDS	✓			✓	✓	✓	✓	✓	✓	
S-SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Administer Drug + Therapy		✓	✓	✓	✓	✓		✓		
Monitoring of BP, Pulse, and Temp.		✓	✓	✓	✓	✓	✓	✓	✓	
SCID			✓	✓	✓	✓	✓	✓	✓	
Belief of Condition Assignment			✓	✓	✓	✓		✓		
Overnight Stay, SOCC			✓	✓	✓	✓	✓	✓	✓	
Integrative Therapy Session				✓	✓	✓		✓		
7 Days Integrative Telephone Contact				✓	✓	✓		✓		
AEs Requiring Medical Attention			✓	✓	✓	✓	✓	✓	✓	
Serious Reported Reactions & All AEs			✓	✓	✓	✓	✓	✓	✓	
Changes in Tinnitus and/or Pain	✓		✓	✓	✓	✓	✓	✓	✓	
AEs of Psychiatric Status or Withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	
Issue Mynarx Aid Card			✓	✓	✓	✓		✓		
Unblinding							✓		✓	
Perception of Experimental Sessions							✓		✓	
RRPO							✓		✓	

Amy Emerson 6/17/13 9:36 PM
Comment: Add a note that says see section xxx for visit windows???

A... First integrative session is one day after experimental session; B... At least 24 hours prior to experimental session; C... Approximately six hours post MDMA; D... At the beginning of the session; E... As needed; F... Approximately every 60 minutes; G... Given on 2nd preparatory session after washout; H... Only for subjects starting LITRU; I... Every face to face visit and Day 2 and Day 7 phone calls only; J... Reactions collected for seven days post experimental session; K... On the day of the first integrative session following the experimental session; L... One month after the second experimental session but before the third experimental session; M... On the day of the third integrative session; N... After unblinding for full dose subjects only; O... Only on Visit 1; P... Only in subjects with pre-existing tinnitus and/or chronic pain; Q... All measures listed except for the NEO-PI.

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9.3 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.

Eligibility for the study will be determined based on psychiatric diagnoses confirmed during screening through medical history, the Structured Clinical Interview for Diagnoses (SCID-I-RV) and the CAPS.

9.3.1 Outcome Measures

The primary outcome measure will be the CAPS, a clinician-administered measure for PTSD diagnosis and assessment of symptom intensity and frequency. A qualified, blinded IR will perform the CAPS at baseline and outcome measurement time points according to the Time and Events Table. The IR will not be present during the subject's experimental sessions nor have any information regarding the experimental sessions. Subjects will be instructed not to inform the IR of any beliefs they or others have concerning their condition assignment during the evaluation session. The CAPS provides a standardized method to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the subject'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 interview takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [130, 131].

The secondary measure of PTSD symptoms will be the PDS, a self-report measure designed to follow DSM-IV criteria for assessing PTSD. The measure is derived from the Posttraumatic Symptom Scale – Self Report (PSS-SR), a measure also intended to tap into diagnostic criteria for PTSD. The PDS contains 49 items, with responses made on a four-point scale, ranging from 0 ("not at all") to 3 ("five or more times a week"). The PDS consists of a list of 12 potential traumatic events, 12 items addressing elements of the traumatic event, of 17 symptom items, and nine items assessing impact on areas of life function [132]. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The 17 items are summed to create a symptom severity scale. Cronbach's alpha for the symptom severity scale is 0.92. The PDS has test-retest reliability of 0.74 after a two-week and one-month interval, and subscales are inter-correlated, with correlations ranging from 0.73 to 0.82, and PDS scores have a moderate to good correlation with SCID-I-RV diagnosis, with kappa = 0.65 [132]. Subjects will complete the PDS questionnaire at baseline, after the first and third experimental sessions, at the primary endpoint, at the end of Stage 1, and equivalent time points in Stage 2 and at the Long Term Follow-up, as specified in the Time and Events Table.

The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the

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self or others. The Independent Rater administering the CAPS will perform the GAF assessment. The GAF will serve as a measure of global functioning and will be performed at the same times the CAPS is administered.

The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [133, 134]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions. Subjects will complete the PTGI according to the Time and Events table.

The BDI-II is a 1996 revision of the BDI, a 21-item self-report measure [135, 136], that will serve as a measure of depression according to DSM-IV criteria [137]. The BDI-II has been validated, has high internal consistency and good test/re-test reliability and is not overly sensitive to daily variations in mood. It takes five to 10 minutes to complete [137]. Score cutoffs indicate: 0-13 minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression. Higher scores indicate more severe depressive symptoms. Subjects will complete the BDI-II according to the Time and Events table.

The NEO-PI will serve as a measurement of personality [138, 139]. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model. Subjects will complete the NEO-PI according to the Time and Events table.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. Possible responses range from 0 to 4 on a five-point scale [140]. The PSQI consists of seven sub-scales: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to 10 minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach's alpha of 0.83 [140, 141]. Global scores correlate with other measures of alertness and self-reported sleep quality [142]. Subjects will complete the PSQI according to the Time and Events table.

The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory [143, 144]. It is an established measure of dissociative symptoms. The scale consists of statements describing facets of dissociation. Respondents indicate how often the specific experience happens to them, from "never" to "always." Responses on the original scale were made via visual analog scales. The DES-II uses the same items but with responses made on a 10-point scale from "0%" to "100%"

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of the time. The scale is scored by treating percentages as single digits to produce a total score. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms [143]. Reliability of the DES-II is high (ranging from 0.79 to 0.96 in an early review), and a reported Cronbach's alpha of 0.95 [144, 145]. There may be a relationship between experiencing dissociation and occurrence of chronic PTSD [144, 146]. Subjects will complete the DES-II according to the Time and Events table.

9.3.2 Safety Measures

Safety measures will be applied as described below to minimize risks associated with drug-assisted psychotherapy sessions. The Clinical Investigators will be available via mobile phone or pager throughout the study to ensure subject safety.

Safety measures, including vital signs and a measurement of psychological distress, will be assessed during all experimental sessions. Subjects will rate their current degree of subjective distress with the SUD scale, which is a single-item self-report scale. The SUD will be completed repeatedly during the experimental sessions, with the degree of distress marked along seven points. Results of the SUD are intended to assist therapists in maintaining subject safety during experimental sessions.

The therapists will assess general wellbeing during each preparatory session, on each integrative session and during telephone calls for seven days. Results of this scale are intended to assist therapists in maintaining subject safety throughout the study.

During the course of each MDMA-assisted psychotherapy session, the Subjective Units of Distress (SUD) scale will be used to assess degree of psychological distress experienced at various points during the session. Subject and Clinical Investigator beliefs concerning subject condition assignment (either full dose or comparator) will be assessed during the non-drug psychotherapy session occurring on the day after each experimental session. Neither the SUD scale nor condition assignment beliefs measures are outcome measures.

The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [147]. It assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation and behavior. The C-SSRS consists of a series of questions, and can be administered during face-to-face interview or over the telephone. C-SSRS scores are sensitive to changes in suicidal ideation or behavior over time, and the measure demonstrates good convergent validity with other measures of suicidality [148]. The C-SSRS will be performed by the PI at baseline, and repeated throughout the protocol to assess suicidality. See the Time and Events Table for a detailed schedule.

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The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [149] is a relatively brief battery of assessments for cognitive function. It consists of 12 subtests that cover verbal and visual memory and attention and takes approximately 30 minutes to administer. Tasks include recall of lists, figures and stories, picture naming, semantic fluency, copying a figure, digit span and coding, and line orientation. Scores on the RBANS subtests can be used to obtain a total score and five index scores: attention, immediate memory, delayed memory, language and visuospatial/constructional scores. Factor analyses of the RBANS and samples of veterans and people with schizophrenia suggest that the RBANS possesses two factors rather than five [150, 151]. The RBANS has alternate forms, allowing repeated administration. Test performance by healthy controls were distinguishable from performance by people with probable Alzheimer's disease or the neurodegenerative condition Huntington's disease [152], and the test has high split-half reliability, with coefficients ranging from 0.80 to 0.88 [149]. Test-retest reliability is good for total RBANS scores in healthy controls and psychiatric patients [153]. The RBANS has been used in community-based and psychiatric samples [150, 154] and in a prospective investigation of the effects of chemotherapy upon cognitive function [155]. Each administration of the RBANS will use one of parallel forms of RBANS, and each participant will not complete the same form twice. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

The Paced Auditory Serial Addition Test (PASAT) is a measure of psychomotor speed, auditory information processing and computation ability [156]. The PASAT was originally designed to assess recovery after traumatic brain injury, and has been used subsequently to assess cognitive function in other populations [156, 157]. It takes approximately ten to 15 minutes to administer. The measure involves the addition of a series of digits presented at a three or two second interval, with responses made by adding each number to the prior digit. The PASAT consists of two alternate forms, permitting repeated administration. PASAT scoring includes collecting number of correct and incorrect responses, time to response (latency of response) and any failure to respond. There was a positive correlation between responses on the PASAT and a non-numerical paced measure. The measure is internally consistent (Cronbach's alpha of 0.90), and it has high test-retest reliability, with reliability ranging from 0.90 to 0.97 [157-159]. The first administration of the PASAT will use one of the two alternate forms, and the second administration will use the other. This measure was employed as a means of assessing safety after two sessions of MDMA-assisted psychotherapy for PTSD [77]. See Time and Events Table for a detailed schedule.

Cardiovascular effects will be assessed via blood pressure and pulse measurement. Blood pressure and heart rate will be assessed periodically during each experimental session by an automatic blood pressure (BP) and pulse monitor. Blood pressure and pulse will be measured at the outset of the experimental session, and once approximately every 30 minutes for the first four hours of the experimental session, and once every hour, or as needed, thereafter. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic, or pulse of 110 are exceeded. Blood pressure will also be measured more frequently if there are symptoms, such as chest pain, shortness of breath or neurological symptoms that may be indicative of hypertension. The therapists will

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measure subject body temperature approximately every 60 to 90 minutes. Cardiovascular effects will be assessed via BP measurement. The timing of these measurements will be adjusted so they do not interfere with the therapeutic process.

A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain [160-162]. The changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from “None” to “Worst Case Imaginable”. This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD [161, 163-165]. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response [161, 164, 165].

All AEs and spontaneously reported reactions will be collected, as described in Section 14.0. AEs and spontaneously reported reactions may be collected during face-to-face visits or over the telephone. Common reactions that are spontaneously reported are collected for seven days after each experimental session on a separate CRF page and will be categorized as mild, moderate, or severe.

9.3.3 Process Measures

All sessions after enrollment may be recorded to audio and video, including introductory, integrative and experimental sessions for research and training purposes. These recordings will be used for further development of the manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.

The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues [166, 167]. Subjects respond to the SOCQ using a six-point Likert-type scale anchored at 0=none at all and 5=extreme (more than ever before in my life). It has seven subscale scores: internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. The measure is a self-report instrument and takes approximately 20 to 30 minutes to complete. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day.

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)

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[168]. Subjects will complete this measure during their final study visit, roughly six weeks after the last experimental session. The RRPQ is intended to assess the subject's experience as a research subject, perceived reasons for consenting to be a research subject and perceived freedom to take part in the study, and is a process measure.

Questions regarding the belief of condition assignment and certainty of the belief will be asked of the therapists and subjects at the integrative session on the day after each blinded experimental session in Stage 1. Each therapist responsible for treating the subject will indicate their belief of condition assignment and certainty based on the full dose (125mg) and comparator dose (50mg) groups. In line with informed consent obfuscation, where the comparator dose is not revealed, subjects will initially be asked if they believe they received MDMA or not during this assessment. If they believe they received MDMA, they will be asked about what dose they think they received. These beliefs are collected as a part of the sponsor's ongoing initiative to optimize the double-blind as a part of dose response studies.

Perceptions of the experimental sessions will be collected from each full dose subject during the primary endpoint visit after unblinding and from Stage 2 subjects during the secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage 2. Perceptions will be collected again at the end of Stage 1/Stage 2 according to the Time and Events Table. These perceptions are collected as a part of the sponsor's ongoing initiative to assess the therapeutic value of the third experimental session and information on the optimal therapeutic dose of MDMA.

The long-term follow-up questionnaire has been developed internally by the Sponsor to assess long-term benefits and harms of MDMA-assisted psychotherapy at the long-term follow-up visit.

9.4 Visit Descriptions

9.4.1 Prescreening, Screening, and Baseline Evaluation (Pre-study)

Prospective subjects will be prescreened by telephone according to an IRB-approved script to learn if they meet basic eligibility criteria. All individuals who are prescreened should be assigned a screening number and recorded on the Subject Screening Log where information on the selection of potential subjects in the trial should be collected.

Upon signing the IRB-approved informed consent form (ICF), the potential subject may commence study-related screening activities. The screening number should also be recorded on the signed ICF. If a subject is enrolled, the study staff should record the enrollment date and assign a subject number. If a subject is not enrolled, an explanation should be recorded on the Screening Log. A CRF will not be completed for subjects who are not enrolled. These subjects will only be documented on the Screening Log and source records. It is the responsibility of the PI to file the Screening Log in the Investigator Site File (ISF) to be readily available for on-site monitoring and/or inspection by relevant authorities.

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Screening may take place over more than one day and should be complete by up to two months prior to enrollment. Screening may take up to two months, with the baseline CAPS being conducted no more than 8 weeks before the first experimental session, leaving room for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, plus one week for stabilization. If the CAPS is completed outside of this window for a subject, the PI should consult the Sponsor CRA and Medical Monitor to determine if the baseline CAPS should be repeated. The maximum window from the start of screening to the first experimental session is 13 weeks. If, after reviewing all information, the PI concludes that a subject is eligible, they will enroll the subject in the study. Visits will be scheduled consecutively as described in the Time and Events Table.

- a. Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any tests or evaluations for the study.
- b. Assign the subject a screening number. Complete the Screening Log.
- c. Review the ability of females of childbearing potential to become pregnant and their commitment to practice appropriate birth control as determined by the PI for the treatment period of the study.
- d. The PI will obtain medical and psychological history by interview.
- e. The PI will collect information on pre-study and current medications.
- f. Tinnitus and chronic pain symptom severity will be collected using a visual analog scale in subjects with a medical history of these conditions.
- g. A physician will perform a general physical examination. The examination will involve the following procedures:
 - Blood pressure.
 - Pulse.
 - Height.
 - Weight.
 - Body temperature.
 - Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities.
 - Brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function).
 - Electrocardiogram (ECG).
 - Serum electrolytes, metabolic profile, urinalysis and complete blood count
 - Thyroid stimulating hormone (TSH), free T3, and free T4.
 - Human Immunodeficiency Virus (HIV) serology.
 - Urine-dip pregnancy test on females with childbearing potential.
 - Urinary drug test.
 - C-SSRS to assess past and current suicide risk.

Results of HIV serology will be kept confidential, and appropriate referral for counseling may be necessary in accordance with local law. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the subject's source record. Clinically significant abnormal values will be captured as medical history in the CRF. If, upon examination, there are questions raised about

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possible medical problems, the PI will request a review of subject medical records and request additional tests or assessments as indicated.

A blinded Independent Rater who will not be present during any of the therapy sessions will administer:

- Structured Clinical Interview for Diagnoses I Research Version (SCID-I-RV) to assess eligibility based on Axis I diagnoses, which includes a self-report questionnaire to focus on modules to use based on symptoms.
- CAPS to assess PTSD symptoms and eligibility, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
- GAF to assess general psychological function.
- PASAT to assess cognitive function.
- RBANS to assess cognitive function.

The subject will complete the following self-report measures:

- PTGI (in reference to time since the trauma)
- PDS to assess self-reported PTSD symptoms
- BDI-II to assess depression symptoms
- NEO-PI to assess changes in personality
- PSQI to assess changes in sleep quality
- DES-II to assess dissociation symptoms

9.4.2 Preparatory Psychotherapy Sessions - Visits 1, 2, 3 (Stage 1), 18 (Stage 2)

Subjects who do not complete all screening activities will not be enrolled. Eligibility may be discussed by phone after screening is complete and at the time Visit 1 is scheduled but the final confirmation will occur at Visit 1. If all inclusion criteria and no exclusion criteria are met, the subject will be enrolled and issued a subject number.

During Visit 1:

- Complete a final review of Inclusion/exclusion criteria.
- Assess general wellbeing.
- Confirm eligibility and willingness to participate in study.
- Assess general wellbeing.
- Ensure medical history and medication history is complete. After enrollment new events will be collected as AEs and new medications will be collected as described in Section 14.0 of the protocol.
- Discuss medication tapering, if applicable. Upon confirmation of eligibility, the PI will consult the prescribing physician to initiate medication tapering for subjects who must refrain from taking a psychiatric medication for the study. Tapering will follow a time course appropriate for the medication as specified in the Medication Tapering Table in Section 14.4 of the protocol, with the first experimental session scheduled to occur one week after complete washout.

The subjects will undergo three preparatory sessions lasting 90 minutes with their therapist team, prior to their first experimental session. The first preparatory session will

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take place at Visit 1 after enrollment confirmation. Preparatory sessions should be scheduled approximately one week apart, with the first experimental session taking place 3-5 weeks after enrollment, and no more than 8 weeks \pm 1 week after the baseline CAPS. In Stage 2 (for comparator dose crossover subjects), only one preparatory session will take place prior to their first full dose open-label experimental session, as described in the Time and Events Table.

Adherence criteria for preparatory sessions should be completed as a part of one of the three sessions. These elements do not have to be accomplished in any specific order or in every preparatory session. Generally, adherence criteria for these sessions include that the therapists will work with the subject to prepare for MDMA-assisted psychotherapy. The therapists and subject will seek to form a strong working relationship with each other, and they will help the subject prepare for upcoming experimental sessions. Preparatory sessions will promote a safe set and setting for confronting trauma-related memories, emotions, and thoughts, which is intended to develop therapeutic alliance.

During the preparatory sessions:

- a. Therapists may record all sessions to audio and video. Subjects may review recordings from these sessions upon request.
- b. Collect AEs and Medications as described in Section 14.0 of the protocol.
- c. The therapists will inquire about any possible changes in the subject's health to ensure that subject continues to meet eligibility criteria and if applicable, will confirm that the subject has appropriately tapered off of medications.
- d. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
- e. The subject and therapists will discuss goals for the experimental session and will review what will happen during the experimental session, following standard procedures and techniques discussed in the treatment manual.
- f. Prior to the experimental session, the therapists will introduce the subject to the attendant that will remain with the subject during each overnight stay after each MDMA-assisted psychotherapy session. The attendant will be an individual with previous training in managing psychological distress.
- g. If a subject would like a companion present during or after the experimental session, a meeting between the therapists and that individual will be scheduled prior to the first experimental session. There must be mutual agreement between the subject and therapists concerning the presence of the companion.
- h. The therapists will administer the C-SSRS just prior to beginning the second preparatory session, unless a subject is still undergoing medication washout. Subjects still undergoing medication washout will complete the C-SSRS during the second preparatory session or at a point after washout is complete prior to the first experimental session.
- i. Assess general wellbeing at each preparatory session.

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- j. During the third and last preparatory session, give the Reminder of Study Rules to the subject, which includes instructions and restrictions for conduct prior to receiving the drug. Subjects must agree to:
- Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the experimental session.
 - Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within twenty-four hours of each experimental session.
 - Not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until therapists deem it safe to do so.

9.4.3 Experimental Sessions - Visits 4, 8 (Stage 1), 13, (Full Dose Group Stage 1), 19 23, 28 (Stage 2)

Experimental sessions of MDMA-assisted psychotherapy should be scheduled approximately three to five weeks apart. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions. The dose of the drug and blinding procedures will vary based on the stage of the study.

Adherence criteria for experimental sessions should be completed as a part of each experimental session. These elements do not have to be accomplished in any specific order. Generally, adherence criteria for these sessions include that the therapists will create and communicate a setting of safety and support the subject during periods of inner focus. Therapists will use a largely nondirective approach, following the lead of the subject's inner healing intelligence. Therapists will provide encouragement for staying present with difficult experiences. Therapists may occasionally offer gentle guidance or redirection as a choice to encourage collaborative exploration if the subject repeatedly avoids trauma related material. Therapists will inquire about somatic symptoms and if necessary encourage release of tension through movement, in whatever way feels appropriate to the subject. Therapists will use music to support the experience without being intrusive.

Pre-drug:

- At least 24 hours prior to the first experimental session the subject will be randomized. The PI will obtain the container assignment using a web-based randomization program prior to the blinded sessions.
- On the day of the experimental session, the subject will arrive approximately 60 to 90 minutes prior to drug administration.
- Confirm continuing eligibility by reviewing inclusion/exclusion criteria.
- Perform a urine drug screen. A positive drug screen will be reviewed by the PI and may be cause for delaying drug administration to a later time, rescheduling the session to a later date, or withdrawing the subject from the study.
- If a woman is of childbearing potential, perform a urine pregnancy test. A positive pregnancy screen is cause for withdrawal from the protocol.
- If the subject continues to meet criteria and the subject reports that they followed appropriate rules and restrictions, the session will proceed.

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- g. Review procedures for the experimental session with the subject.
- h. Record the entire session to video and audio if possible. Subjects may review audio or video recordings of their experimental sessions upon request.
- i. The session will last for approximately eight hours or longer, followed by an overnight stay at the study site.
- j. The therapists will administer the C-SSRS prior to drug administration.
- k. Before drug administration, discuss and review the subject's goals, intentions and concerns and some of the commonly experienced effects of MDMA.
- l. Instruct the subject not to use caffeine or nicotine two hours before or six hours after the dose of drug.
- m. Subject body temperature will be measured at baseline prior to initial dose administration and approximately every hour after that. The therapists may make more frequent measurements if body temperature exceeds more than 1°C above baseline.
- n. Subjects will complete the SUD at baseline prior to initial dose administration. Subjects will complete the SUD every 60 to 90 minutes, until the session is over, allowing a window of up to 30 minutes to fit into the psychotherapy process where a natural break occurs. If necessary, the therapists can make a greater number of measurements as their clinical judgment dictates.
- o. Measure blood pressure and pulse at baseline prior to the experimental session, and once every half-hour throughout the experimental session if the established thresholds for normal blood pressure and pulse have not been exceeded for the duration of the experimental session. More frequent measures will be taken if the established thresholds of 160 systolic, 110 diastolic, or pulse 110 are exceeded. Measurements should be taken more frequently 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 PI to be safe. The therapists may also make more frequent measurements if a subject exhibits symptoms indicative of hypertension.

During:

- p. At approximately 10:00 in the morning, subjects will receive the initial dose of drug along with a glass of water.
- q. The subject will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided if the subject wishes to use them. Subjects may speak to the therapists whenever they wish, who will provide guidance and support as needed.
- r. After the first hour, if the subject has not spoken spontaneously, check in with him/her about the nature of the experience. For the rest of the experience, as appropriate, the therapists will support and encourage the subject in emotional processing and resolution of whatever psychological material is emerging as described in the treatment manual.
- s. Record any spontaneously reported reactions during the session.
- t. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
- u. Provide water and electrolyte containing fluids throughout the session but not to exceed 3L overall.

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- v. An optional supplemental dose half the size of the initial dose may be administered approximately 1.5 to 2.5 hours after the initial dose unless contraindicated.
- w. Provide food during the latter part of the session.
- x. If there is a companion who has previously been asked and has agreed to be present during part or all of the MDMA-assisted session, that person may arrive during the session at whatever time has been agreed upon, but will wait in the waiting room until brought back to the session room by one of the therapists. Alternatively, the support person may arrive after the session has ended.
- y. If it is appropriate to do so, initiate the first question of the C-SSRS at any point in the session if the subject is experiencing significant psychological distress that does not respond readily to processing with the therapists according to the methods described in the treatment manual. The C-SSRS is required at least once during the session. It is preferable to administer it towards the end of the session at about six hours after the initial dose.
- z. End the session if all medical and psychiatric parameters are acceptable and the subject is alert, ambulatory, and emotionally stable.

Table 5. Example Schedule of Procedures and Measures for Experimental Sessions

Approximate Time	Procedure or Action
9:00	Urine drug screen, pregnancy test, C-SSRS
9:45	Baseline BP, pulse, SUD
9:55	2 nd Baseline BP, pulse, BT, SUD
10:00	Drug Administration , begin recording to audio and video
10:30	BP, pulse
11:00	BP, pulse, SUD, BT
11:30	BP, pulse, May administer supplemental dose
12:00	BP, pulse, BT
12:30	BP, pulse, SUD
13:00	BP, pulse
13:30	BP, pulse, BT
14:00	BP, pulse, SUD
Every hour, and as needed	BP, pulse
Every 60 to 90 minutes	SUD, temperature
Approximately six hours after administration	C-SSRS, General Wellbeing

Post-drug:

- aa. Give the subject the SOCQ to be completed after the end of the experimental session and prior to leaving the treatment facility the next day.
- bb. The therapists will depart the site when they have concluded that the subject is emotionally and medically stable. Clinical Investigators shall remain available to subjects during the experimental session and for one week after via twenty-four-hour cellular phone for integration as needed.
- cc. If the PI decides not to administer any optional supplemental or clinical titration doses, as described in Section 8.3, in a given experimental session, the unused

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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 reside near the offices of Dr. Pacey, and both can quickly return to

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capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the pharmacy safe.

dd. Spontaneously reported reactions, AEs, and Medications will be collected as described in Section 14.0 of the protocol.

Subjects will remain overnight in an appropriately furnished room at the study site. With the approval of the therapists, a companion may accompany the subject during the overnight stay. An attendant will check in periodically on the subject during the overnight stay, even if a companion is present. The attendant will monitor subject condition and will help subjects relax during the overnight stay. The attendant will be an individual with some previous training in managing psychological distress. If there is an emergency or the subject needs additional support, the attendant can contact the therapists. The subject and a companion (if applicable) will receive information that will allow them to contact the therapists during the overnight stay in the case of an emergency or request for additional support. Subjects 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.

9.4.4 Integrative Sessions 24 Hours after Experimental Session - Visits 5, 9 (Stage 1), 14 (Full Dose Group Stage 1), 20, 24, 29 (Stage 2)

On the morning after each experimental session, both of the therapists from the subject's team will meet with the subject during a 60 to 90-minute integrative therapy session.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or all in each and every integrative session. Generally, adherence criteria for these sessions include discussing material that emerged during experimental sessions and helping subjects integrate their experiences both internally and into daily life. Therapists will validate the choices of the subject about how much they wish to communicate their thoughts, feelings and experiences at this time, but will elicit enough information to be able to assess the subject's level of emotional stability and state of emotional and physical wellbeing. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone for additional meetings if needed. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative psychotherapy sessions:

- The integrative psychotherapy session may be recorded to audio and video. Subjects may review these data upon request.
- The therapists will administer the C-SSRS during each integrative session.
- Prior to integrative psychotherapy, the subject and both therapists will indicate their beliefs concerning subject condition assignment.
- Discuss and review events that occurred with the subject during the experimental session, including thoughts, feelings, and memories. If necessary, the therapists will

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Participants will remain overnight in an appropriately furnished room in the offices of Dr. Pacey. 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

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- help the subject to reduce any residual psychological distress he or she is experiencing. The therapists will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in experimental sessions to emotionally threatening everyday situations. The therapists will be supportive, validating the experience and facilitating understanding and emotional clearing.
- The therapists will remain accessible any time the subject needs support outside the scheduled integration sessions.
 - Assess the subject's mental health, general wellbeing and the presence of any remaining reactions during integrative psychotherapy immediately after each experimental session.
 - Integrative psychotherapy sessions can also serve as an opportunity for the therapists to gather information about the effects of the drug on the subject in an unstructured manner.
 - If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
 - After the integrative psychotherapy session following the experimental session, a person previously selected by the subject will provide a ride home to the subject. If the subject 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 subject due to unforeseen events, the therapists will assist the subject in finding an alternative means of returning home.
 - Spontaneously reported reactions, AEs, and Medications will be collected as described in 14.0 of the protocol.
 - Remind the subjects that they will have daily phone contact for the next seven days.

9.4.5 A Week of Daily Contact

During daily phone contact:

- Clinical Investigators will follow the most recent version of the treatment manual in all matters relating to follow-up subsequent to the experimental psychotherapy sessions.
- Starting on the day of the integrative psychotherapy session following each experimental session, one of the therapists will contact the subject via telephone or in person on a daily basis for one week. The goal of daily contact is assessment of changes in general wellbeing, safety of the subjects, and offering support for subjects.
- The integrative phone contact will be for a brief check-in lasting five to 15 minutes, or as long as necessary to address any subject's concerns and to assess subject's wellbeing. Additional telephone contact can be initiated at the request of the therapists or subject.
- On the second and seventh day of phone contact after the experimental session, the therapists will administer the C-SSRS.
- General wellbeing will be assessed at each phone call.
- Spontaneously reported reactions, AEs, and Medications will be collected as described in Section 14.0 of the protocol.

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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 [... [68]

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9.4.6 Integrative Psychotherapy Between Experimental Sessions - Visits 6, 7, 10, 11, (Stage 1), 15, 16, (Full Dose Group Stage 1), 21, 22, 25, 26, 30, 31 (Stage 2)

In addition to the session the morning after each experimental session, the subject will have two additional integrative psychotherapy sessions with the therapists lasting 90 minutes with the therapists between each experimental session and in the month following the last experimental session. The therapists may conduct more sessions if they and the subject deem it necessary.

Adherence criteria for integrative sessions should be completed as a part of one of the three sessions following each experimental session. These elements do not have to be accomplished in any specific order or in each integrative session. Generally, adherence criteria for these sessions include integration of material that emerged as a part of experimental sessions and afterward into daily life. Therapists will emphasize their commitment to support the subject during the integration period and will be available via phone or pager. Subjects will be encouraged to relax and rest as much as possible for several days after the experimental session.

During integrative psychotherapy sessions:

- a. Record each integrative session to audio and video if possible. Subjects may review these recordings upon request.
- b. The C-SSRS will be administered just prior to beginning each integrative session.
- c. General wellbeing will be assessed at each integrative session.
- d. If subjects who have pre-existing tinnitus or chronic pain mention any changes, use the visual analog scale to collect the changes in symptoms.
- e. The subject will complete the PDS questionnaire on the third integrative session after the first and third experimental sessions, according to the Time and Events Table.
- f. The subject and therapists will continue to work on supporting the subject as she or he considers his or her experiences during experimental sessions.
- g. The therapists will use clinical judgment to assess the subject's psychological wellbeing during this period of time. If there are any indications of continuing anxiety or distress, the therapists may arrange to work on reducing the distress at a specially scheduled integrative therapy session, through continuing contact, or at the next regularly scheduled integrative therapy session. The subject may also initiate contact with the therapists at any time throughout the study.
- h. Collect AEs and medications as described in Section 14.0 of the protocol.
- i. NOTE: If an integrative session falls within the period of telephone contact and additional phone call is not required that day, all data normally collected during the telephone call will be completed in person.

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9.4.7 Evaluation at Primary Endpoint and Unblinding - Visit 12 (Stage 1)

The primary endpoint evaluation in Stage 1 will occur one month (within a window of plus or minus two weeks) after the second blinded experimental session. This visit will consist of two meetings that may be completed on separate days, one with the Independent Rater and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point one month after their last experimental session.

At the primary endpoint:

- a. Subjects will meet the Independent Rater for at least an hour and a half.
- b. The blinded Independent Rater will administer:
 - CAPS to assess PTSD symptoms, which may be recorded to video in as many instances as necessary to establish inter-rater reliability.
 - GAF to assess general psychological function.
 - PASAT to assess cognitive function.
 - RBANS to assess cognitive function.
- c. The subject will complete the following self-report measures:
 - PTGI to assess post-traumatic growth (in reference to start of the study)
 - PDS to assess PTSD symptoms.
 - BDI-II to assess depression symptoms.
 - NEO-PI to assess changes in personality.
 - PSQI to assess changes in sleep quality.
 - DES-II to assess dissociation symptoms.
- d. After completing all assessments and measures, the subject will meet with the therapists for approximately 30 minutes.
- e. The therapists will assess suicidality with the C-SSRS.
- f. General wellbeing will be assessed.
- g. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- h. The blind will be broken for the subject's condition assignment. Only the Independent Rater will remain blind to condition assignment at this time.
- i. If the subject was assigned to receive the comparator dose, the therapists will discuss continuation to Stage 2. Comparator dose subjects will not complete the third experimental session and associated integrative sessions in Stage 1.
- j. Collect perceptions of experimental sessions from full dose subjects after unblinding.
- k. Collect AEs and medications as described in Section 14.0 of the protocol.
- l. If the subject was assigned to receive full dose MDMA, the subject will complete a third open-label experimental session, with associated daily phone calls and integrative sessions in Stage 1.

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9.4.8 End of Stage 1 - Visit 17 (Full Dose Group Stage 1)

Full dose subjects will repeat outcome measures and meet with the therapists again two months (within a window of plus or minus two weeks) after their final open-label experimental session, which will be their final visit in Stage 1. This visit will consist of two meetings that may be completed on separate days, one with the Independent Rater and the other with the therapists.

At the end of Stage 1:

- a. The Independent Rater will administer the CAPS, GAF, RBANS and PASAT.
- b. Subjects will complete the PDS, BDI-II, DES-II and PSQI, PTGI (in reference to start of the study).
- c. Full dose subjects who complete Stage 1 and comparator dose subjects who elect not to participate in Stage 2 will complete the RRPQ and continue on to the Long-term Follow-up.
- d. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- e. The therapists will assess suicidality with the C-SSRS.
- f. Collect perceptions of experimental sessions.
- g. Subjects who will continue on to the Long-term Follow-up may return to taking psychiatric medications after the End of Stage 1 if necessary.
- h. Subjects who will continue on the Long-term Follow-up will receive a memory aid card for use between their End of Stage 1 visit and the 12-month follow-up. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the termination visit. Memory Aids will not be collected.
- i. Collect AEs and medications as described in Section 14.0 of the protocol.

9.4.9 Open-label Stage 2 (Comparator Dose Subjects from Stage 1)

During Stage 2:

- a. Subjects will be reminded that participation in Stage 2 is voluntary and optional.
- b. Subjects who elect to cross over to Stage 2 will undergo the same course of therapy and evaluation as in Stage 1, with the exception that the subject will complete a single preparatory psychotherapy session instead of three (see Section 9.4.2), and varied active doses of MDMA will be administered in an open-label context to explore the optimal therapeutic dose (e.g. without unblinding). Visits will be scheduled consecutively according to the Time and Events Table.
- c. Assessment of PTSD symptoms at the primary endpoint will serve as baseline assessments in Stage 2. If the start of Stage 2 is delayed for more than 8 weeks from the primary endpoint (Visit 12) to the first preparatory session in Stage 2 (Visit 18), the Independent Rater will re-administer the CAPS and GAF. The subjects will complete the PDS, BDI-II, PSQI, PTGI (in reference to start of the study), and the DES-II. These scores will be used as the baseline for comparison to assessment at the secondary endpoint and end of Stage 2.
- d. Experimental sessions will be conducted according to procedures described in Section

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9.4.3.

1. During the first experimental session, subjects will receive a 100mg initial dose of MDMA and may receive a 50mg optional supplemental dose of MDMA.
 2. At the beginning of the second and third experimental sessions, the co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg initial dose of MDMA. If a 100mg initial dose of MDMA is selected, an optional supplemental dose of 50mg MDMA may be administered. If a 125mg initial dose of MDMA is selected, an optional supplemental dose of 62.5mg MDMA may be administered
 3. If the PI decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the pharmacy safe.
- e. Integrative sessions will be conducted according to procedures described in Sections 9.4.4 and 9.4.6.
 - f. Phone calls will be conducted according to procedures described in Section 9.4.5.
 - g. At the secondary endpoint based on procedures described in Section 9.4.7, the Independent Rater will administer the CAPS and GAF. Subjects will complete the PDS, BDI-II, PSQI, PTGI (in reference to start of the study), and DES-II as described in the Time and Events Table.
 - h. At the end of Stage 2 based on procedures described in Section 9.4.8, the Independent Rater will administer the CAPS, GAF, RBANS and PASAT. Subjects will complete the PDS, BDI-II, DES-II, PSQI, PTGI (in reference to start of the study), and NEO-PI as described in the Time and Events Table.
 - i. The End of Stage 2 will be completed in the same manner as the End of Stage 1 as described in Section 9.4.8.
 - j. Clinical Investigators will follow the most recent treatment manual in all matters relating to the psychotherapy sessions.

9.4.9 Long-term Follow-up

All subjects will be evaluated for long-term effects 12 months (within a visit window of plus or minus one month) after their last MDMA-assisted psychotherapy session. This visit will consist of two meetings, one with the Independent Rater and the other with the therapists. Subjects who have withdrawn from treatment but have continued for follow-up will also complete this time point. This visit may be audio and video recorded.

At the Long-term Follow-up visit:

- a. The Independent Rater will administer the CAPS and GAF.
- b. Subjects will complete the PDS, BDI-II, NEO-PI, PSQI, PTGI (in reference to start of the study), and DES-II.
- c. Subjects will have a final meeting with at least one of the therapists to review specified AEs and medications since the last visit. Subjects should bring the Memory

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- Aid Cards to this visit, to be used as aids in recollection. These cards will not be collected. AEs and Medications will be collected as described in Section 14.0 of the protocol.
- d. The therapists will assess suicidality with the C-SSRS.
- e. Subjects will complete a questionnaire assessing positive and negative long-term effects of the study.
- f. A researcher who is a part of the study team may ask the subject questions about positive or negative effects about the study in person or on the phone.
- g. The visual analog scale will be used to collect changes in pre-existing tinnitus and chronic pain symptoms.
- h. Subjects will complete the termination visit at this time.

10.0 Removal of Subjects from Therapy or Assessment

Subjects can withdraw consent at any time without prejudice. The PI 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 elements of the protocol that are critical for safety and/or for the scientific integrity of the study. If the PI withdraws a subject from the study, the PI will explain the reason for withdrawing the subject. The reason for early termination will be recorded in the subject's source records and CRF.

Subjects will be clinically monitored after withdrawal, the cause of which will be recorded in the subject's source records and CRF. Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI and/or sponsor.

If the subject develops any exclusion criteria, which in the opinion of the Medical Monitor, affects the safety of the subjects (including psychiatric diagnosis, pregnancy or excluded medications), the subject will discontinue treatment but remain in the study for follow-up purposes. Whenever possible, the tests and evaluations listed for the primary endpoint and 12-month follow-up will be carried out. Efforts will be made to obtain information about AE outcomes, if deemed necessary by the PI, Medical Monitor and/or Sponsor.

Subjects who discontinue treatment prior to the primary endpoint will be replaced. Individuals who replace these subjects will be assigned the next available subject number. Subjects who discontinue treatment after the primary endpoint in Stage 1 or after continuation to Stage 2 will not be replaced. If Stage 1 subjects discontinue treatment before the primary endpoint, the site should contact the randomization monitor for replacement instructions. Detailed instructions will be provided to the site in a separate document.

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11.0 Premature Discontinuation of the Study

The sponsor or the PI (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the PI 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 and will be treated in accordance with national and provincial regulations.

12.0 Data Analysis

The sponsor will judge the clinical and statistical significance of the study based on a comparison of observer-blind data collected at baseline and the primary endpoint using the primary outcome measure, which is the CAPS. Descriptive statistics will be computed overall and within the two dose conditions for all available data from outcome measures, including minimum, maximum, average, and standard deviation. Distributional characteristics will be examined for outliers and extreme values and, if either is evident, nonparametric statistics will be utilized in the analysis. Cohen's techniques will be used to estimate effect sizes between conditions for all outcome measures for Stage 1, Stage 2, and 12-month follow-up.

The sponsor will examine full dose and comparator dose groups for homogeneity through comparing demographic characteristics. There is no expectation that conditions will differ in composition by gender, race or ethnicity, duration of PTSD diagnosis or presence versus absence of other permitted psychiatric disorders, as depression. However, owing to small sample size, such variations may arise by chance.

The sponsor will examine CAPS scores for the primary outcome analysis at baseline and the primary endpoint in full dose and comparator dose conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05.

For exploratory purposes, the sponsor will examine PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, and DES-II scores at baseline and the primary endpoint in full dose and comparator dose conditions using difference scores, and independent sample t-tests will be used to test for significance between groups, with p value set at 0.05. Changes in outcome measures from the primary/secondary endpoint to the 2-month follow-up in Stage 1/Stage 2 will be compared for a within-subject analysis with p value set at 0.05 to see whether a third session produces further decline in symptoms.

An exploratory repeated measures analysis of variance (ANOVA) will be performed upon PDS scores at baseline, after each experimental session, at the primary endpoint, and at the end of Stage 1 with p value set at 0.05. Condition will serve as a between-subjects factor. Results of ANOVA analysis will be used to examine the effects of each experimental session on self-reported PTSD symptom severity. PDS and CAPS scores may be correlated via Pearson's product moment correlation at baseline and the primary

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endpoint to provide a comparison of a self-report measure with a clinician-administered measure of PTSD symptoms.

Formal statistical comparisons between Stage 1 and Stage 2 scores may only occur if, at minimum, three subjects complete Stage 2. Data from the open-label third experimental session in Stage 1 will be compared statistically to Stage 2 data, and data from this session will only be utilized if they are equivalent to Stage 2 data.

The sponsor will compare CAPS, PDS, GAF, BDI-II, PSQI, PTGI, and DES-II, scores at the final assessment prior to the 12 month follow-up to the 12-month follow-up using difference scores in an independent t-test for a within-subject analysis with p value set at 0.05.

The sponsor will compare baseline and primary endpoint RBANS and PASAT scores in full dose and comparator dose conditions using difference scores in an independent sample t-test to test for significance between groups, with p value set at 0.05. The sponsor will examine the effects of maximal exposure to MDMA on neurocognitive function using the RBANS and PASAT by performing a within-subject repeated measures ANOVA with time of administration as a within-subjects factor and with p. set at 0.05.

The sponsor will collect Changes in Tinnitus and/or Pain visual analog scale scores from any subject reporting tinnitus or chronic pain during each point of administration, including baseline, experimental and integrative sessions, the primary endpoint, and two-month follow-up. The sponsor will plot out and examine all Changes in Tinnitus and/or Pain visual analog scale scores across both groups and in the full dose and comparator dose groups for trends. Formal analysis of Changes in Tinnitus and/or Pain visual analog scale scores will only occur if three or more subjects complete Changes in Tinnitus and/or Pain visual analog scale at baseline and primary endpoint. Likewise, formal between-groups analyses will not be performed if all primary endpoint scores are from subjects assigned to the same condition. The sponsor will perform an independent t-test on the difference between baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores in the full dose and comparator dose conditions, with p. set at 0.05. If the only scores available are for subjects in a single condition, then a paired t-test will be performed comparing baseline and primary endpoint Changes in Tinnitus and/or Pain visual analog scale scores, with p. set at 0.05.

Descriptive statistics will be computed for vital signs and subjective distress during each experimental or open-label session. The sponsor will compare peak blood pressure, heart rate, and body temperature for subjects after sessions with full dose MDMA or comparator dose MDMA whenever possible. Frequency tables will be produced on prevalence of spontaneously reported reactions and AEs.

The sponsor will collect ratings of adherence to the treatment manual from specifically selected types of sessions. Descriptive statistics will be computed for each adherence scale within a specific type session. The sponsor will explore the factors and structure of the measures of adherence to assist in further development of adherence and competence measures. If sufficient data is available, the sponsor will correlate the mean adherence

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On the basis of findings from research in humans

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

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

The first US phase II trial with MDMA to be completed in September, 2008, was conducted in an outpatient setting with a "crash cart" of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately ten minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study MDMA was administered on 51 different occasions at a dose of either 125 mg. by mouth or 125 mg. followed in 2.5 hours by an additional 62.5 mg. Blood pressure, pulse and temperature were closely monitored, but never reached levels that required intervention, nor were there any other medical problems requiring treatment during the MDMA sessions. Subsequently a similar study has been approved

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ratings for adherence scale and session type with Global CAPS scores to investigate the effects of adherence to the treatment manual on reduction in PTSD symptoms. If it is found that there are specific factors within the adherence scales, then the factor will be correlated with global CAPS score.

The sponsor will compute descriptive statistics for SOCQ scores from after each MDMA-assisted psychotherapy session, and average SOCQ scores for blinded experimental sessions will be compared between conditions. The data will be explored for effects of condition on domain scores in the SOCQ.

Perception of experimental sessions will be examined during Stage 1 and Stage 2, before and after subjects have undergone a third experimental session. The results of this analysis will inform the sponsor of expectancies and the value of the third session for future protocol development. These data may be correlated with difference scores calculated from the primary/secondary endpoint CAPS data compared to end of Stage 1/Stage 2 CAPS data to assess the potential contribution of expectation and self-reported response to changes in PTSD symptoms.

Subjects who discontinue treatment prior to the primary endpoint will be asked to complete an outcome assessment prior to continuing to the long-term follow-up. The data from these subjects will be tested for equivalence to data from subjects completing the study per protocol. If found to be equivalent, data from these subjects will be presented as an exploratory intent-to-treat analysis to examine results without bias towards subjects more likely to complete the study per protocol.

An interim analysis may be completed when all subjects have completed Stage 1 and Stage 2, but not all subjects have completed the 12-month follow-up evaluation. Additionally, an interim analysis may be performed after all subjects have completed Stage 1 but not necessarily before all eligible subjects complete Stage 2. This analysis will address safety, efficacy and process measures. Results of the interim analysis will have no effect on study conduct.

12.1 Statistical Power

This study is a pilot investigation intended to estimate effect sizes of 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. Analyses of MAPS' completed US study of MDMA-assisted psychotherapy in 20 people with PTSD found an effect size of 1.24 for treatment efficacy, as represented by changes in CAPS score [77]. The estimated effect size for this study may be lower as a result of comparing the full dose of MDMA with a comparator dose of MDMA instead of with inactive placebo. The sponsor intends to combine effect size estimates to develop a dose response curve as a meta-analysis of CAPS scores across MAPS-sponsored pilot studies.

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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 0.75 for the impact of two sessions of MDMA-assisted psychotherapy on symptoms [169], reducing the effect size to account for the hypothesized effects of using a comparator dose. The software calculated an estimated power of 0.21, indicating an underpowered study. Had we used the higher effect size of 1.1, power analysis still indicates that this study is underpowered, with an estimated effect size of 0.37. Statistical power estimates were not available for secondary and exploratory measures, as they were previously not used in sponsor-supported studies.

13.0 Risk Mitigation

Careful review of medical screening data will be utilized to exclude potential subjects with pre-existing exclusionary medical conditions from the study. Study procedures have been developed to mitigate the risks of receiving MDMA described in detail in the IB. Ambient temperature will be kept at a comfortable level during experimental sessions. Subjects will not be allowed to drink more than 3L of fluids over the course of the experimental session, and fluid intake will be spread out appropriately during the session. Fluids administered will include electrolytes. If a subject exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an experimental session, the subject will not receive an other experimental session unless it is approved by the PI and the Medical Monitor.

13.1 Medical Emergencies

Psychotherapy sessions will take place in the offices of the PI. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. They can be heated or cooled with fans. One therapist can reach the offices within five to 10 minutes of contact if necessary. The study site will contain equipment for assessing blood pressure, pulse, and body temperature and there will be an automatic external defibrillator (AED) on site. The Clinical Investigators will maintain basic life support (BLS) certification or its equivalent in Canada in cardiopulmonary resuscitation (CPR) including training in using an AED. The site is five minutes from the University of British Columbia emergency department and eight to 15 minutes away from St. Paul's Hospital emergency department. In the event of a medical emergency paramedics will be summoned and study subjects will be transported to either hospital as appropriate. This is an adequate level of emergency backup based on experience with previous Phase 2 studies in the U.S. and Switzerland during which there have been no adverse events during experimental sessions requiring emergency treatment.

The first U.S. Phase 2 trial with MDMA was conducted in an outpatient setting with a "crash cart" of emergency equipment on hand and an emergency physician and nurse in the building. The estimated transport time from this site to the nearest hospital emergency department was approximately 10 minutes with an estimated response time for an emergency medical services ambulance of approximately eight minutes. In this study, MDMA was administered on 51 different occasions at a dose of either 125 mg by mouth or 125 mg followed in 2 to 2.5 hours by an additional 62.5 mg. Blood pressure, pulse, and

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temperature were closely monitored but never reached levels that required intervention nor were there any other medical problems requiring treatment during the MDMA-assisted sessions. Subsequently, a similar study was completed in Switzerland and was conducted in an outpatient psychiatry office, approximately five minutes from the nearest hospital without a crash cart or emergency personnel on site. The Swiss Clinical Investigators have administered 125 mg followed by 62.5 mg MDMA on 39 occasions and administered 150 mg MDMA on four occasions without medical incident.

14.0 Adverse Events

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

An *unexpected adverse event* is one that is not listed in the current IB or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the PI and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the PI as:

- Mild: No limitation in normal daily activity.
- Moderate: Some limitation in normal daily activity.
- Severe: Unable to perform normal daily activity.

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

- “Not Related”: The AE is not related if exposure to the investigational product has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject’s pre-existing condition.
- “Possibly Related”: The administration of the investigational product and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational product.

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

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

14.1 Serious Adverse Events

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

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

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

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

14.2 Adverse Event Collection

The PI will be responsible for reviewing and confirming all AEs and SAEs collected during the study. The PI will collect AEs during study visits after enrollment.

All SAEs will be collected for the duration of the protocol. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours of the PI’s awareness of their occurrence. All SAE

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reports should be faxed to the Sponsor. A fax number will be provided to the site in separate site-specific instruction for SAE reporting. In addition to the fax, the PI, or designee should call the CRA during normal working hours and verbally inform the CRA of the SAE. During off business hours or if medical advice is needed immediately please call the Sponsor Medical Monitor. An SAE reporting instruction with all contact numbers will be provided to the site prior to study start.

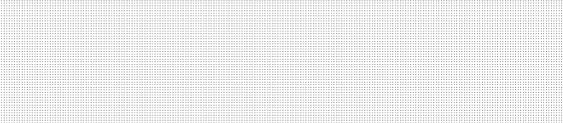
SAE Reporting:

MAPS Office

Telephone: 831-429-6362, ext. 104

Fax: 831-429-6370

Medical Monitor:



Study Monitor contact information will be provided in a separate contact list.

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

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- All SAEs will be collected through subject termination.
- All AEs and spontaneously reported reactions will be collected on the day of drug administration and for seven days after each experimental session.
- Events requiring medical attention will be collected from enrollment through the subject's last two-month follow-up.
- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any Adverse Event leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

A Memory aid card will be provided to the subject on the last visit prior to the 12-month follow-up to record information on medications taken to treat SAEs, AEs leading to withdrawal and psychiatric AEs during the follow-up period between the end of Stage 1/Stage 2 and the 12-month follow-up evaluation. The memory aid card will not be collected, but information from the card will be used to aid the subjects in providing information to the Clinical Investigator. This information may be collected by phone.

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Additional adverse events collected for seven days after each experimental session are: -
<#>Common side effects.
<#>Exacerbation of anxiety. -

Collection of Concomitant Medications -
All prescription concomitant medications will be recorded at baseline. The investigators will keep track of any newly initiated medications taken during the course of the

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Laboratory Assessments -
Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance. -
After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator. -

Study Monitoring, Auditing and Documentation -
Investigators and/or their study staff will be trained during the initiation visit. During each monitoring visit, source data verification will be performed by qualified staff representing the sponsor
Monitoring visits w ... [69]

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14.3 Spontaneously Reported Reactions

Commonly expected spontaneously reported reactions are collected on a separate CRF page and will be categorized as mild, moderate, or severe. Common, expected reactions are defined as those most frequently reported in the literature and include: Anxiety, Diarrhea, Difficulty Concentrating, Dizziness, Drowsiness, Dry Mouth, Fatigue, Headache, Heavy Legs, Impaired Gait/Balance, Impaired Judgment, Increased Irritability, Insomnia, Jaw Clenching or Tight Jaw, Lack of Appetite, Low Mood, Muscle Tension, Nausea, Need More Sleep, Nystagmus, Parasthesias, Perspiration, Restlessness, Rumination (increased private worries), Sensitivity to Cold, Thirst, and Weakness. Spontaneously reported reactions will be collected during the experimental session and the seven days of telephone contact following the integrative session that occurs on the day after each experimental session. Each reported reaction will be followed during follow-up phone calls or visits until resolution.

14.4 Collection of Concomitant Medications and Tapering Instructions

The PI will record concomitant medications during screening. If the subject is being treated with psychiatric drugs at the time he or she is recruited into the study, the prospective subject will be encouraged to discuss medication tapering with his or her outside treating physician, if any, and will be required to give the PI 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 session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug's and active metabolites half-life).

The therapists will request information about any changes in medication just prior to each experimental session. The PI will be responsible for reviewing and confirming all medications collected during the study.

All medications, over the counter (OTC) and prescription will be collected from screening through seven days after the last MDMA session. From seven days after the last MDMA session through study termination only prescription or OTC medications taken to treat AEs will be collected. Throughout the protocol all medications used to treat AEs will be collected, as described in Section 14.0, and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

Subjects must be willing to refrain from taking any psychiatric medications during Stage 1 and Stage 2, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for 10 days after each experimental session.

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Table 6. Medication Tapering Table

<u>Generic Name</u>	<u>Brand Name</u>	<u>Half-life (hours) including active metabolites</u>	<u>Days for Washout</u>
alprazolam	Xanax	11	3
aripiprazole	Abilify	75	16
atomoxetine	Strattera	5-24	5
bupropion	Wellbutrin	21	5
citalopram	Celexa	35	8
clonazepam	Klonopin	30-40	8
diazepam	Valium	20-70	15
duloxetine	Cymbalta	12	3
escitalopram	Lexapro	32	7
fluoxetine	Prozac	7-9 (days)	45
imipramine	Tofranil	6-18	4
lamotrigine	Lamictal	25	6
lorazepam	Ativan	12	3
mirtazapine	Remeron	20-40	8
olanzapine	Zyprexa	21-54	11
paroxetine	Paxil	21	5
prazosin	Minipress	2-3	1
quetiapine	Seroquel	6	2
risperidone	Risperdal	3-20	4
sertraline	Zoloft	26	6
temazepam	Restoril	8-12	3
trazodone	Desyrel	9	2
venlafaxine	Effexor	12	3
ziprazidone	Geodon	7	2
zolpidem	Ambien	2.5	<1

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session (e.g. insomnia or severe anxiety that does not respond to other management outlined in the treatment manual). Rescue medications may be a benzodiazepine, zolpidem or other anxiolytic or sedative according to the physician's clinical judgment. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

Subjects must agree that, for one week preceding the MDMA session:

- a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
- b. They will refrain from taking any prescription or nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs, acetaminophen, birth control pills, thyroid hormones, or other medications approved by the research team).

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Subjects will receive a memory aid card for use between the end of Stage 1/Stage 2 visit and the 12-month follow-up. Subjects will use this card to record changes in psychiatric medications that they will be asked about at the termination visit. Memory aids will not be collected. Subjects may return to taking psychiatric medications and discontinue birth control after the final two-month assessment if necessary.

14.5 Clinical Laboratory Assessments

The PI will examine laboratory assessments gathered in screening for assessing subject eligibility. The PI will use a list of normal ranges to conclude whether subjects are eligible for the protocol, and will indicate justification for admitting subjects with abnormal values, after consultation with the medical monitor.

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

- Serum electrolytes and metabolic profile
 - ALT/SGPT
 - Albumin:globulin (A:G) ratio
 - Albumin, serum
 - Alkaline phosphatase, serum
 - AST/SGOT
 - Bilirubin, total
 - BUN:creatinine ratio
 - Calcium, serum
 - Carbon dioxide
 - Chloride, serum
 - Creatinine, serum
 - Glucose, serum
 - Potassium, serum
 - Protein, total, serum
 - Sodium, serum
- CBC
 - Hematocrit
 - Hemoglobin
 - MCV
 - MCH
 - MCHC
 - RDW
 - Percentage and absolute differential counts
 - RBC
 - Red blood cell count
 - White blood cell count
- Urinalysis
 - Color
 - Appearance
 - Specific gravity
 - pH

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- Protein
- Glucose
- Ketones
- Blood in urine
- Leukocyte esterase
- Nitrite
- Thyroid function.
 - TSH high sensitivity
 - Free T4
 - Free T3
- HIV serology.
- Urine-dip pregnancy test for females of childbearing potential.
- Urinary drug test will be performed.

The clinical lab assessments and ECG will be performed by:

LifeLabs Medical Laboratory Services

3680 Gilmore Way

Burnaby, BC, V5G 4V8

15.0 Study Monitoring, Auditing, and Documentation

The PI, therapists, and/or their study staff will be trained prior to the start of the study. The clinical study site will be monitored by site visits and regular contact with the PI by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate to ensure compliance, including accurate and complete recording of data in CRFs, source documents, and drug accountability records, while maintaining the blind during Stage 1. CRFs will be supplied by the sponsor will be completed for each subject enrolled. Monitoring and auditing procedures of the sponsor will be followed in order to comply with GCP guidelines and to ensure validity of the study data. Monitoring and auditing procedures will be supplied in a separate document.

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 IB, the Protocol, the CRFs, and the Subject Information and Consent Form.

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

16.0 Risks of Participation

16.1 Risks and Discomforts Associated with Psychotherapy Sessions and Assessment of Measures

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In preparation for drug-assisted psychotherapy sessions, blood draws and a full medical examination are required to establish eligibility for the study. Temporary discomfort, inflammation, or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

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

All psychotherapy sessions may be recorded to audio and video for research and training purposes. Subjects may feel uncomfortable with having their sessions recorded. Subjects may have access to recordings if they request them. The recordings are necessary for developing the experimental treatment and assessing adherence to the treatment manual. Subjects will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

16.2 Risks of Receiving MDMA

Spontaneously reported reactions and common adverse effects of MDMA are modest and have generally not been associated with serious discomfort by healthy volunteers in previous studies. Common reactions include lack of appetite, insomnia, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance, dry mouth, ruminations, and thirst. Other slightly less common reactions include restlessness, paresthesias (odd somatic feelings, such as tingling, feeling hot or cold), impaired judgment, perspiration, drowsiness, and nystagmus (eye-wiggling). While anxiety, headache, fatigue, insomnia and lack of appetite were spontaneously reported by 40% to 80% of subjects in both conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition, and irritability was slightly more likely to be reported in the placebo condition. Additionally, subjects in the MDMA condition were more likely to report muscle tension in various body parts and diarrhea.

These effects are transient and diminish as drug effects wane. Sub-acute effects that may either continue for the next 24 hours or appear later include insomnia, fatigue, needing more sleep, weakness, heavy legs, dry mouth, low mood or irritability. Sub-acute effects

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are reported less often than acute effects. More information on spontaneously reported reactions is described in the IB.

MDMA may produce mild alterations in sensory perception and altered perception of time [74, 170, 171]. Women may be more sensitive to these effects [124]. MDMA acutely affects attention, information processing, and memory. MDMA acutely impairs verbal memory and recall for object location without affecting recall of complex scene changes [172]. For this reason, subjects will stay at the site overnight and will not be permitted to drive after experimental sessions.

MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness.

Further information on the risks associated with MDMA, including information drawn from case reports and studies of ecstasy users, can be found in the sponsor's IB.

16.2.1 Cardiovascular and Sympathomimetic Effects

The full dose of 125 mg, followed by a supplemental dose of 62.5 mg after 1.5 to 2.5 hours, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. These changes should last no more than six hours. In less than 5% of volunteers in Phase I studies, peak blood pressure values were higher than 140/90 mmHg. Clinical intervention was not required in any of these cases. Nonetheless, careful monitoring of subjects and predefined contingency plans will allow the researchers to rapidly identify and manage any related toxicity. For more information, see the sponsor's IB.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing hypertension and monitoring blood pressure and pulse, as described in Section 5.1.2. During experimental sessions the co-therapists will continually evaluate the patient for increasing blood pressure and signs or symptoms of a developing hypertensive or other cardiovascular emergency. Subjects reporting chest pain, shortness of breath or neurological symptoms or other potential indicators of hypertension will have more frequent measurements and assessment by the PI. Any subject who experiences medical complications during an experimental session will not be given another experimental session unless it is approved by the PI and the Medical Monitor.

In case of need, subjects will be transferred to the emergency room at the closest hospital, as described in Section 13.1. Reasons for moving a patient to an Emergency Department (ED) would include, but not be limited to, severe headache in the setting of hypertension, angina, or neurological deficits regardless of blood pressure. The PI may, at any time, make a clinical judgment to transfer the patient to the ED for closer monitoring and additional treatment.

The P will be prepared to respond to rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). The therapists will attend to any signs or

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Cardiovascular and Sympathomimetic Effects

In doses similar to those proposed for this study, MDMA produces sympathomimetic effects similar to the effects of a moderate dose of methamphetamine or other stimulants

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Deleted: The amount of MDMA used in all experimental conditions in this study is not likely to produce changes in blood pressure or heart rate greater than 40% of resting values. These changes should last no more than six hours. These changes have been well-tolerated by volunteers in previous studies and should not pose large risks to participants who have been carefully screened for cardiovascular and related problems. In less than 5% of volunteers in phase I studies, increases in blood pressure were higher.

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MDMA may produce mild alterations in perception and altered perception of time

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symptoms of neurological deficit or confusion that is more extensive than might be expected from MDMA or from psychological distress, and will notify the PI if this occurs for on-site evaluation or a decision to initiate transfer to the ED. If any subject has neurological deficits, as assessed by the PI, whether or not they are associated with hypertensive crisis, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and if necessary, they will be transported to the emergency department at the closest hospital for further management. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be time to administer recombinant tissue plasminogen within the three-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [173, 174].

The therapists will observe the subject and note any complaints of chest pain. If a subject experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, paramedics will be summoned to initiate the applicable protocols for further evaluation and stabilization and, if necessary, he or she will be transported to the ED or a location in the hospital where appropriate care can be given. He or she will be given nitroglycerin 0.4 mg SL q 5 minutes PRN chest pain pending transport to the hospital. If further evaluation at the hospital reveals that the subject has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/ American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [175].

16.2.2 Psychological Distress

Mild anxiety and depressed mood are occasionally reported one to three days after MDMA administration [72, 124, and see the IB]. Psychological distress from MDMA could arise from the first indications of drug effects until the last effects have dissipated (approximately three to five hours after drug administration), or even later. Anxiety or distress during the session may last for as little as five minutes or for as long as five hours or more. In addition, psychological distress could arise following an MDMA session as a result of subjects having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting, and have responded well to reassurance from the therapists, with occasional use of benzodiazepines for anxiety. In this study, subjects will have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, panic or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

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Proper preparation and follow-up support will reduce the difficulties subjects might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder-1 or with psychotic disorders).
- Preparatory non-drug psychotherapy sessions before the experimental session.
- Creating an atmosphere of trust during the experimental session.
- Close monitoring.
- Daily contact with subjects for the period of a week after the experimental session
- Providing non-drug integrative psychotherapy sessions.
- Subjects will remain at the study site for the night of each experimental session to further reduce psychological distress. Qualified personnel will be available during the overnight stay to respond to the needs of the subject. Attendants will be instructed to contact the therapists upon request or at the appearance of signs of a potential serious adverse event.

During the preparatory sessions, subjects will be made aware of the fact that difficult emotions, including grief, rage and fear or panic, may arise during experimental sessions. Every effort will be made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the experimental session, including empathic listening on the part of the therapists and performance of diaphragmatic breathing by subjects.

At the end of the six to eight hour experimental session, if the subject is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

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

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- If a subject remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the PI will decide between the following options:
 1. A psychiatric nurse, therapeutic assistant, physician, or therapist will stay with the subject until the time of his or her appointment with the therapists the next day. The therapists will then meet with the subject daily until the period of destabilization has passed.
 2. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the PI may prescribe a rescue medication such as a benzodiazepine, zolpidem or other anxiolytic or sedative according to the physician's clinical judgment. This medication will be captured on the concomitant medications CRF page. The physician should not prescribe an SSRI, SNRI or MAOI in this context unless it has been determined that the subject will be withdrawn from the study. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the therapists.
 3. Hospitalization for stabilization. If a subject should become psychotic arrangements will be made to stabilize them and transfer them to the ED if necessary.

Subjects hospitalized after a severe panic reaction will be suspended from the protocol until after recovery or stabilization, at which time the Clinical Investigators will carefully evaluate the subject's emotional status.

For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject's outside therapists will be involved in the management of any psychiatric complications. For those subjects engaged in an ongoing psychotherapeutic relationship with the Clinical Investigator(s), the management of any psychiatric complications will be undertaken by them in their capacity as therapists.

16.2.3 Body Temperature

MDMA administered in a controlled setting produces only a slight increase in body temperature [124], and ambient temperature does not enhance or attenuate this slight elevation in humans [75].

If temperature rises more than 1°C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. If at any time the temperature rises more than 1.5°C above baseline despite these efforts, the PI will be consulted for further evaluation and treatment.

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Immunological Changes
MDMA may produce modest changes in immune functioning, lasting up to 48 hours. -
A research team in Spain has studied the acute immunological effects of one or two doses of 100 mg MDMA

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16.2.4 Reproductive and Developmental Risks

Risks posed by MDMA to pregnant women are not known. One of two studies of Ecstasy users suggests that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [176, 177], and a third reported some developmental delays in mothers reporting use of ecstasy and other drugs during pregnancy [178].

Pregnant and lactating women will be excluded from participation in the study, and women who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental session and must agree to use birth control for the treatment portion of the study.

16.2.5 Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [179]. However, they are basing their case on studies that employed inappropriately high doses of MDMA utilized in animal studies, and on human studies comparing the effects of repeated use of ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [180]. We have carefully considered the risks of such neurotoxicity and conclude that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. More information on the potential neurotoxicity of MDMA can be found in the IB.

16.3 Abuse Liability

Findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine. More information on abuse liability is provided in the IB.

Whether MDMA-assisted psychotherapy will cause PTSD patients to develop symptoms of abuse is an open question that the sponsor is addressing on an ongoing basis. Based on long-term follow-up data from two sponsor-supported studies (N=32), only one subject took Ecstasy after completing the study and failed to reproduce the experience from the study, and a number of subjects volunteered that they would never seek out Ecstasy outside a legal, controlled, therapeutic setting. In addition, negative results from MDMA-specific drug testing data obtained from the Swiss study MP-2 (N=12) supports that none of these subjects took Ecstasy outside of the study during the long-term follow-up period.

Diversion is not an issue in this protocol because MDMA will only be administered a few times under the supervision of the PI and no take-home doses will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

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16.4 Risks and Discomforts of Receiving the Comparator Dose of Study Drug

Receiving the comparator dose of 50 mg MDMA followed 1.5 to 2.5 hours later by 25 mg MDMA may be associated with some of the risks above. People receiving low doses of MDMA report only a few subjective effects and do not exhibit significant cardiovascular changes [71, 109]. It is possible that the addition of the supplemental dose will produce slight increases in positive and negative mood and slightly elevate blood pressure, as reported after administering approximately 35 mg to 40 mg [72]. The comparator dose of MDMA is not expected to produce most or all of the potentially therapeutic effects of the drug, such as increased positive mood, facilitated recall, changed perception of meaning, and increased feelings of closeness to others. Hence people receiving comparator doses may experience a lesser reduction in PTSD symptoms from MDMA-assisted sessions.

17.0 Alternative Treatments and Procedures

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

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

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

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Risks posed by MDMA to pregnant women are not known. One of two studies of ecstasy users suggests that use of ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association, as discussed below in the "Pharmacology" section and in pp. 29-30 in the Investigator's brochure (Bateman et al. 2004; McElhatton et al. 1999). Pregnant ... [72]

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18.0 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of subjects in their role as research subjects. Removing identifying information from data and restricting access to researchers directly involved in assessing the subjects should prevent the dissemination of confidential data, with or without identifying information. Except for the screening log, the ICF, and a subject contact information sheet that will be stored separately from other documents, all data will be identified only by the subject's secondary identifier number on the source document and five-digit subject number. If past medical records are needed, subjects will sign forms for the release of information upon consent to permit screening for protocol enrollment.

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Deleted: all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials on the source document and by a randomly generated numeric code on all secondary documents and databases. The investigators will retain a key associating these new numbers with those assigned to participants upon study enrollment. All measures, records, audio and video recordings

All psychotherapy sessions and the 12-month follow-up may be recorded to video and audio. In addition the CAPS assessment may also be recorded to audio and video to establish inter-rater reliability. These recordings will be used for manual development and potentially for training therapists to perform MDMA-assisted psychotherapy. They are intended to record the events occurring during therapy, and will not serve as outcome measures. Full names and addresses will not appear in these recordings. Audio and video recordings will only be marked with the subject's subject number. Video data will be stored on a HIPA-compliant remote server with encryption and authentication in place to ensure confidentiality. Study subjects will only be able to view their own video data by logging in to a secure HIPA-compliant server. Only HIPA-certified researchers who have signed a Data Confidentiality Agreement, completed Good Clinical Practice training, and received approval from the PI will be permitted to access video data for research and training purposes.

Any materials mailed to subjects will be sent along with stamped return envelopes using the office address of the PI both as main and return address. All assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the Clinical Investigators directly involved in the protocol, with access to data will not be provided with any information that would identify subjects by name or by other means, such as social security number.

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19.0 Costs to Subjects

There will be no costs to subjects for any study-related procedures. Only Canadian residents with Canadian health insurance will be enrolled in the study. The sponsor (MAPS) will pay for all assessments, laboratory work, or physical examinations needed to determine study eligibility. The sponsor will also cover costs of the study drug and remaining at the study site on the night after each experimental session. The sponsor will pay for all study drugs and study procedures. The sponsor will not reimburse subjects for travel, food, and lodging. Subjects will not be paid for their participation in this study.

Charges for treatment of the subject's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the subject or to the subject him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study except in the case of subjects who previously received therapy from the Clinical Investigators and who will continue to receive ongoing treatment that is not related to participating in the study.

20.0 Record Retention

The PI must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility for 25 years in accordance with Health Canada regulations. The PI must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the PI as to when these documents no longer need to be retained.

21.0 Publication Policy

The sponsor recognizes the importance of communicating medical study data and therefore encourages publications in reputable scientific journals and presentations at seminars or conferences. It is understood by the PI that the information generated in this study will be used by the sponsor in connection with the development of the investigational product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the PI is obliged to provide the sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analysis is done on the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician.

Any results of medical investigations with the sponsor products and/or publications/lectures/manuscripts based thereon, shall be exchanged and discussed by the PI and the sponsor clinical research representative(s) prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g. manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other studies in the

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

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

Administering the study drug exposes study participants to a number of potential risks and discomforts that would not otherwise occur. The experimental dose of MDMA is liable to produce common physiological and psychological side effects during each experimental dose MDMA-assisted session, such as increased blood pressure or elevated anxiety. People with PTSD receiving MDMA within a therapeutic setting may very well experience strong negative emotions during the session, as fear, rage or grief. There are reports of a number of serious adverse events in people in uncontrolled, non-medical settings after taking ecstasy. However, there is good evidence that conducting three separate experimental sessions administering initial doses of 125 mg followed by 62.5 mg MDMA in a clinical setting poses a low risk to participants. Conference presentations of ... [73]

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same field.

The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.

MDMA Psychotherapy for PTSD

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Final Copy-Revised: 11/17/08

**A Randomized, Active Placebo-controlled Pilot Study of 3,4-
methylenedioxyamphetamine (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]**

SPONSOR

Multidisciplinary Association for Psychedelic
Studies (MAPS),
3 Francis Street, Belmont, MA 02478

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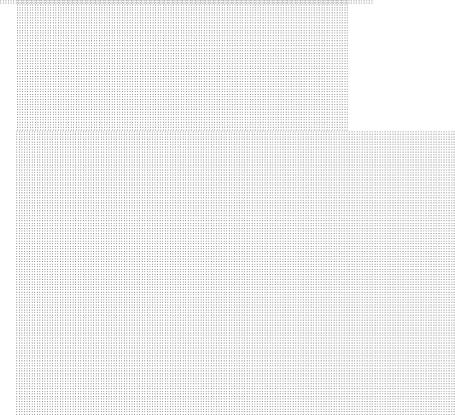


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STUDY MONITOR [CRA]



Ethics Board

Sponsor Signatory

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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 (EMA) 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 [REDACTED]. 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 [REDACTED] and one in Israel, under the direction of [REDACTED]

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 [REDACTED] 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 I 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%. (Perkonig 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 remain overnight at Dr. Pacey's clinic after each experimental session until the non-drug session occurring the next morning. An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. 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
<i>Active Placebo</i>	25 mg	12.5 mg	37.5 mg
<i>Experimental Dose</i>	125 mg	62.5 mg	187.5 mg

Method

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

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

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

Time and Events for Randomized Study segment

Time and Events M-P4	Baseline and Screening			Therapy and Evaluation 1						Therapy and Evaluation 2						Therapy and Evaluation 3				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Visit #																				
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	85	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-exam session 1	Between V8 and V11	Post V9	>3d wks post V8	24 h post V11	Post V11	Post V13	<3-5 w post V11*	24 h post V15	Post V15	Post V17	8 wk post V15	May be same day as V19
Study Staff	Ingrid/Andrew	Ingrid/Andrew	Ingrid/Andrew, Ingrid/Andrew, Karen	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid/Andrew, Karen	Ingrid/Andrew
Telephone Screening	X																			
Provide consent materials		X																		
Study informed consent		X																		
Medical Examination			X																	
ECC			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					
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					X
Unblinding																				X
Consent for Stage 2/open-label																				X
RRPQ																				x
End Randomized phase																				x

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

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

Psychotherapy

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

Introductory Sessions

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

MDMA-assisted Psychotherapy

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

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

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

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

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

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

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

Table 3. Schedule of procedures and measures for experimental sessions

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

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

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

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

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

Participants will remain overnight in an a

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 of additional support. Participants will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

Integrative Psychotherapy

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

Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy

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

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

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

Weekly Integrative Sessions

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

Daily Telephone Contact

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

Evaluation Six weeks after the Third experimental session

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

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

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

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

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

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

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

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

Assessment Six weeks after Third Open-Label Session

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

Removal of Subjects from Therapy or Assessment

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

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

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

Premature Discontinuation of the Study

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

Data Analysis

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

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

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

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

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

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

Statistical power

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

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

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low (Baggott et al. 2001; Dumont and Verkes 2006; Jerome 2004; 2005; 2007). Approximately 390 people have received MDMA during controlled trials without the occurrence of any drug-related serious adverse event, and psychiatrists in the US and

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

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

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

Hypertension and related cardiovascular Effects

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

Angina or Myocardial Infarction:

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

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

Stroke:

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

Psychological Distress:

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

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

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

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

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

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

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

B. Hospitalization for stabilization

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

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

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

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

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

Hyperthermia:

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

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

Dehydration:

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

Hyponatremia:

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

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

Liver toxicity:

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

Neuropsychological toxicity:

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

Abuse and dependence:

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

Medical Emergencies

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

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

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

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

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

Mild: no limitation in normal daily activity.

Moderate: some limitation in normal daily activity.

Severe: unable to perform normal daily activity.

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

1. Not Related

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

2. Possibly Related

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

3. Probably Related

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

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

Serious Adverse Events

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

Results in death

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

Requires or prolongs inpatient hospitalization

Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)

Results in a congenital anomaly/birth defect

Requires intervention to prevent permanent impairment or damage

Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

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

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

Adverse Event Collection

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

Medical Monitor:

Study Monitor:

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

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

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

- Common side effects.
- Exacerbation of anxiety.

Collection of Concomitant Medications

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

Laboratory Assessments

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance. After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

Study Monitoring, Auditing and Documentation

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

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

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

Risks and Discomforts

Risks and Discomforts Associated with Drawing Blood

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

Risks and Discomforts Associated with Screening Procedure

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

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

Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

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

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

Risks and Discomforts of Receiving the Study Drug (MDMA)

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

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

Cardiovascular and Sympathomimetic Effects

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

Perceptual Alteration

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

Psychological Distress

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

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

Immunological Changes

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

Toxicity

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

Potential Neurotoxicity Associated with Ecstasy Use

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

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

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

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

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

Abuse Liability

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

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

Reproductive and Developmental Risks

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

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

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

Alternative Treatments and Procedures

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

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

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

Confidentiality

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

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

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

Costs to Participants

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

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

Risk/Benefits Analysis

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

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

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

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

Chemistry, Manufacturing and Control Information

The drug product is (+/-)-(3,4)-methylenedioxymethamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by

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

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

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

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

Pharmacokinetics and Pharmacodynamics

Primary Pharmacology

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

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

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

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

Though they differ in some respects, early and later pharmacological profiles of MDMA reported an affinity for specific serotonergic, noradrenergic, cholinergic and histaminergic receptors (see Table 3 below). It is possible but not yet demonstrated that 5HT_{2B} and α_2 receptors may contribute to at least some of the subjective effects of MDMA, while little is known as to whether there are any potential contributions from M₃ or H₁ receptors. 5HT_{2B} receptors in the medial amygdala may contribute to the anxiolytic effects of MDMA, as may also be true for the serotonin releaser and 5HT_{2B} agonist fenfluramine. Direct MDMA stimulation of postsynaptic α_2 adrenoceptors may also help individuals remain emotionally calm despite noradrenergic activation, as with related α_2 agonists clonidine and guanfacine, possibly through altering the balance between α_1 to α_2 stimulation (Franowicz and Arnsten 1998).

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

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

Primary Pharmacodynamics

Drug Activity Related to Proposed Action

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

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

Secondary Pharmacology

Safety Pharmacology

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

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

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

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

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

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

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

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

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

Hyperthermia

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

Psychiatric Problems

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

Hepatotoxicity

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

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

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

Hyponatremia

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

Neurotoxicity

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

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

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

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

Developmental Toxicity

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

Common side effects

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

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

Acute Adverse Effects

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

Abuse Liability

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

Pharmacokinetics/Toxicokinetics

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

significance of these differences are unclear, and this is the first detailed study of MDMA pharmacokinetics in men and women.

As can be seen in Table 5, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.

Table 5. MDMA Pharmacokinetics

MDMA Dose	N	C _{max} µg/l	T _{max} H	AUC ₀₋₂₄ µg*h/l	AUC/dose µg*h/(l*mg)	Reference
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8.6	Mas et al. 1999
75	1 2	178 (no SD)	3	Not reported	NA	Lamers et al. 2003
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	24.31 ± 7.7	(de la Torre et al. 2000c)
100	9	180 ± 33	2 ± 0.26	1452 ± 771	14.52 ± 7.7	Farre et al. 2004
100	7	208.7 ± 17.1	16 ± 0.4	Not reported	NA	(Pizarro et al. 2004)
100	7	232.9 ± 45.3	1.5	Not reported	NA	Segura et al. 2005
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	(de la Torre et al. 2000a)

MDMA Dose	N	k _a /h	k _e /h	T _{1/2} H	MDA T _{1/2a} H	Reference
50	2	Na	na	2.7 and 5.1	Na	(de la Torre et al. 2000c)
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.7 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	(de la Torre et al. 2000c)
100	7	na	0.07 ± 0.03	11.8 ± 4.4	na	Pizarro et al. 2004
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	(de la Torre et al. 2000a)

Farre and colleagues reported the pharmacokinetics of a second dose of 100 mg MDMA given 24 hours after an initial 100 mg dose in nine men (Farre et al. 2004). C_{max} was 232. ± 39 µ/L, AUC₍₂₄₋₄₈₎ was 2564 ± 762 µg*h/L, T_{max(24-48)} was 25.5 ± 0.33 h, and AUC/dose was 25.64 ± 7.6 µg*h/l*mg. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), probably as a result of non-linear pharmacokinetics. De la Torre was first to report evidence of non-linear pharmacokinetics, and a recent report supports these findings (de la Torre et al. 2000a; Kolbrich et al. 2008). Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly

higher maximal values than expected after the supplemental dose only or the combined dose, or whether it will instead lengthen T_{max} .

Summary of Pharmacokinetic Parameters :

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called α -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la Torre et al. 2000a; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002)(de la Torre et al. 2000; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004). HMMA appears to be the main metabolite in humans (Pizarro et al. 2004). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

Although a number of researchers hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, an examination of the research does not support this concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997). Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant.

Relatively recent reports in humans found no evidence that having a CYP2D6 “poor metabolizer” genotype is by itself a major risk factor for acute MDMA toxicity (de la Torre et al. 2004). At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (de la Torre et al. 2005) (Segura et al. 2005) without any adverse events occurring. The individual had 60% greater MDMA AUC after a first and a second dose, but the only other reported difference for this participant was a statistically significant increase in amount of NK cells. A comparison of MDMA metabolism in poor and extensive metabolizers found that reduced CYP2D6 function was associated with higher MDMA AUC after the first of two doses of MDMA, but similar levels of MDMA and metabolites after the second dose (de la Torre et al. 2005). The same lack of effects was originally reported in a participant given the similar compound methylenedioxyethylamphetamine, or MDE (Kreth et al. 2000).

Two teams of researchers have investigated the enzymes involved in the formation of MDA from MDMA in human liver microsomes (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their

experiments. In a publication focusing on MDE metabolism, Kreth and colleagues reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

MDMA is a chiral compound, meaning it comes in two forms or enantiomers. However, all investigations in humans and most in nonhuman animals have almost exclusively administered the racemate (a mixture of both enantiomers). Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-(+)-enantiomer having a shorter elimination half-life and greater excretion than the R-(-)-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Crifasi and Long 1996; Ramcharan et al. 1998). The stereoselective pharmacokinetics of MDMA is reflected in formation of MDA and DHMA enantiomers (Fallon et al. 1999; Pizarro et al. 2004; Pizarro et al. 2003). In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). By contrast, R/S ratios of HMMA are more similar to those for MDA (greater amounts of R-(-)-HMMA than S-(+)-HMMA during the first 24 hours), or there is no findings of a difference between concentrations of the two enantiomers of HMMA (Pizarro et al. 2004; Pizarro et al. 2003).

Absorption, Distribution, Metabolism, Excretion

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a non-enzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylenation, including CYP1A2 and CYP3A4.

Table 6. Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

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

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Pizarro et al. 2004; Pizarro et al. 2003; Segura et al. 2005; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA reported after administration of 100 mg MDMA to four men are 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Toxicology

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed (Frith et al. 1987), and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Acute toxicity

Acute toxicity is described above in “Safety Pharmacology”, including both common side effects and effects occurring in ecstasy users. The estimated LD₅₀ for MDMA in humans is between 10 and 20 mg/kg (Frith et al. 1987; Hardman et al. 1973). To date, most controlled studies rarely administered doses above 2 mg/kg. The proposed doses of 150 followed by 75 mg (cumulative dose of 225 mg) or approximately 2.1 mg/kg followed by approximately 1 mg/kg (cumulative dose of 3.21 mg/kg) is below the estimated LD₅₀ in humans.

Reproductive Toxicity

Investigations of the reproductive and developmental toxicity of MDMA are described in “Safety Pharmacology” above. These studies include inconclusive findings in humans and findings in rodents suggestive of a critical period during which exposure to MDMA

may impair learning or memory. Pregnant women will not be enrolled in this training program.

Previous Human Experience

Several accounts describe the use of MDMA as an adjunct to psychotherapy prior to its placement in schedule 1 (Adamson 1985; Stolaroff 2004), and between 1988 and 1993 in Switzerland (Gasser 1994; Widmer 1998). This therapy did not occur in the context of a controlled clinical trial. MDMA may have been given to thousands of individuals during these time periods without any fatalities or serious adverse events (Gasser 1994; Holland 2001; Rosenbaum and Doblin 1991). Psychotherapists used MDMA-assisted psychotherapy in the treatment of moderate psychological difficulties (“neuroses”), relationship difficulties, posttraumatic stress disorder, and anxiety in response to diagnosis with a potentially fatal illness. Therapists described relying on a mixture of therapeutic techniques that included confronting and working with the experience as it occurred and speaking openly with others during the experience.

In the 1980s, two researchers independently published an uncontrolled clinical trial and an uncontrolled investigation into MDMA-assisted psychotherapy (Downing 1986; Greer and Tolbert 1986). The psychotherapy that Greer and Tolbert conducted took place in a setting similar to that used for psychedelic-assisted psychotherapy, including focusing on inner experience. Greer and Tolbert used doses between 75 and 150 mg MDMA, sometimes with supplemental doses administered later (Greer and Tolbert 1986). Participants in the uncontrolled study of MDMA-assisted psychotherapy reported changes in attitudes and benefits afterwards.

The first controlled investigation of MDMA took place almost a decade after the uncontrolled studies (Grob et al. 1996), followed two years later by another controlled trial (Vollenweider et al. 1998). Starting in the mid to late 1990s, at least seven research teams in Europe and the US began conducting and publishing clinical MDMA research using healthy volunteers, and two recent reviews summarized findings from many of these studies (Baylen and Rosenberg 2006; Dumont and Verkes 2006). Since then, a second team of researchers in the Netherlands and a team based in Maryland published their first findings from human MDMA studies (Dumont et al. 2008; Kolbrich et al. 2008). Findings from controlled human studies of MDMA are also discussed in detail in the investigator’s brochure (Baggott et al. 2001; Jerome 2004; 2005; 2007; Jerome and Baggott 2003), and they are addressed earlier in this section. The first studies assessed physiological, subjective, psychological and neuroendocrine effects, and reported that MDMA possessed a unique pharmacological profile. Some of these first studies examined brain activity (Frei et al. 2001; Gamma et al. 2000) cardiac function (Lester et al. 2000), and effects of MDMA on attention and information processing (Cami et al. 2000b; Gamma et al. 2000).

To date, MDMA has been administered to approximately 390 research participants, without any occurrences of drug-related serious adverse events. Human MDMA studies have continued to investigate the subjective and physiological effects of MDMA, and its metabolism and detectability in several body fluids. In published reports, investigators

administered doses ranging from approximately 35 mg (0.5 mg/kg) to 145 to 150 mg (2 mg/kg) (Freedman et al. 2005; Harris et al. 2002; Lester et al. 2000) (Kolbrich et al. 2008), and in an unpublished report, researchers administered 0.25 and 2.5 mg/kg MDMA as well (Grob 2001). The average dose examined in human MDMA studies is between 1 and 2 mg/kg. Studies of the physiological effects of MDMA include investigations of immunological effects (as Pacifici et al. 2004; Pacifici et al. 1999b; Pacifici et al. 2002; Pacifici et al. 2001b), neuroendocrine effects (Forsling et al. 2001; Grob et al. 1996; Harris et al. 2002; Liechti and Vollenweider 2001), cardiovascular and cardiac effects (Lester et al. 2000; Mas et al. 1999) and body temperature (Freedman et al. 2005), and employed brain imaging and quantitative electroencephalography (Frei et al. 2001; Gamma et al. 2000). Researchers have studied self-reported subjective and reinforcing effects (Cami et al. 2000b; Dumont et al. 2008; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003) and observed effects (Harris et al. 2002), and they have studied such specific effects as enhancement of pre-pulse inhibition (Vollenweider et al. 1999), performance on attentional and information processing tasks such as the continuous performance, Stroop and digit symbol tasks (Cami et al. 2000b; Dumont et al. 2008; Gamma et al. 2000), cognitive skills related to driving motor vehicles (Kuypers and Ramaekers 2005; 2007; Kuypers et al. 2006; Ramaekers and Kuypers 2006; Ramaekers et al. 2006), including specific effects of nocturnal dosing (Kuypers et al. 2007), and similarity to a stimulant versus a serotonergic drug (Johanson et al. 2006). As described above, researchers have also examined the role of serotonin release, 5HT_{2A} and D₂ receptors in producing MDMA effects and MDMA pharmacokinetics (de la Torre et al. 2004; Farre et al. 2007; Liechti and Vollenweider 2001; Tancer and Johanson 2007).

A team of researchers in the US are about to complete their research study of MDMA-assisted psychotherapy in people with PTSD, while researchers in Switzerland are engaged in an ongoing study of MDMA-assisted psychotherapy (Mithoefer 2007a; b; 2008; Oehen 2006) and researchers in Israel are conducting a study of MDMA-assisted psychotherapy in people with PTSD (Mojeiko 2006). After undergoing introductory and preparatory psychotherapy, study participants in these studies receive two to three day-long sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Participants receive integrative psychotherapy on the day after each session and often on a weekly basis in between and after each MDMA-assisted session. These studies employ an initial dose of 125 mg MDMA followed 2 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. One of the two ongoing studies has enrolled all study participants, and preliminary results appear promising (Mithoefer 2007b). The other study has enrolled half of the 12 subjects planned for this study. Another study will soon be recruiting people with advanced-stage cancer to examine MDMA-assisted psychotherapy as a means of reducing anxiety arising from the cancer diagnosis (Halpern 2006). To date, the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored three of four studies, with the fourth sponsored by the principal investigator and private benefactors.

Previous experience with MDMA indicates that it can be safely administered to humans within a research or therapeutic setting, and preliminary examination of data from a study of MDMA-assisted psychotherapy in people with PTSD suggests that MDMA improves

PTSD symptoms when used as a psychotherapeutic adjunct. The independent rater conducted a preliminary analysis of CAPS scores at baseline and two months later detected a significant condition effect ($p < 0.05$). Average baseline scores for people in both conditions were comparable (79.6 for MDMA condition and 78.4 for placebo), but two months after the second experimental session, the average CAPS score for people in the MDMA condition was 27.6, while the average CAPS for people in placebo was 59.1. Eight of 13 participants no longer met criteria for PTSD two months after the second experimental session while only two of eight placebo participants no longer met criteria for PTSD diagnosis. Furthermore, a comparison of baseline assessment of neurocognitive function and assessment two months after the second experimental session did not find any significant differences in either MDMA or placebo participants (Wagner 2008, personal communication). The data examined in this analysis has not yet been subjected to quality assurance and data from one participant remains to be added, but there were few outliers in the data and it is unlikely that additional data will change results.

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Additional Information

Facilities

Introductory, MDMA-assisted and integrative psychotherapy

The offices consist of a set of three rooms, including a private bathroom and kitchen and include a refrigerator and microwave. The main room is comfortably furnished and private. There is artwork on the walls, and stained glass in some windows. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. The offices are lower than ground level. They can be heated, and fans are used for cooling. The offices have an enclosed courtyard. The office will contain equipment for assessing blood pressure, pulse, and body temperature and an automatic external defibrillator. The offices are not within a hospital, but the location is a five to fifteen minute drive from two hospitals with emergency departments, the University of British Columbia Hospital and St. Paul's hospital. One therapist can reach the offices within five to ten minutes of contact if necessary.

Abuse Liability

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will "pay" higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

Appendix A: Visit by Visit Description

Participants who consent to take part in the study will undergo the following sequence of events:

- *Randomized sessions*
- **Screening/Evaluation (Visit 3):** A two to three hour long medical and psychiatric evaluation. A physician working with the investigators will perform medical history and physical examination and ECG. The independent assessor will diagnose psychiatric disorders with the SCID, and will perform a face to face interview and administer the ASIQ to assess suicide risk. The physician or principal investigator will draw blood for laboratory tests. The independent rater will administer the CAPS and the participant will complete the BDI. The independent rater will administer the RBANS and PASAT. If a participant meets study eligibility criteria after evaluation, he or she will be scheduled for an introductory psychotherapy session. The independent assessor will re-evaluate any participant who undergoes the screening and baseline evaluation prior to discontinuing psychiatric medication. During re-evaluation, the independent assessor will administer the CAPS and the participant will complete the PDS and BDI during a visit occurring after an interval of at least five times drug half-life.
- **Introductory Psychotherapy visits (Visits 4-6):** Three 60 to 90 minute introductory psychotherapy sessions with both psychotherapist investigators. These sessions will help the therapists and participant to learn about each other and discuss the participant's goals, hopes and fears in relation to upcoming MDMA-assisted psychotherapy, and the events and procedures that will occur during MDMA-assisted psychotherapy. Introductory sessions will be recorded to audio and video, and participants will have an opportunity to review the recordings. On the third introductory session, participants will receive instructions and restrictions relating to food and drug consumption for the night before and morning of the MDMA-assisted session. Participants must be randomized to one of the two conditions (active placebo or experimental dose) prior to the first MDMA-assisted psychotherapy session.
- **MDMA-assisted Psychotherapy Session 1 (Visit 7):** First eight-hour long randomized (active placebo versus experimental dose) MDMA-assisted psychotherapy session. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapists deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of the session recording upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant during the experimental session or at some time after it has ended. The significant other can remain overnight with the participant but does not have to do so. All participants will remain at [REDACTED] overnight. A same-sex attendant versed in caring for people

- undergoing difficult psychological experiences will remain with the participant during the overnight stay.
- **Integrative Psychotherapy On the Day After Experimental Session (Visit 8):** A ninety-minute long psychotherapy session with both psychotherapist-investigators always occurring on the morning of the day after MDMA-assisted psychotherapy. The participant will discuss his or her thoughts, feelings, memories or experiences that occurred during the experimental session and the participant and investigators will seek to integrate this material into everyday life. The session will be recorded to audio and video and participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.
 - **Integrative Psychotherapy Sessions Between Experimental MDMA-assisted Session 1 and 2 (Visit 9-10, 10.x):** Two or more sixty to ninety minute psychotherapy sessions with both psychotherapist-investigators during which they and the participant continue to integrate material from MDMA-assisted psychotherapy sessions. The investigators and participant may schedule additional integrative sessions upon participant request and therapist-investigator mutual agreement. These sessions will be recorded to audio and video and participants may view session recordings upon request.
 - **MDMA-Assisted Psychotherapy Session 2 (Visit 11):** The second eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during the experimental session or after the experimental session is over. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.
 - **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 2 (Visit 12):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the second experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.

- **Integrative Psychotherapy After MDMA-Assisted Session 2 (Visits 13-14, 14.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the second MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
- **MDMA-Assisted Psychotherapy Session 3 (Visit 15):** The third eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during or after the experimental session. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 3 (Visit 16):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the third experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.
- **Integrative Psychotherapy After MDMA-Assisted Session 3 (Visits 17-18, 18.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the third MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
- **Evaluation Six weeks After Third MDMA-assisted Session (Visit 19):** A ninety to 120 minute long (1.5-2 hour long) evaluation. The independent assessor will administer the CAPS, RBANS and PASAT, and the participant will complete the BDI and PDS.
- **Study Blind Broken for Individual Subject (Visit 19):** A 30 to 60 minute long meeting with the therapist-investigators. The participant and both therapists will learn participant condition assignment. The independent rater will remain blind to participant condition

assignment. If the individual received active placebo MDMA, then he or she will receive consent materials for the open-label study segment, Stage 2. Any participant who received active placebo and does not consent to take part in Stage 2 will complete the RRPQ.

- *Open-label Sessions for Active Placebo Participants (Stage 2)*
- **Consent for stage 2 (Visit 20):** A 30 to 60 minute meeting with the investigator therapists for participants who learn they received active placebo. They will receive consent materials concerning the open-label study segment. They must give written informed consent to take part in this study segment. Visit 20 may occur on the same day as Visit 19.
- **Stage 2 Baseline Evaluation (Visit 21):** Baseline evaluation for stage 2 (active placebo participants only). CAPS, PDS and BDI scores from the evaluation six weeks after the third experimental session (Visit 19) will serve as baseline scores except in the case where thirty days have passed between those evaluations and the time when the participant entered Stage 2, in which case the independent assessor will perform and additional evaluation, administering the CAPS and BDI prior to entry into Stage 2.
- **Review and Introductory Psychotherapy (Visit 22):** A sixty to ninety minute psychotherapy session with both therapist-investigators and the participant enrolled in Stage 2. The participant and therapist-investigators will re-acquaint themselves with each other, and the participant will review information about MDMA-assisted therapy and all three will discuss, review and possibly revise goals for MDMA-assisted psychotherapy. The session will be recorded to audio and video. Participants may listen to or view recordings upon request.
- **Open-label MDMA session 1 (Visit 23):** The first eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in Stage 2 only.** This option is not applicable to participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and 125 mg MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of their open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of 62.5 mg MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during the experimental session or after the session is over. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 1 (Visit 24):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the first open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to integrative psychotherapy sessions after experimental MDMA-assisted therapy sessions. This session will be recorded to audio and video. Participants can listen to or view recordings upon request.
- **Integrative Psychotherapy Between Open-Label Session 1 and 2 (Visits 25-26, 26.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the first and second Stage 2 open-label

MDMA-assisted session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can review session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.

- **Open-label MDMA session 2 (Visit 28):** The second eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in stage 2 only.** Participants not enrolled in Stage 2 may decline to take part in this session. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants may receive copies of their open-label sessions upon request. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during or after the experimental session to remain with the participant. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 2 (Visit 29):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the second open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. The session will be recorded to audio and video, and participants can listen to or view session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.
- **Integrative Psychotherapy Between Open-Label MDMA 2 and 3 (Visits 30-31, 31.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the second and third Stage 2 open-label MDMA-assisted session. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request. These will be the final integrative sessions for participants not enrolled in stage 2. The therapists and investigator will continue working on integrating MDMA session material into everyday life.
- **Open-label MDMA session 3 (Visit 32):** The third eight-hour long open-label session with a full dose of MDMA (125 mg) for participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body

temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive sometime during the experimental session or after it has ended or near the end of the session to remain with the participant. All participants will remain overnight

Significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 3 (Visit 33):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the third open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. This session will be recorded to audio and video. Participants can listen to or view their recordings upon request. Participants will complete the ASIQ after completing psychotherapy.
- **Integrative Psychotherapy After Open-Label Session 3 (Visits 34-35, 35.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval after the third open-label session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request.
- **Evaluation Six weeks after Third Open-Label Session for Participants Enrolled in Stage 2 (Visit 36):** A ninety to 120-minute visit with the independent assessor and the therapist-investigators for participants enrolled in Stage 2 occurring six weeks after the third open-label session. The independent assessor will administer the CAPS and the participant will complete the BDI and PDS.
- **Study Termination for Stage 2 Participants (Visit 37):** After completing CAPS, PDS and BDI, the participant will meet for approximately a half hour (0.5 hours) with the therapist-investigators. The participant will complete the RRPQ.

Appendix B: Case Report Forms

These are sample case report form drafts for the study “A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Posttraumatic Stress Disorder (PTSD)-Canada.”

The series of case report forms represents the series of events from screening up through the first experimental session of MDMA-assisted psychotherapy. The series does not include CRFs for subsequent experimental sessions or open-label sessions as the information contained is identical or nearly identical in content and format.

CONTAINS

SCREENING AND BASELINE EVALUATION
INTRODUCTORY PSYCHOTHERAPY
FIRST EXPERIMENTAL SESSION
INTEGRATIVE PSYCHOTHERAPY
FINAL EVALUATION
MEDICATION AND ADVERSE EVENTS

Study Entry Criteria

Subject screened under protocol version: Original Amendment # _____

Did subject meet all study entry criteria specified in the protocol Yes No

If No, please mark nature of deviation in the chart below and on the following pages

Inclusion not Met / Exclusions Met	Criterion number (as listed in protocol)	Protocol deviation entry granted?	If yes, date granted (dd-mmm-yy)
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___

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Baseline Clinical Labs Visit #1

Date of Result _____ - _____ - _____

If any clinically significant lab results, please record in Adverse Event CRF

dd mmm yy

Comprehensive Metabolic Profile	Result	Unit	Clinically Significant?
AG ratio			<input type="checkbox"/> Yes <input type="checkbox"/> No
Albumin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Alkaline Phosphatase			<input type="checkbox"/> Yes <input type="checkbox"/> No
AST (SGOT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
ALT (SGPT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
BUN			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bun/Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Calcium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Chloride			<input type="checkbox"/> Yes <input type="checkbox"/> No
Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Globulin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose			<input type="checkbox"/> Yes <input type="checkbox"/> No
Potassium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
Sodium			<input type="checkbox"/> Yes <input type="checkbox"/> No

Urinalysis	Result	Clinically significant?
Specific gravity		<input type="checkbox"/> Yes <input type="checkbox"/> No
PH		<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein		<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose		<input type="checkbox"/> Yes <input type="checkbox"/> No
Ketones		<input type="checkbox"/> Yes <input type="checkbox"/> No
Occult blood		<input type="checkbox"/> Yes <input type="checkbox"/> No
Leukocyte Esterase		<input type="checkbox"/> Yes <input type="checkbox"/> No
Nitrite		<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin		<input type="checkbox"/> Yes <input type="checkbox"/> No
Urobilinogen		<input type="checkbox"/> Yes <input type="checkbox"/> No

Thyroid Panel with TSH	Result	CS= Clinically significant
Thyroxine		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid hormone binding ratio		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid Stimulating Hormone		<input type="checkbox"/> Yes <input type="checkbox"/> No
Free Thyroxine Index		<input type="checkbox"/> Yes <input type="checkbox"/> No

Past Psychiatric Medical History

Record any Psychiatric Diagnosis made prior to visit 1. If Diagnosis date is not known write UNK, try to provide at least a year.

Diagnosis	Diagnosis Start date mm-dd-yyyy	Ongoing?	Stop Date mm-dd-yyyy
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	

Type and Duration of Previous Therapy

Record any non drug therapy prior to visit 1 using the codes provided to the side of this chart. If date is not known write UNK, try to provide at least a year. Record any drug therapy on the Psychotropic Medication page.

Type	Other Therapy Type	# Sessions	Per	Start Date mm-dd-yyyy	Ongoing ?	Stop Date mm-dd-yyyy
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	

Type of Psychotherapy Code
1 = CBT (Cognitive Behavioral Therapy) 2 = Behavioral 3 = Prolonged Exposure
4 = EMDR 5 = IPT (Interpersonal Therapy) 6 = Psychodynamic
7 = Holotropic Breathwork 8 = Group Psychotherapy 9 = Other

History of Suicide Attempts or Thoughts

Suicidal Tendencies: Check the box that in your opinion most represents the frequency which the subject has thoughts of death or suicide, as determined via psychiatric interview.

- None at all
- Slight: occasional thoughts of death without suicidal thoughts
- Mild: frequent thoughts of being better off dead/occasional thoughts of suicide (without a plan)
- Moderate: often thinks of suicide or has thought of specific method
- Severe: frequent suicidal thoughts, mentally rehearsed plan, has made a suicide gesture
- Extreme: made recent preparations for serious suicide attempt
- Very

Adult Suicidal Ideation Scale at Screening

Score at Screening: _____

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Past Use of Ecstasy

Has the subject ever used "Ecstasy"? YES NO

If Yes, # of Occasions _____

If Yes, when

- Within the last six months
- Seven to 11 months ago
- 12 to 24 months ago
- 25 to 36 months ago
- 37 to 48 months ago
- 49 to 60 months ago
- 61 months to 120 months
- Over 120 months ago.

Past Substance Use

Previous Alcohol Abuse/dependence yes no # of prior treatments_____

In the last six months yes no

Previous Drug Abuse/dependence ***yes*** ***no*** # of prior treatments_____

In the last six months ***yes*** ***no***

CAPS Scoring – Baseline PTSD Diagnosis Visit #3 Date of Evaluation - -
 mmm dd yy

Criterion A met (traumatic event)	Specify	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO	Frequency	Intensity
B (re-experiencing) sx (≥ 1)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
C (Avoidance) (≥ 3)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
D (Hyperarousal) (≥ 2)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
E (duration ≥ 1 month)?	Duration in Months	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
F(Distress/impairment)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
CURRENT PTSD (Criteria A-F)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
PTSD Global	Score			

Check this box if assessment occurred after screening and appropriate drug washout

Associated Features

#25	#26	#27	#28	#29	#30

Psychiatric History: SCID-Baseline diagnoses Visit #1

Date of Evaluation ____ - ____ - ____
 dd mmm yy

DSM Diagnosis	Yes	No
PTSD		
Unipolar Depression		
Panic Disorder		
Generalized Anxiety Disorder		
Bipolar Affective Disorder-1		
Bipolar Affective Disorder-II		
Dissociative Identity Disorder		
Psychosis		
Eating Disorder		
if Yes Active Purging?		
Borderline Personality Disorder		
Substance Abuse or dependence (60 days)		
Other DSM IV diagnosis-1		
Other DSM IV diagnosis-2		

General Well Being -Non-Experimental Sessions- Baseline

	Visit Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit #4			
Visit #5			
Visit #6			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of significant deterioration.
B= Probably faces risk of significant deterioration.
C= Faces risk of significant deterioration.

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Experimental Session # 1 Visit #7

Review of Inclusion and Exclusion Criteria

Has the subject refrained from consuming prohibited food or beverages? Yes No

Have all meds finished tapering? Yes No NA

Urine Pregnancy Test

Positive

Negative

Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen

Positive

Negative

Does subject continue to meet **All Inclusion** and **No Exclusion Criteria**? Yes No

If No Specify _____

Dosing

Date _____ - _____ - _____
 dd mmm yyyy

Record time initial dose MDMA administered _____

Record Bottle number of active placebo/ experimental MDMA _____

Second Dose of active placebo/experimental dose MDMA Administered?

Yes No

If yes, Record time second dose was administered _____

Record Bottle number of MDMA _____

Vital Signs -Experimental Session #1 Visit #7

Mark point where supplemental dose given. Make no mark if supplemental dose not given.

Monitoring: Blood Pressure and Pulse

Postdrug (h.min)	Time	SBP	DBP	Pulse
15 min predrug				
5 min predrug				
30 min postdrug				
1 hour post-drug				
1 h 30 min postdrug				
2 h postdrug				
2 h 30 min postdrug				
3 h postdurg				
3 h 30 min postdrug				
4 h postdrug				
4 h 30 min postdrug				
5 h postdrug				
5 h 30 min postdrug				
6 h postdrug				
6 h 30 min postdrug				
7 h postdrug				
7 h 30 min postdrug				
8 h postdrug				

Temperature

Postdrug (h.min)	Time	BT <input type="checkbox"/> F <input type="checkbox"/> C
15 min predrug		
1 hour post-drug		
2 hours post-drug		
3 hrs post-drug		
4 hrs post-drug		
5 hrs post-drug		
6 hrs post-drug		

Record any additional time points here:

SUDS -Experimental Session #1 Visit #7

Postdrug (h.min)	Time	SUDS						
15 min predrug		1	2	3	4	5	6	7
5 min predrug		1	2	3	4	5	6	7
1 h postdrug		1	2	3	4	5	6	7
2 h postdrug		1	2	3	4	5	6	7
3 h postdrug		1	2	3	4	5	6	7
4 h 30 min postdrug		1	2	3	4	5	6	7
6 h postdrug		1	2	3	4	5	6	7
7 h postdrug		1	2	3	4	5	6	7
8 h postdrug		1	2	3	4	5	6	7

Record any additional time points here:

		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7

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Integrative Psychotherapy After Experimental Session #1 (Visit 8)

Subject Belief of Condition Assignment Visit #8

Indicate what condition the subject believes they were assigned

- Low dose MDMA
- Experimental Dose MDMA

Indicate the subject's certainty about this belief of condition assignment

- Not at all certain
- Somewhat certain
- Certain
- Very certain

Adult Suicidal Ideation Scale After Experimental Session 1

Please administer the ASIQ after completion of integrative psychotherapy during Visit 8. Record the total score below.

Score: _____

Spontaneously Reported Side Effects Post Experimental Session #1 Visit #7-9

Please record the maximum intensity of any spontaneously reported effects for 7 days after drug administration.
 Report Duration for the first 24 hours.

Visit/Day	Visit 7 Day 0	Visit 7 Day 0	Visit 8 Day 1	Phone Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Duration in hours	Intensity								
Report Max Intensity for the 24 hour period 0= None Reported 1= Mild 2= Moderate 3= Severe	Report Duration to the nearest ½ hour for the first 24 hours only									
Check None if no symptoms are reported for the 24 hour period	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None
Anxiety										
Difficulty Concentrating										
Dizziness										
Drowsiness										
Dry mouth										
Fatigue										
Headache										
Heavy legs										
Impaired gait/balance										
Increased irritability										
Increased private worries										
Insomnia										
Jaw clenching, tight jaw										
Lack of appetite										
Low mood										
Nausea										
Need more sleep										
Nystagmus										
Parasthesias										
Perspiration										
Restlessness										
Sensitivity to cold										
Thirst										
Weakness										

General Well Being Visit #8-10

Complete at Visit 8; Since the Experimental Session at Visit 7 the subject has:

worsened remained pretty much the same improved

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit # 8			
Phone Day 1			
Phone Day 2			
Phone Day 3			
Phone Day 4			
Phone Day 5			
Phone Day 6			
Phone Day 7			
Visit #9			
Visit #10			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of significant deterioration.
B= Probably faces risk of significant deterioration.
C= Faces risk of significant deterioration.

Additional Non-Drug Psychotherapy

Check this box if the participant did not schedule any additional non-drug psychotherapy sessions in the period between Visit 8 and Visit 10. If this box is checked, then draw a diagonal line through the page. If any additional non-drug psychotherapy visits were scheduled, complete general well-being ratings for all additional visits and draw diagonal lines through any empty rows. Label each additional non-drug psychotherapy session with a fraction after 10, using consecutive numbers for each session (as 10.1, 10.2, etc).

Number of additional Visits = _____

General Well Being

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit 10.__			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of significant deterioration.
B= Probably faces risk of significant deterioration.
C= Faces risk of significant deterioration.

Final Evaluation (Visit 19)

CAPS Scoring – PTSD Diagnosis Visit #19

Date of Evaluation _____ - _____ - _____
 dd mmm yy

Criterion A met (traumatic event)	Specify	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO	Frequency	Intensity
B (re-experiencing) sx (≥ 1)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
C (Avoidance) (≥ 3)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
D (Hyperarousal) (≥ 2)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
E (duration ≥ 1 month)?	Duration in Months	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
F(Distress/impairment)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
CURRENT PTSD (Criteria A-F)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
PTSD Global	Score			

Associated Features

#25	#26	#27	#28	#29	#30

General Well Being Visit # _____ (16, 26, 35)

	Visit Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit # 19			

- 1= Very stable and calm
- 2= Stable and calm
- 3= Slightly stable and calm
- 4= Slightly distressed
- 5= Distressed
- 6= Very distressed

- A=** Does not face risk of significant deterioration.
- B=** Probably faces risk of significant deterioration.
- C=** Faces risk of significant deterioration.

Please check only one Visit 20 (End Randomized) Visit 37 (End Stage 2))

Reactions to Research Participation Questionnaire (RRPQ)

Please write in the numbers corresponding to the three top-ranked reasons for participating (the numbers to the left of each reason on the form. Write the number “1”, “2” or “3”) for each reason.

_____ 1. I was curious	_____ 4. I don't know	_____ 7. For the money
_____ 2. To help others	_____ 5. Thought it might improve my access to health care	_____ 8. I didn't want to say no
_____ 3. To help myself	_____ 6. Felt I had to	_____ 9. Other: _____ _____

Please write in the scale scores the RRPQ below.

- 1. Participation 1 _____
- 2. Personal Benefits 2 _____
- 3. Emotional Reaction 3 _____
- 4. Perceived Drawbacks 4 _____
- 5. Global Evaluation 5 _____

Subject Number _____

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Concomitant Medication CRF

Page X1 Series ____ √ if Last Page

Non Psychotropic Concomitant Medications

At Visit 3 record all non psychotropic medications currently being taken and check the prestudy box (include start date if known) Provide diag# (from Med Hx page). Record all new prescription and non-prescription non psychotropic medications taken after visit 3 through termination visit. Provide AE# (from AE page) or other Reason for Treatment. Check the continuing box if continuing at study termination. **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Med HX Diag #	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			

Subject Number _____

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Psychotropic Medication CRF

Page X2 Series _____ √ if last page

Psychotropic Medication and Tapering

- Record psychotropic medications previously used **and** psychotropic medications subject is on at visit1. Check the Prestudy box (include start date if known) and provide Disorder Code. Check Tapered box for medications tapered from V2 or V3. Provide route, dose and stop date for all medications.
- Record **all new psychotropic medications** taken after visit 1 through termination visit. Provide route, dose and start date. Provide AE# (from AE page) and check Rescue box if used as a rescue medication or complete Other Reason for Treatment. Check the Continuing box if continuing at study termination. **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Prestudy Disorder Code#	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	

***Code for prestudy disorders**

- 1 = Depression
- 3 = Panic Disorder
- 5 = Pain management (PRN)
- 7 = Obsessive-Compulsive Disorder (OCD)

- 2 = Anxiety
- 4 = Pain management (routine)
- 6 = Illness-related anxiety
- 8 = PTSD

Adverse Events

CHECK IF NONE

AE #	Adverse event Diagnosis	Serious? a	Onset date (dd/mmm/yy)	Resolution date (dd/mmm/yy)	Severity b	Frequency c	Action taken for Study d	Action taken- treatment e

a Serious?

- 1 = Serious*
- 2 = Not serious

* Serious = Fatal, life-threatening, requires prolonged hospitalization, results in persistent or significant disability, or requires medical or surgical intervention to prevent one of the outcomes defined as "serious" listed above.

b Severity

- 1 = Mild
- 2 = Moderate
- 3 = Severe

c Frequency

- 1 = Single/Intermittent
- 2 = Continuous

d Action Taken: Study

- 1 = None
- 2 = Interrupted session
- 3 = Delayed experimental session
- 4 = Discontinued experimental session
- 5 = Removed from study

e Action Taken: Treatment

- 1 = None
- 2 = Procedure or therapy
- 3 = Blood or Blood products
- 4 = Withdrawn from study due to AE
- 5 = Prescription Med
- 6 = Non Prescription Med
- 7 = Hospitalization
- 8 = IV Fluids
- 9 = Other specify

f Outcome

- 1 = Full recovery/return
- 2 = Persists, diminish
- 3 = Persists, worsen
- 4 = Persists, the same
- 5 = Alive with sequelae
- 6 = Death



Tuesday, July 16, 2013

Dr. Ingrid Pacey
3369 West 4th Ave.
Vancouver, BC V6R 1N6

Dear Dr. Pacey,

Re: Multidisciplinary Association for Psychedelic Studies (MAPS), Protocol No.: MP-4

Final Protocol Title: A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

IRB APPROVAL/REB ATTESTATION

IRB Approval of Amendments/Modifications to Initially Approved Research

Approved Item(s) include:

- Final Amended Protocol Version 2 dated 2013-JUN-20, incorporating Protocol Amendment No. 1
- Informed Consent Form Version Date: v2 2013-JUN-26
- Informed Consent Form Version Date: v3 2013-JUN-26 (Videotaping)

Approved by: ON IRB
IRB Chair: Dr. Morris Blajchman
Approval date: 2013-JUL-12

Current IRB Approved Consent Document(s)

Enclosed you will find the following personalized consent document(s):

- Informed Consent Form Version Date: v2 2013-JUN-26
- Informed Consent Form Version Date: v3 2013-JUN-26 (Videotaping)

The consent document(s) have been stamped *IRB Services Approved* on each page and are valid for use at your site.

Membership List

Attached you will find the current IRB Membership list for the IRB that reviewed this study.

Regulatory Authority Authorization

In addition to IRB approval, you are reminded that the protocol and any amendments require notification to or approval/authorization from Health Canada prior to implementation, except to remove an immediate hazard to subjects. **You must not implement the protocol and any amendment(s) until the regulatory requirements have been met.**



Compliance Statement/Attestation

IRB Services attests that the above document(s) have been approved, as described above, and the membership of the IRB complies with the requirements defined in Health Canada regulations, 21 CFR parts 56 and 312.3 and 45 CFR 46. The IRB carries out its functions in accordance with good clinical practices (e.g., ICH GCP Guidelines) and Health Canada regulations and in compliance with FDA 21 CFR parts 50 and 56, DHHS 45 CFR part 46, and the Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans, as appropriate to the research.

Should you require additional information please contact Jessica Cardin at 905-727-7989 ext. [REDACTED], or via email at [REDACTED]@irbservices.com.

Sincerely,
Institutional Review Board Services

[REDACTED]

[REDACTED]

Client Services
(Amendments & Ongoing Reporting Team)

Enclosure(s)

Cc [REDACTED] MAPS

SUBJECT INFORMATION AND CONSENT FORM

Study Title: A Randomized, Double-Blind, Dose Comparison
Phase 2 Pilot Study of Manualized 3,4-
methylenedioxymethamphetamine (MDMA)-assisted
Psychotherapy in 12 Subjects with Treatment-
Resistant Posttraumatic Stress Disorder (PTSD)-
Canada

PROTOCOL NO.: **MP-4**
Study Sponsor: Multidisciplinary Association for Psychedelic Studies
(MAPS)
1215 Mission Street, Santa Cruz, CA USA 95060
Phone: 831-429-6362 Fax: 831-429-6370

Investigator: **Dr. Ingrid Pacey MBBS FRCP[C]**

Address:
3369 West 4th Ave.
Vancouver BC V6R
1N6

Daytime telephone number(s): 604-732-9309

24-hour contact number(s):

Cellular number(s):

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This consent form describes a research study and your role as a participant. Please read this form carefully. Feel free to ask anything about the information provided; it is expected that you will have questions about it.

You are being asked to participate in this research study because you have been diagnosed with posttraumatic stress disorder (PTSD) and because your symptoms have not gone away after psychotherapy or medications for PTSD. You may also be in this study if you had trouble with treatments for your symptoms and had to stop using them.

Please ask the study therapists to explain any words or information in this consent that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE AND BACKGROUND

This small study is designed to provide information on whether MDMA-assisted psychotherapy is safe and helpful for subjects with posttraumatic stress disorder (PTSD). The study therapists plan to use the results of this study to design future studies of MDMA-assisted psychotherapy.

The study is sponsored by a US-based non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). MAPS' first small study of MDMA-assisted psychotherapy in 21 people with PTSD is finished in the U.S. MAPS has completed another MDMA/PTSD pilot study in 12 people in Switzerland. Three studies are currently enrolling, two in the U.S. and one in Israel.

MDMA is experimental, which means it has not been approved by Health Canada for medical use, except within research studies like this one. MDMA is illegal to use outside of research and is sometimes known as "Ecstasy" (which is supposed to contain MDMA but can often contain other drugs instead of or in addition to MDMA).

Before it became illegal, some psychotherapists combined MDMA with psychotherapy ("talk therapy") to help people with psychological problems, sometimes including PTSD. Though we do not know if it helps people with PTSD, we know that MDMA increases positive mood and also changes the way we see and think about the world around us, making it easier to think about and recall upsetting experiences, and people say they feel caring and forgiving toward themselves and others after MDMA. Most types of therapy that treat PTSD involve facing the trauma and PTSD symptoms and going over trauma-related emotions. Doing this reduces fear, defensiveness, avoiding things, places or feelings that trigger unwanted feelings or thoughts, and feeling emotionally numb or distant from relationships. If MDMA can temporarily decrease fear and avoidance and increase trust and connection between the person with PTSD and their therapist, then MDMA may make the therapy stronger and more likely to work. It is possible that these effects, when combined with psychotherapy, help people confront and go through the thoughts, memories and emotions related to PTSD.

This study will compare full dose MDMA with a comparator dose, meaning a dose that may or may not contain MDMA in it. During experimental sessions participants will receive full dose of MDMA or a comparator, possibly followed one and a half to two and a half hours later by a second dose equal to half the size of the first dose.

Length

This study can take up to fifteen months and 18 visits if you get the full dose from the beginning. The study can last an additional three months that include 12 more visits if you get the comparator dose and decide to go on to have MDMA-assisted therapy in a second part of the study, "Stage 2." The study also includes a long-term follow-up visit 12 months after the last experimental or open-label session.

Subject Responsibilities

If you and Dr. Pacey agree that you can and want to be in the study, you will have to come to all study visits. You will have to avoid taking any psychiatric medications from the beginning of the study up until your last study visit unless the study therapists make a specific exception, such as giving you medication for sleep or anxiety if needed temporarily between experimental sessions. If you are taking psychiatric medication, you will need to give Dr. Pacey permission to talk with your doctor about how best to stop taking your medication.

If you are currently seeing a psychotherapist, you may not begin any new psychotherapy or change the frequency or length of visits with your psychotherapist until after the final evaluation session.

For your safety, it is very important to tell the study doctor about all medications you are taking, including herbal or "natural" remedies, and to check with the study doctor before you begin taking a new medication while in this study.

Any study visit you have may be audio and/or video recorded for research and training purposes to help the researchers understand and learn about this type of therapy. The study therapists can give you access to these recordings to watch.

PROCEDURES/WHAT WILL HAPPEN TO YOU

SCREENING/EVALUATION AND BEGINNING OF STUDY

If you agree to take part in this study, you will first sign this form before any study-related procedures are performed. Before you can be in the research study, the study therapists must first make sure that you qualify for the study and that you are generally physically healthy. The screening process will take about 6 hours and may be done over multiple visits.

The tests will include the following:

- A questionnaire about your PTSD symptoms and how you deal with them in your everyday life. Your score on this questionnaire will be used to decide if you can be in the study. The study doctor asking you these questions will be a different person from the study doctors. This interview may be video recorded for research purposes.
- A questionnaire about your personality.
- A questionnaire about the quality of your sleep.
- A questionnaire about any detachment symptoms.
- A questionnaire about feelings of depression or other symptoms or feelings you might experience.
- A questionnaire about your mental health.
- Questions about your medical history, including questions about your emotional and psychiatric history. This may include any previous medical or psychiatric problems or treatment and may include questions about difficult experiences you may have had during childhood or at other times of your life.

- Questions about thoughts and feelings you might have about hurting or killing yourself.
- Two different tests of attention, memory and different types of problem solving. These are not tests of intelligence.
- A visual scale of pain and/or tinnitus (ringing in your ears) levels if you have these symptoms.
- A physical examination that will include measures of your blood pressure, pulse, temperature, and body weight.
- An ECG (electrocardiogram) will also be taken, which is a recording of the electrical activity of your heart.
- A sample of your blood (about 2 tablespoons, or about 30 mL) and a urine sample for routine laboratory testing, including tests of metabolism and liver function. An HIV test will also be run.
- A urine test for drugs of abuse. Your urine drug screen must be negative before experimental sessions.
- A urine pregnancy test if you are a woman and are able to get pregnant. Your urine pregnancy test must be negative for you to take part in the study.

BEGINNING OF STUDY

If you have decided that you want to be in the study and if the study therapists find that you are eligible, you will schedule your first introductory psychotherapy session with the two study therapists. If you were taking psychiatric medicines when the study therapists first checked to see if you could be in the study, you may have your PTSD and other symptoms measured again after you have stopped taking your medication.

You must let the study therapists know about any medical conditions or procedures that you had or are having, like surgery, within 48 hours of their occurrence.

You will need to give the study therapists the name and contact information (telephone number, cell phone number or email) of a relative, spouse or close friend to contact in case of medical emergency, as when you might be at risk of hurting yourself, or someone else, so they can reach that person to let them know what is going on.

SCHEDULE OF EVENTS

The types of visits in the study consist of screening, preparatory visits, experimental sessions, integrative visits, and follow up visits. Time is counted from the first study visit after you are selected to be in the study. The tables below show the type of visits you will have in Stage 1 and Stage 2 (if you are in the comparator group)

Table 1. Schedule of Events – Stage 1

Stage 1	Screening	Intro and Preparation			Therapy 1				Therapy 2				Evaluation	Therapy 3				Evaluation	Long Term Evaluation
		Both Groups												Full Dose MDMA Group Only					
Study Visit		¹ Enroll	2*	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Screening	X																		
Measure Symptoms	X							X				X	X				X	X	X
Memory/Attention tests	X												X					X	
Psychotherapy		X	X	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with Drug					X				X					X					
Medical Exam	X																		
Learn What You Received													X						

Table 2. Schedule of Events – Stage 2

Stage 2	Preparation	Therapy 1				Therapy 2				Evaluation	Therapy 3				Evaluation	Long Term Evaluation
		Comparator Group Only														
Study Visit #	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
Measure Symptoms	X*				X				X	X				X	X	X
Memory/Attention tests															X	
Psychotherapy	X		X	X	X		X	X	X			X	X	X		
Psychotherapy with MDMA		X				X					X					

* Symptoms may be measured again if more than 8 weeks passes between Visit 12 and 18.

 Experimental Sessions
 Study Measures

INTRODUCTORY PSYCHOTHERAPY SESSIONS:

Once screening is complete and you are enrolled in the study you will meet with the study therapists three separate times before the first experimental session. These visits will last from 60 to 90 minutes. During each introductory session, you will talk about the traumatic incidents that led to your PTSD, the ways PTSD symptoms are affecting your life and what you would like to achieve during these sessions. You will be asked questions about thoughts or feelings you might have about hurting or killing yourself during one of these preparatory sessions. You will also learn more about what to expect during experimental sessions. The introductory session may be recorded to audio and video, so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask the study therapists to let you hear or see these recordings if you wish.

SELECTION OF DRUG – FULL DOSE OR COMPARATOR DOSE?

This study is double blind, meaning that neither you nor the study researchers will know what you will get. However, in the event of an emergency the researchers can find out. The drug you get will be decided at random, as if by tossing a coin. Seven people will receive the full dose and five people will receive the comparator. You will have a 58% chance of receiving full dose MDMA and a 42% chance of receiving the comparator. You will find out what you received about 1 month after your second experimental session is complete. There will be 12 participants in this study.

Neither you, the person measuring your PTSD symptoms, nor the study doctors will know who is getting the high dose of MDMA and who is getting the low dose (known as “double blinded”) until after the study is completed. However, this information is available if needed in an emergency.

EXPERIMENTAL SESSIONS:

After you have completed three introductory therapy sessions, you will have two day-long experimental sessions with psychotherapy. During both sessions, you will have full dose MDMA or comparator dose. The sessions will happen three to five weeks apart. Each experimental session will last about eight hours, though one or both study therapists will remain with you for a longer time if needed.

One week before each of the experimental sessions, you will need to avoid taking:

- Any herbal supplement (except with prior permission);
- Any non-prescription medications, unless you have permission (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen [Tylenol]);
- Any prescription medications, unless you have permission (with the exception of birth control pills, thyroid hormones or other medications). You will need to talk to the study therapists about which medications are okay to keep taking.

You must not eat after midnight on the night before each session, but you can drink non-alcoholic liquids during this time, such as water or juice. You cannot use nicotine or

caffeine for 2 hours before and 6 hours after receiving the capsule. The study therapists will give you a paper with these instructions before your first experimental session.

First, you and the study therapists will discuss your goals for the experimental session, and the study therapists will answer any questions you still have about your experimental session.

Before an experimental session:

- Your urine will be tested for drugs of abuse.
- If you are a woman who can become pregnant, a urine pregnancy test will be done.

Throughout an experimental session:

- Your blood pressure and pulse will be measured every 30 minutes.
- Your temperature will be measured every 60 to 90 minutes.
- You will also complete a very short, simple test of how comfortable or upset you feel by marking a number on a sheet of paper that shows the way you feel at that moment. You will complete it every 60 to 90 minutes during each experimental session.
- About an hour before taking the capsule and about 6 hours afterward, you will answer questions about thoughts you might have about hurting or killing yourself.
- The study therapists will check in on you every hour or so to see how you are doing.

The experimental session may be audiotaped and videotaped, so that the study therapists will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. The study therapists can give you access to these recordings for you to watch or hear if you want them.

After urine test results come back, you will be given a capsule containing either the comparator dose or full dose MDMA. After taking the capsule, you will sit or lie down in a comfortable position. You can ask for an eye-shade if you wish. You will be able to listen to music through headphones during much of each experimental session. You might be asked to remove the headphones to talk to the study therapists, and you may also remove them yourself if you want to talk to the study therapists or for periods of silence. Lying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about the trauma. Both study therapists will stay with you, and they will help you if you need them to do so. They will talk to you and ask you to talk to them at least once an hour, but you can talk to them whenever you wish. There may be times when the study therapists will suggest that you stop talking for a while in order to pay attention to your thoughts and feelings. There will be water, juices or drinks containing electrolytes available to drink whenever you like within the limits of what is safe for your body. Later on, food will also be provided.

About one and a half to two and a half hours later, you and the study therapists will talk about taking a second capsule. The second dose will be half the amount of the first

dose. If you and the study therapists agree, then you will take the second dose. If you or the study therapists notice problems after the first capsule, then you will not get the second capsule.

The study therapists will continue to measure blood pressure, pulse and temperature, and they will watch for any side effects (unwanted effects or health problems), which will be treated if they occur. If this happens, the study therapists will let you know what they are doing.

If you are still confused or very upset eight or more hours after the start of the experimental session, the study therapists will stay with you until you have recovered more fully. If the study therapists think you are at risk for hurting yourself or someone else, they will either stay with you all night or have you stay in a nearby hospital until they are certain you are not at risk. If the study therapists decide that the effects of the drug have worn off and you are in an okay frame of mind, they will leave the office with the attendant in charge. The study therapists will ask you about thoughts of killing or harming yourself before and after taking the first capsule.

You will spend the night If you request and Dr. Pacey agrees, you may also have a companion stay with you at the office during or after an experimental session. An attendant will stay in another room at the same location from the time after you are done with the experimental session until the non-drug session on the next day. The attendant will offer dinner and breakfast, help you with any physical needs if requested, and contact Dr. Pacey to speak with her or to have her return to the office at your request or if the attendant thinks it is needed.

On the next day, you will have a non-drug therapy session with the study therapists. You will need to arrange ahead of time to have someone take you home from this session, because we don't know how the experimental session will affect you and some people report feeling tired or less alert. If you cannot find anyone to take you home, the study therapists will either call a taxi or make arrangements for someone to drive you home.

After you return home, one of the study therapists will telephone you every day for a week to ask about how you are feeling and decide whether you should see them for your next non-drug (integrative) psychotherapy session. These telephone calls will take approximately 5 to 15 minutes, though they can last as long you need them to. You may schedule additional meetings with the study therapists besides those that are scheduled as part of the study.

You can contact the study therapists at any time. The study therapists will give you a card with telephone numbers for reaching them, the organization sponsoring the study, or the Institutional Review Board – IRB Services (an independent committee that reviewed the ethical parts of this study to help protect the rights and welfare of study participants). At least one of the study therapists will be on call (reachable by telephone or pager) 24 hours a day throughout the research study.

If there are delays in following the usual study schedule, the study therapists will telephone you at least once a week to talk about how you're doing. These telephone calls will take approximately 15 minutes, and you should call the study therapists if any of the following things happens: you have an increase in symptoms for which you were previously took medication, you need to contact your outside therapist other than for the usual appointments, you start or stop taking prescribed medication, and/or you go to the hospital for any reason.

If you have very high blood pressure, get sick, or have a significant lasting unwanted effect or health problem after the first experimental session, you or the study therapists may decide that you should not participate in the second experimental session. If the study therapists decide to take you out of the study, they will let you know that they are doing this and their reason for doing this. If you are taken out of the study or decide you do not want to be in the study, the study therapists will ask you to complete final questionnaires about your PTSD and other symptoms and tests of memory and problem solving. If you decide you do not want to continue in the study during an experimental session, you will still have to stay in the office until the study therapists think that you are well enough to go and that all the effects of the drug have worn off.

The experimental sessions will occur three to five weeks apart. The experimental sessions will also be carried out in an identical manner.

At this time MDMA is not available for use outside of research studies. The study therapist will discuss treatment options with you at your last study visit.

PSYCHOTHERAPY AFTER EXPERIMENTAL SESSIONS :

After the experimental sessions, you will have regular psychotherapy to help you express, understand and integrate (bring together and connect to your life) any thoughts or feelings you may be having about your symptoms and their causes and about your experiences during experimental sessions. You will have psychotherapy with the study doctors the morning of the day after each experimental session and then during two additional sessions after each experimental session. These sessions will last 60 to 90 minutes. You and the study therapists will also discuss ways to use what you learned to help work on treating your PTSD, face and solve difficulties you may have faced during the experimental sessions and gain maximum benefit and understanding from experimental sessions. Each regular psychotherapy session may be recorded to audio and video and you can hear or see these recordings if you wish.

Before starting psychotherapy on the day after each experimental session, you will be asked to guess whether you received MDMA. You will not be told if your guess is correct. After you finish psychotherapy on the day after an experimental session, you will answer questions about thoughts and feelings you might have about hurting yourself. The study therapists will ask you these same questions about hurting or killing

yourself during each psychotherapy session, and during the second and seventh day of telephone contact with the study therapist. This is so the study therapists can have another way of making sure you are no in danger of hurting yourself.

You will complete a questionnaire about your PTSD symptoms on the third psychotherapy session after an experimental session.

If you had tinnitus or chronic pain before the study and mention any changes in these symptoms the study therapists will help you to record the changes.

MEASURING PTSD, DEPRESSION AND OTHER TESTS AFTER EXPERIMENTAL SESSIONS

Approximately three months after the start of the study (six weeks after the third experimental session), a study researcher will ask you about your PTSD and other symptoms. You will also have the same tests of attention, memory and different types of problem solving that you had at the beginning of the study. This visit should last about two and a half hours. These tests are so that the study therapists can tell if your symptoms have changed or stayed the same over time. As before, the tests will be given by another researcher who is not one of the study therapists.

After you complete these tests, you will meet with the other study therapists and they will ask you about thoughts about hurting or killing yourself. You and the study therapists will learn whether you got the comparator dose or full dose MDMA. The study researcher that measured your PTSD symptoms will not find out.

If you learn that you got the comparator dose, then you will have the option to go on to the next part of the study without finishing Stage 1, described below (Stage 2).

If you will not go on to Stage 2, then you will complete a questionnaire about your experience as a research subject. The study therapists will give you a memory aid card. This is for you to keep track of your health during the months in between your last visit with the researchers and the 12-month follow up visit, described below. The card will help you to remember to tell the researchers about any new problems or medical conditions, or changes in medication that happened during this time. You may have your regular doctor fill out this card for you. Your next study assessment will be the 12-month long-term follow-up.

OPEN-LABEL MDMA SESSION FOR PEOPLE WHO RECEIVED FULL DOSE

If you are one of the seven participants in the full dose group, you will have a third day-long experimental session with the same dose MDMA in Stage 1. After learning that you were in the full dose condition, you will schedule and complete your last experimental session, which will be "open label," meaning you will receive MDMA, but this time you will know. You will have the same regular psychotherapy visits after this last experimental session.

Approximately six months after the start of the study (two months after the third experimental session), you will meet with the study researcher again. The researcher will ask about your PTSD symptoms and you will fill out a questionnaire on feelings of depression, a sleep quality questionnaire, a dissociation symptoms questionnaire, and a PTSD symptom questionnaire. You will complete the two tests of memory, attention and problem solving. You will also be asked if you have had any thoughts about hurting or killing yourself. This visit should last about 2.5 and 3.5 hours.

OPEN-LABEL MDMA SESSIONS FOR PEOPLE WHO RECEIVED COMPARATOR DOSE (STAGE 2)

If you are one of the five subjects who got the comparator dose, you can take part in three open-label MDMA-assisted sessions scheduled 3 to 5 weeks apart as part of Stage 2. In this part of the study, you will receive an active dose of MDMA during each session. Signing this consent form means you agree to take part in the second part of the study. **The seven people who receive a full dose of MDMA during Stage 1 cannot take part in Stage 2.**

If you take part in Stage 2, you will have 12 more visits with the study therapists. These sessions will be like experimental sessions you had during the first part of the study, except that you will know you are getting an active dose of MDMA. You will also only have one preparatory session rather than three sessions. The study timing and procedures will be similar to Stage 1. In the first experimental session, you will receive an active dose of 100mg MDMA with an optional supplemental dose. If this dose feels optimal you have the option to receive the same dose in the second and third experimental sessions in Stage 2. If it does not feel optimal, you can discuss increasing the dose to 125mg MDMA in either one of the experimental sessions with your study therapists. The study therapists will make the final decision about the dose you will receive in the second and third experimental sessions.

You will have the same tests of your PTSD and other symptoms, personality and mental health two months after the third open-label experimental session. You will have the tests of memory, attention and problem solving with the study researcher. You will complete a questionnaire about your PTSD symptoms on every third psychotherapy session after the first and third experimental sessions. You will complete the scale of pain and tinnitus levels if you had them before the study. You will complete a questionnaire about your experience as a research subject.

At the two-month follow-up after your second experimental session, you will receive a memory aid card to help you keep track of your health in between your last visit and a follow up visit 12 months after the final experimental session. The card will help you to remember to tell the researchers about any new problems or medical conditions, or changes in medication that happened during this time. You may have your regular doctor fill out this card for you.

LONG-TERM FOLLOW-UP 12 MONTHS AFTER LAST EXPERIMENTAL SESSION

About 12 months after your last experimental session, you will either complete measurements of your PTSD symptoms over the phone or in person. You will complete questionnaires about your other symptoms and you will fill out a questionnaire on the positive and negative effects of being in the study. If you were only in Stage 1, then this will happen 12 months after your third experimental session, and if you were in Stage 2, then this will happen 12 months after the third experimental session in Stage 2.

The same study researcher who asked you about your PTSD symptoms will do so again, either in person or over the telephone. You will also answer the questionnaire about feelings of depression or other symptoms you might have, and questionnaires about your personality, any changes in your PTSD symptoms, any thoughts you have about the good and bad points of MDMA-assisted therapy, and your thoughts about taking MDMA. The study therapists will ask you questions about thoughts or feelings about killing yourself. If you completed the visual scale of pain and tinnitus before the 12-month follow-up, then you will complete it at 12-month follow up to measure changes in tinnitus and chronic pain symptoms if you had them before the study. There are no right or wrong answers to these questions.

The questionnaires may be mailed to you for you to fill out. It will come with an envelope that is already stamped and has only the researcher's address on it. Do not put your name on the questionnaires.

A researcher who is part of the study may ask you about any changes in medication or your mental health, including any benefits or harms, during the follow-up period between your last visit and the 12-month follow-up visit in person or over the phone.

The researchers will use your answers to these questionnaires to see if there are any long-lasting effects of being in the study, such as changes in PTSD symptoms or other life events.

POSSIBLE RISKS OR DISCOMFORTS

MDMA has not been widely tested in humans but as of May 2013 about 845 people have received MDMA in clinical research settings, without any serious unexpected problems happening.

Side effects during the MDMA experience that are less severe but more frequently reported, are:

- Lack of appetite (68%)
- Dry mouth (64%)
- Teeth grinding or tight jaw muscles (60%)
- Decreased concentration (53%)

- Thirst (48%)
- Restlessness (46%)

In two studies of MDMA in a total of 37 people with PTSD, these reactions were commonly reported after a full dose of MDMA:

- Fatigue (77%)
- Anxiety (74%)
- Muscular tightness/tight jaw (62%)
- Insomnia (61%)
- Headache (51%)
- Lack of appetite (48%)

Forty eight to 77% of subjects in previous studies and in a placebo-controlled study of MDMA-assisted psychotherapy in people with PTSD reported nausea, low mood, feeling cold, dizziness, impaired balance, disturbance in attention, restlessness, perspiration, thirst, feeling weak, and need for more sleep (from most to least commonly reported). When any of these side effects occur, they usually last less than four hours, though some people report that some of these side effects can last for more than twenty-four hours, and rarely longer, but no more than four days.

Risks from MDMA

Changes in vision, hearing or other senses: In other studies where MDMA was given to volunteers, most people reported experiencing minor changes in vision and hearing, such as sounds seeming closer or farther away than usual, or objects seeming brighter than usual, with these changes lasting 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness (12%-33% in healthy controls, 7% of people with PTSD given full dose MDMA). These studies did not report exactly how many people experienced perceptual changes.

Blood pressure and heart rate. These effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate. Average increase in systolic blood pressure is 35 mmHg (measurement unit for blood pressure) and average diastolic blood pressure increase is 20 mmHg. Heart rate may increase by 20 beats per minute (BPM).

Blood pressure rose well above normal levels in a few people (a little less than 5%) after MDMA was given in previous studies, but these people did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in people with pre-existing heart or blood vessel defects. These serious problems could include irregular heart beat, heart attack or stroke. We will screen all potential participants for preexisting heart problems before they are allowed to be in this study.

This doesn't guarantee that no heart problems will occur, but it does greatly reduce the risk of this happening.

Anxious or jittery feeling: Some people in previous studies (16%) felt over-stimulated or anxious. It usually lasted less than 30 minutes. Due to your PTSD, you may be more likely to have severe anxiety or panic attacks. Panic attack was reported by 4% of participants with PTSD. Letting yourself accept and feel those emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study therapists will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask the attendant to call the study therapists immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study therapists may require you to stay in a nearby hospital.

Serious problems and death: There have been some serious problems, and even deaths, associated with the use of Ecstasy, an illegal substance that may contain some MDMA, outside of controlled clinical or laboratory settings. Serious problems have included high fever, drinking too much liquid, convulsions, and liver damage. Some recreational users of Ecstasy have become severely anxious, depressed or paranoid (thinking that other people are against them). Since you will be taking moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur during or after the experimental session, but this does not guarantee that they could not occur. If they do occur, the study therapists are prepared to respond to these problems. There has been one case of irregular heartbeat in a controlled, clinical study of MDMA in a person with PTSD.

Insomnia & drowsiness: In previous studies, less than 23% of subjects without PTSD have reported insomnia (difficulty sleeping), and feeling tired, irritable, or drowsy for as long as 3 days after MDMA. Sixty-one percent of people with PTSD reported some insomnia, and 4% of people in two completed and one ongoing study in people with PTSD reported insomnia lasting more than 7 days.

Mood: Some after-effects of MDMA may be noticeable up to 2 or 3 days later. In people with PTSD, 39% reported low mood and 17% reported some rumination (private worries). In healthy people, a few people feel that their mood is better, but 14% feel it is worse.

Immune System: You will probably have a less active immune system for 2 or 3 days after MDMA. This may make you more likely to become sick with a cold or other

infection during this time. The study describing this finding did not say how many people in the study showed these changes.

Addiction: There is a small chance that you could become addicted to MDMA. One study found that up to 6% of people using Ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory, and in two completed studies in 37 people with PTSD, only one person reported trying ecstasy after being in the study. People who have had problems with drug abuse in the last 6 months should not take part in this study.

There may be unknown side effects or risks from the use of MDMA.

Possible Brain Damage

Experiments in rats and monkeys show that high and repeated doses of MDMA can change brain cells that release a chemical called serotonin; in mice only, the affected cells release dopamine. The changes include loss of the part of the cell (called "axons") that connects different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult tests of memory. Recent studies in monkeys and rodents suggest that the doses in studies finding damaged axons are too high to reflect typical human doses of ecstasy or MDMA used in studies.

Many studies found that people who had used Ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use Ecstasy and performed less well on tests of planning and impulse control. These differences are not big, but they have lasted for at least a year after people had stopped taking Ecstasy. Not all studies have found Ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use Ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take Ecstasy than people without these problems.

Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA, and did not see any changes in the brain, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change in the amount of blood found in a specific part of the brain, and did not see signs of brain injury. The decrease in blood volume might be from temporary lowering of a type of brain receptor, or it might be a sign of reduced function in this area. Findings from these

studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a medical laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few Ecstasy tablets in a recreational setting with people who did not take them found less improvement in memory in the people who took Ecstasy, and no other changes in thinking or planning. A study of MDMA-assisted psychotherapy in the US found that memory and learning were the same in people who got MDMA and people who got placebo. It is believed that the amount of MDMA you will receive will not produce any lasting changes in memory or planning ahead, though this cannot be guaranteed. You will not get a second dose of MDMA if they believe you are showing signs of memory problems.

Other Risks:

You should not drive or use machinery immediately after each experimental session (up to 24 hours afterwards). This is because the study medication may cause drowsiness, lack of co-ordination or slower reaction time.

If you are tested for drugs of abuse within three days of each experimental session, you may test positive. The study therapists will provide you with an information card in case you are tested for drugs of abuse, and if you are tested for drugs of abuse while you are in this study, you can have the person(s) testing you call the study therapists to verify that you are in this study.

The interviews you will have during the course of the study involve no specific risks or discomforts beyond those of a standard clinical interview situation. You may feel upset at the review of your emotional experiences, or you may feel boredom or fatigue. The medical evaluations involve some blood tests. The risks of blood drawing include temporary discomfort from the needle stick, bruising and, rarely, infection at the site of the needle stick. Fainting could also occur.

It is possible that after you stop taking psychiatric medication (as for depression or anxiety) as part of the study, you may start to have symptoms again. If this happens, you should talk with your outside therapist and the study therapists. If you have to start taking medication again, then the study therapists will have to take you out of the study.

Reproductive Risks:

Effects of MDMA on the growth and development of an unborn baby are not known, therefore you will not be allowed to enter the study if you are pregnant.

Women who are able to become pregnant must use one of the allowed birth control methods, such as birth-control pills or shots, IUD, and diaphragm used along with spermicide and with partner use of condom while they are in the study. The study doctors will explain these methods to you and will help you decide which might be best for you, and they can suggest to you where you can get more information and advice.

You will be tested at the start of the study and again before each experimental session to see if you are pregnant. If, at any time during the study, you suspect that you may be pregnant or are concerned that you may become pregnant, you must advise the study therapists immediately. If you should become pregnant during the study, the study therapists will help you get proper advice while you are pregnant and you will need to let them know about the health of your baby when he or she is born.

NEW FINDINGS

If any new information becomes available about MDMA while you are participating in this study, the study therapists will tell you about it as soon as possible.

POSSIBLE BENEFITS

Your symptoms of PTSD may improve while taking part in this study. There is no guarantee that you will benefit from being in this research study. Information learned from this study may help researchers to improve treatment for PTSD in the future.

COSTS

The sponsor of this study, Multidisciplinary Association for Psychedelic Studies (MAPS), will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for medical examinations, and for the experimental drug. You, your private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study.

You or your insurance will remain responsible for on-going treatment unrelated to the study.

REIMBURSEMENT FOR PARTICIPATION

The Sponsor, MAPS, will not pay for meals and lodgings or travel expenses.

The sponsor is paying your study therapists and study researchers for the time, effort and expenses to conduct this study.

ALTERNATIVES

One alternative to being in this study is to decide not to participate. You may decide to try other treatments for PTSD. There are other medications, such as Paxil (paroxetine) or Zoloft (sertraline) and anti-anxiety medications such as Xanax (alprazolam) and other forms of psychotherapy that you could try. If you are currently receiving psychotherapy and/or medication, you could continue with these.

CONFIDENTIALITY

All information collected will be treated and handled as confidentially as possible, except where disclosure is required by law. Although complete confidentiality is something the study team will try for, absolute confidentiality cannot be guaranteed.

As part of this research, the study doctor will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. When not in use, information will be stored in a locked office and will be kept for 25 years after study completion, as required by Canadian clinical trial regulations. Audio and video recordings will be stored for up to 25 years after their creation.

Some people need access to the information to monitor the study. Any paperwork copied will have any information that could be used to identify you removed first. Session recordings will not have your name or initials printed on them, only a number.

Medical records, including audio and video recordings, which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes.

Medical records may be looked at, at the study site, by

- Representatives of the sponsor, MAPS
- Health Canada and similar agencies in other countries, as the U.S. Food and Drug Administration (FDA)
- Governmental agencies in other countries; and
- IRB Services

Information from this study will be submitted to the sponsor, and to Health Canada and to governmental agencies in other countries (e.g. U.S. FDA). Information sent from the study site will not contain your name.

Results from this study may be presented in meetings or in publications. Your identity will not be disclosed in those presentations, which will mostly give averages of data.

All records in British Columbia are subject to subpoena by a court of law.

Audio and video recordings: Any information that could directly identify you will be removed from recordings (except unique voice or image identity). Access to recordings will be limited to research purposes.

You will be asked to give an additional consent at the end of the study in order for your audio or video recordings to be viewed by others, such as researchers working with the sponsor or therapists learning how to perform MDMA-assisted psychotherapy, but you do not have to agree to this in order to participate in the study. You may request to hear or see these recordings.

You have the right to check your study records and request changes if the information is not correct.

By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

TREATMENT AND COMPENSATION FOR INJURY

In the event of a study-related injury, the Sponsor will cover any costs that arise from treating the injury that is not covered by the provincial health plan or your private medical insurance (if any). Injuries that are not related to participation in the study will not be covered.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your decision to take part in this research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to participate.

In addition, you may withdraw from the study at any time. If you choose to do this, notify your study doctor before you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic to answer questions or complete tests.

WITHDRAWAL

The study therapists, the sponsor company, Health Canada and the US Food and Drug Administration (FDA) has the right to stop the study at any time, with or without your consent, for any of the following reasons:

- If you have an adverse event (unwanted effect or health problem) from the study drugs
- If for any other reason the study doctor judges that it is not in your best interest to continue in the study,
- If you need a treatment not allowed in this study, such as restarting medication for depression or anxiety,
- If you do not keep appointments and follow study rules
- If you do not take the study drug as instructed,
- If you become pregnant,
- If the study is canceled by the FDA, Health Canada or the sponsor company

QUESTIONS

If you have any questions about this study, its procedures, risks, benefits or your alternatives or rights or if at any time you feel you have experienced a research-related injury, contact:

Dr. Ingrid Pacey MBBS FRCP[C]
3369 West 4th Ave.
Vancouver BC V6R 1N6
Office: 604-732-9309
Cell: 604-767-8570

In case of an emergency, please contact Dr. Ingrid Pacey at phone number 604-732-9309/ 604-767-8570 OR go to the nearest hospital emergency department.

Please contact the Director, Human Research Protection Program, IRB Services, who is not affiliated with the research or the research team, if you:

- have questions about your role and rights as a research participant
- wish to obtain more information about clinical research in general
- have concerns, complaints or general questions about the research, or
- wish to provide input about the research study

You can do so in the following ways:

In writing: 300-372 Hollandview Trail, Aurora, ON L4G 0A5

By phone: 1-866-449-8591

By email: subjectinquiries@irbservices.com

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

SUBJECT'S STATEMENT OF CONSENT

Your participation in this study is voluntary. You may refuse to take part in or you may stop taking part in this study at any time. You should call the study doctors if you decide to do this. Your decision will not affect your current or future regular medical care or any benefits to which you are entitled at this site. The study doctors and/or the sponsor may stop your participation in this study at any time without your consent if they decide it is in your best interest or if you do not follow the study doctors' instructions.

You will need to have someone drive you home on the day after the experimental session. If you cannot find anyone to take you home, the study doctors will find someone to drive you.

You have read the information in this consent form and it has been discussed with you. All of your questions so far about the study and your participation in it have been answered. You freely consent to participate in this research study.

You will not donate blood while you are in the study and for at least 30 days after.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. **You will be given a copy of the consent form signed by you and the investigator.**

The study therapists have my permission to tell my regular doctor about my being in this study:

YES NO

SUBJECT	
Printed name	
Signature	
Date	

PERSON ADMINISTERING CONSENT	
Printed name	
Signature	
Date	

STATEMENT OF INVESTIGATOR:

(Investigator preferably to sign the consent form on the same date as the subject, but prior to first patient visit)

I acknowledge my responsibility for the care and well being of the above subject, to respect the rights and wishes of the subject, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

INVESTIGATOR	
Printed name	
Signature	
Date	

MAPS Study MP-4

SUBJECT INFORMATION AND CONSENT ADDENDUM FOR VIDEOTAPING

Study Title: "A Randomized, Double-Blind, Dose Comparison, Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada "

PROTOCOL NO.: M-P4

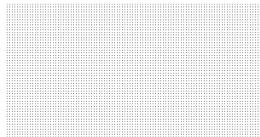
Study Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
1215 Mission St., Santa Cruz, CA USA 95060
Phone: 831-429-6362 Fax: 831-429-6370

Investigator: **Dr. Ingrid Pacey M.B.B.S. FRCP[C]**

Address:
3369 West 4th Ave.
Vancouver BC V6R
1N6

Daytime telephone number(s): 604-732-9309

24-hour contact number(s):



Cellular number(s):

PURPOSE

This consent addendum applies to your decisions about what the study therapists should do with video recordings of sessions in the research study for which you already signed an informed consent form. You will be asked what you would like the study therapists to do with the recordings of your study sessions.

BACKGROUND

The study therapists will record each introductory, MDMA-assisted and integrative psychotherapy session to audio and video. Psychotherapy sessions will be recorded so that the study therapists will have accurate records of the session and for research on the therapy and how it is performed. The study therapists may also use the video recordings to train therapists for future research studies. In addition, the interview at the beginning of the study about your PTSD symptoms may be video recorded for research purposes. You can either give permission for these recordings to be shown to people in the training program or not. The study therapists may also use your recordings to show other scientists how drug-assisted psychotherapy works. The study therapists, other

MAPS Study MP-4

scientists involved in this study and the sponsor of this study may review these videotapes to refine and improve this experimental treatment.

The recordings of experimental sessions will begin shortly before you take MDMA and continue for six to eight hours with the exception of some periods of silence. You may stop the recording at any point in time, and you may request that portions of the video recordings be erased. Your full name, initials and address will not be included in the recording.

At the end of Stage 1 or Stage 2 (your last visit before the 12-month follow up visit), when you have completed all of the questionnaires and measures, you can make a decision about what to do with audio and video recordings of your study sessions.

CONFIDENTIALITY

All information collected will be treated and handled as confidentially as possible. The study therapists will listen to or watch the video and audio recordings and no identifying information will be written or otherwise attached to the recordings.

Absolute confidentiality cannot be guaranteed.

This does not limit the duty of the researchers, study therapists and others to protect your privacy.

When not in use, information and video data will be stored in a locked storage area. Any copies of the video recordings used for training purposes will also be kept in a locked storage area and on a secure web server.

VOLUNTARY PARTICIPATION

Your decision to take part in this component of the research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to take part.

You may stop the recordings at any time during the session or request to have part or all of them erased.

In addition, you may withdraw your consent to use the audio or video recordings at any time.

There will be no penalty or loss of benefits if you decide you don't want recordings of your psychotherapy sessions to be saved.

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QUESTIONS

If you have any questions about this study, its procedures, risks, benefits or your alternatives or rights or if at any time you feel you have experienced a research-related injury, contact:

Dr. Ingrid Pacey MBBS
3369 West 4th Ave.
Vancouver BC V6R 1N6
Office: 604-732-9309
Cell: [REDACTED]

Please contact the Director, Human Research Protection Program, IRB Services, who is not affiliated with the research or the research team, if you:

- have questions about your role and rights as a research participant
- wish to obtain more information about clinical research in general
- have concerns, complaints or general questions about the research, or
- wish to provide input about the research study

You can do so in the following ways:

In writing: 300-372 Hollandview Trail, Aurora, ON L4G 0A5

By phone: 1-866-449-8591

By email: subjectinquiries@irbervices.com

SUBJECT'S STATEMENT OF CONSENT

The decision about how to use your video recordings is yours. Your decision will not affect your current or future regular medical care or any benefits to which you are entitled at this site, or your participation in the study.

You have read the information in this consent form and it has been discussed with you. All of your questions so far about the study and your participation in it have been answered. You freely decided what will be done with your video recordings.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. **You have been told that you will be given a copy of the consent form signed by you and the study therapist.**

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Your signature below indicates your consent. Please select all that apply of the following options:

- You would like the study therapists to erase the video recordings of all or some of your sessions so that no copies will be saved.
If you request only portions or certain sessions to be erased, which are they?

- You would like the study therapists to keep your recordings but not show them in training programs or scientific presentations.
- You would like to allow your recordings to be shown to therapists as part of a training program for therapists to do MDMA-assisted psychotherapy.
- You would like to allow your recordings to be shown as part of scientific presentations about MDMA-assisted psychotherapy.

SUBJECT	
Printed name	
Signature	
Date	

PERSON ADMINISTERING CONSENT	
Printed name	
Signature	
Date	

INVESTIGATOR	
Printed name	
Signature	
Date	

CLINICAL TRIAL SITE INFORMATION FORM

INSTRUCTIONS: ALL FIELDS MUST BE COMPLETED PRIOR TO SUBMITTING THIS FORM TO THE RELEVANT DIRECTORATE.
PLEASE REFER TO THE GUIDE IN ITS ENTIRETY WHEN COMPLETING THIS FORM.

PART 1 – CLINICAL TRIAL PROTOCOL INFORMATION				
Please select the appropriate box				
Type of Submission:	Reason(s) for Change: Sponsor contact			
<input type="checkbox"/> Clinical Trial Application (CTA) <input checked="" type="checkbox"/> Clinical Trial Application Amendment (CTA-A)	<input checked="" type="checkbox"/> Change of Address (please specify): 1215 Mission St, Santa Cruz, CA 95060_ <input type="checkbox"/> Change in Qualified Investigator _____ Name of Previous QI: <input type="checkbox"/> Change in Research Ethics Board <input type="checkbox"/> Change in Ongoing Site <input type="checkbox"/> Addition of a New Site <input checked="" type="checkbox"/> Other (please specify): _Change in protocol title			
1. Clinical Trial Protocol Title				
A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada				
2. Clinical Trial Protocol Number MP-4	3. Clinical Trial Control Number (if assigned) 127822	4. Health Canada's Central Registry (CR) file Number (if assigned) 9247-M2554-21C		
PART 2 – DRUG PRODUCT / SPONSOR INFORMATION				
A) Drug Product Information				
5. Brand Name: NONE				
6. Proper, Common or Non-Proprietary Name: (+/-)-3,4-methylenedioxymethamphetamine				
B) Sponsor Information				
7. Name of Sponsor (Full Name – No Abbreviation) Multidisciplinary Association for Psychedelic Studies				
8. Street Number 1215	Street Name: Mission Street	Suite	P.O Box	9. City/Town: Santa Cruz
10. Province/State: CA	11. Country: USA		12. Postal/Zip Code 95060	
Contact Person for Sponsor				
13. Salutation: Ms.	First Name	Surname	14. Telephone	15. Fax
16. Language Preference <input checked="" type="checkbox"/> English <input type="checkbox"/> French		17. Title Clinical Research	18. Email address: @maps.org	
C) Contact for THIS Clinical Trial				
Please complete this section ONLY when this contact is NOT the same as the Contact Person for the Sponsor.				
19. Salutation	First Name	Surname	20. Email address	
21. Company/Organization Name (Full Name – No Abbreviations)				

22. Street Number	Street Name	Suite	P.O Box	23. City/Town
24. Province/State	25. Country		26. Postal/Zip Code	
27. Telephone (area code - ### - #####)		28. Fax (area code - ### - #####)		29. Language Preference <input type="checkbox"/> English <input type="checkbox"/> French
PART 3 – CLINICAL TRIAL SITE INFORMATION				
A) Clinical Trial Site				
30. Name of Site (Full Name – No Abbreviation)				
31. Street Number:	Street Name	Suite	P.O Box	32. City/Town:
33. Province/Territory			34. Postal/ Code:	
35. Commencement Date of the Clinical Trial (YYYY-MM-DD) or Clinical Trial Amendment: 2013-Sep-15				
B) Qualified Investigator Same as A Above <input type="checkbox"/>				
A Qualified Investigator Undertaking (QIU) form must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified above. The completed undertaking must be retained for a period of 25 years.				
36. First Name: Ingrid		Surname Pacey	Medical Designation(s): M.B.B.S., F.R.C.P.[C]	37. Title: Psychiatrist, Research Affiliate, CARBC
38. Language Preference <input checked="" type="checkbox"/> English <input type="checkbox"/> French	39. Street Number 3369	Street Name: West 4 th Ave		Suite
40. City/Town Vancouver	41. Province/Territory: BC		42. Postal Code: V6R 1N6	
43. Email Address: Ingridpacey@gmail.com		44. Telephone (604)-732-9309		45. Fax N/A
C) Research Ethics Board Approval				
A Research Ethics Board Attestation (REBA) form must be completed by the Research Ethics Board that reviewed and approved the protocol and informed consent form for the clinical trial at the site specified above. The completed attestation must be retained for a period of 25 years.				
46. Name of Research Ethics Board, including affiliations (if applicable) (Full Name – No Abbreviation) IRB Services IRB Services				
47. Date of Approval (2013-07-12)				
48. Street Number 372	Street Name: Hollandview Trail		Suite: 300	49. City/Town: Aurora
50. Province/Territory: ON	51. Postal Code: L4G 0A5	52. Salutation Ms.	First Name: Jessica	Surname: Cardin
53. Telephone (905)-727-7989 Ext. 296		54. Fax (905)-727-7990		55. Language Preference <input checked="" type="checkbox"/> English <input type="checkbox"/> French
56. Title: Senior Co-ordinator, client services			57. Email Address jcardin@irbservices.com	

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized
3,4-methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects
with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada**

Amendment 1 Version 2

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC,
University of Victoria

Study Number: M-P4

Control # 167090 Parent CTA Control # 127822

2.1 Table of Contents

Module 2: Common Technical Document Summaries - Quality (Chemistry and Manufacturing) Information

2.1 Common Technical Document Table of Contents

2.3.1 Quality Overall Summary – Final

2.3.2 Quality Overall Summary – Tracked changes

Module 3: Quality - Additional supporting Quality Information

A_1 2010 Analysis of Stability

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized
3,4-methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada
Amendment 1 Version 2**

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate,
CARBC, University of Victoria

Study Number: M-P4

Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title:

A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC, University of Victoria

Co-Investigators: Andrew Feldmar; Zach Walsh, Ph.D R. Psych. Assistant Professor, Department of Psychology, University of British Columbia

Expected Study Dates Sept 15, 2013 – May 2016

Approved by: IRB Services, Ontario Committee, July 12, 2013

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 125 mg (full dose-initial dose), 100 mg (active dose Stage 2-initial dose), 62.5 (full dose-supplemental dose), 50 mg (comparator-initial dose; also active dose Stage 2-supplemental dose), 25 mg (comparator- supplemental dose, and optional titration initial dose for Stage 2), 12.5 mg (optional titration supplemental dose, Stage 2), [Full dose strength capsules are used in Stage 1. Supplemental doses are used in both stages and are administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose; Titration dosing occurs in Stage 2, See Table 1 and 2 for dosage by visit.]

Table 1. Stage 1 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

Experimental Session	Dose	Initial Dose	Optional Supplemental Dose	Min-Max Cumulative Dose	Min-Max Cumulative Dose with Titration
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

Primary Efficacy and Safety Objectives: Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

Safety Objectives: The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (CSSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.
- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.

- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

Secondary Objectives:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint

In specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

Study Design and Duration

3.5 Purpose

This Phase 2 pilot study is a randomized, double-blind, dose comparison study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment.

After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.

A therapy team will conduct psychotherapy visits according to the treatment manual provided. The team will include two licensed therapists who will work together as cotherapists.

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months
- Comparator dose subjects who complete Stage 2: 18 months.

Number of Centres

The study will take place at the offices of [REDACTED]. All psychotherapy, including both non-drug and MDMA-assisted sessions, [REDACTED]. Assessments of PTSD symptoms and neurocognitive function will also be performed in the offices of the Principal Investigator.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the primary study endpoint.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with chronic, treatment-resistant PTSD and with a CAPS score of 60 or higher. Treatment resistance is defined as being unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to inability to tolerate psychotherapy and/or pharmacotherapy. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must

meet all of the inclusion criteria without meeting any of the exclusion criteria. Participants must reside in Canada.

Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 50, 62.5, 100 and 125 mg. The initial full dose of MDMA is 125 mg and the supplemental full dose is 62.5 mg. The initial comparator dose is 50 mg, and the supplemental comparator dose is 25 mg. The initial active dose for the first Stage 2 session consists of an initial dose of 100 mg and a supplemental dose of 50 mg, with optional titration doses of 25 mg initial and 12.5 mg supplemental dose available in the second and third open-label experimental sessions of Stage 2. MDMA has been obtained from Lipomed AG. All doses of MDMA will be compounded with the inactive substance lactose to ensure that all the blinded capsules weigh the same amount.

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [1-6]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [3, 11, 12]. The initial full 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 drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25 mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions. The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.

The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

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 1.5 to 2.5 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 the supplemental dose of MDMA is contraindicated or not necessary.

There will be not be any changes in dose regimen across the first two blinded sessions. Full dose participants will receive the same dose regimen during a third session in an open-label context after unblinding per protocol. Subjects in the comparator dose condition will not complete Stage 1, but will continue to Stage 2. In Stage 2, they will receive the active dose for the first Stage 2 session, and they can receive the active or full dose during the second and third sessions via a clinical titration dosing strategy.

If the participant experiences hypertension that required clinical intervention or had a serious adverse event that is possibly or probably related to study drug, then no further doses of MDMA will be administered.

S Drug Substance

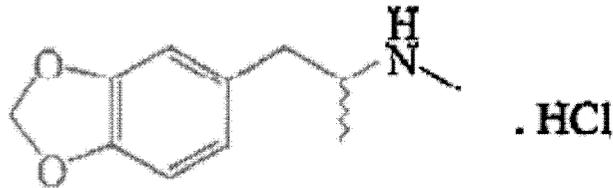
S.1 General Information

The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by [REDACTED] This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no [REDACTED] with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually by [REDACTED] between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street “ecstasy” (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report submitted for in Modules 2 and 3 of the CTA approved on March 17, 2009, control # 127822).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.

Step 2: MDA-nitrostyrol + LiAlH₄ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [REDACTED] of the University of Bern. Specifications of manufacture, including solvent and procedures, are translated in the second report of [REDACTED] in Modules 2 and 3 for CTA approved on March 17, 2009, control # 127822.

S.2.3 Control of Materials

See above and contained in report by Brenneisen, p. 1

S.3 Characterization:

Batch number is [REDACTED]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]. One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2 of report supplied in Modules 2 and 3 of CTA approved March 17, 2009, control # 127822).

Validation: From manufacturer, data available upon request ([REDACTED])

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] (see attachment and reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(Max)}=1\ 234 \pm 1\ \text{nm}$

$\epsilon_{mol} = 3800 \pm 500$

Melting Point: $149 \pm 3\ \text{C}$

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: $0.3 \pm 0.3\%$

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by Brenneisen:

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

Injection: 250 C, splitless 1 μL

Detection: full scan

Identity (HPLC-DAD): TR = 5.8 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA) 154 (basepeak) 162, 289 (M⁺) MDMA-TFA

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from [REDACTED]

S.4.4 Batch Analysis:

As listed above, the batch is [REDACTED]

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

UV, in distilled water, $\lambda_{(\text{MAX})}.1 = 234.0 \text{ nm}$

$\epsilon_{\text{mol}.1} = 3939$

$\lambda_{(\text{MAX})}.2 = 285.0 \text{ nm}$

$\epsilon_{\text{mol}.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%

Freebase content: 83.51%

Water content: 055%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 100 ppm

Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: **Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%**

Tests for presence of heavy metals: **Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm**

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED] and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [REDACTED] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment 4 in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

██████████ reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

██████████ also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

In an analysis performed in February 2010, the material was 99.9% pure and there was no evidence of decomposition products (see attached document). Heavy metals were < 100 ppm, and residues below 1%.

P. Drug Product

The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: initial Stage 1 full dose of 125 mg; supplemental Stage 1 full dose of 62.5 mg; initial Stage 1 comparator dose of 50 mg; supplemental Stage 1 comparator dose of 25 mg; initial Stage 2 active dose of 100 mg; supplemental Stage 2 active dose of 50 mg; optional initial Stage 2 titration dose of 25 mg; optional supplemental Stage 2 titration dose of 12.5 mg, plus lactose to reach equivalent weight of 236.5 ± 1.5 mg per capsule for all blinded doses. There are no other ingredients in these capsules. The capsules were prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but have been compounded by Kerrisdale Pharmacy, in Vancouver, BC. The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies [1, 8, 11, 13-15] and on narrative reports of MDMA-assisted therapy [12, 16]. The dose of 125 mg from the same supply has been used in a previous sponsor-supported research study conducted in Switzerland [15]. The sponsor chose the comparator dose on the basis of research in people with PTSD and in healthy controls [4, 8, 13, 15], with 50 mg expected to exhibit some activity without producing the same degree of effects. The active dose or doses close to it have been used in studies in healthy controls and is expected to produce most but possibly not all of the effects produced by the full dose [6, 17-20]. The sponsor selected an inactive material to help maintain the blind by ensuring that all blinded doses are of equivalent weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

The encapsulation has been performed by a compounding pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all blinded capsules have similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of blinded full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed in Kerrisdale Pharmacy, 5591 West. Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk, the licensed dealer, has encapsulated all doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy supplied the capsules and lactose. Compounded MDMA was weighed to the appropriate dose and placed in clear gelatin capsules, one dose per capsule. All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A "packing stat" was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. All 108 capsules are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose 125 mg (23 capsules), 50 mg (27 capsules), 62.5 mg (23 capsules), 25 mg (22 capsules), 12.5 mg (10 capsules) and a varying amount of lactose to maintain equal weight for all blinded doses.

The lactose monohydrate (chemical formula = $C_{12}H_{22}O_{11} \cdot H_2O$) was manufactured by

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

Randomization will be performed via the use of a web-based randomization program. An unblinded randomization monitor will generate the randomization list at the beginning of the study. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions.

P.3.3 Batch Formula

The batch analyses for [REDACTED] lactose monohydrate are provided in the reports supplied by the manufacturer. [REDACTED] passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA.

Full initial dose: 125 mg + 113.5 mg lactose

Full supplemental dose: 62.5 mg + 174.1 mg lactose

Active Stage 2 initial dose: 100 mg + 143.0 mg lactose

Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose

Comparator initial dose: 50 mg + 184.9 mg lactose

Comparator supplemental dose: 25 mg + 211.0 mg lactose

Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose

Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose

Capsules placed in individual inner envelopes, which are placed in a numbered primary container.

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all capsules of the product to ensure that blinded capsules are of equivalent weight.

The lactose used will be Lactose Monohydrate [REDACTED]

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is [REDACTED]

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, [REDACTED], issued by the manufacturer, [REDACTED] lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of < = 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of clear capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and will be stored with the rest of the capsules in a separate closed bottle in Kerrisdale Pharmacy. Pharmacist Colin Holyk will test these capsules for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

P.7 Container Closure System

All doses of MDMA will be in the form of clear capsules. The MDMA capsules will be stored in clear cellophane packages. Each package (primary container) will be assigned a container number intended for use in the randomization process so as to maintain the double blind. All packages will be appropriately stored in the Kerrisdale Pharmacy.

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

A Attachments:

1. Attachments containing manufacturer sheets, requested analyses and certificates of suitability contained in Modules 2 and 3 submitted in CTA approved March 17, 2009, control # 127822

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects*. J Clin Psychopharmacol, 2000. **20**(4): p. 455-66.
2. Freedman, R.R., C.E. Johanson, and M.E. Tancer, *Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2005. **183**(2): p. 248-56.
3. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations*. Behav Brain Res, 1996. **73**(1-2): p. 103-7.
4. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. **162**(4): p. 396-405.
5. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function*. Psychopharmacology (Berl), 2006. **187**(4): p. 467-75.
6. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA*. Psychopharmacology (Berl), 2001. **154**(2): p. 161-8.
7. de la Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans*. Br J Clin Pharmacol, 2000. **49**(2): p. 104-9.
8. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
9. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans*. J Pharmacol Exp Ther, 1999. **290**(1): p. 136-45.
10. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP*. Drug Alcohol Depend, 2003. **72**(1): p. 33-44.
11. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. J Psychoactive Drugs, 1986. **18**(4): p. 319-27.
12. Stolaroff, M., *The Secret Chief Revealed: Conversations with a pioneer of the underground therapy movement*. 2004, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.
13. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder*. J Psychoactive Drugs, 2008. **40**(3): p. 225-36.
14. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study*. J Psychopharmacol, 2011. **25**(4): p. 439-52.
15. Oehen, P., et al., *A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)*. J Psychopharmacol, 2013. **27**(1): p. 40-52.

16. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.
17. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss*. *Psychopharmacology (Berl)*, 2010. **209**(1): p. 69-76.
18. Farre, M., et al., *Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics*. *Psychopharmacology (Berl)*, 2004. **173**(3-4): p. 364-75.
19. Ramaekers, J.G. and K.P. Kuypers, *Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol*. *Neuropsychopharmacology*, 2006. **31**(5): p. 1048-55.
20. Bedi, G., et al., *Effects of MDMA on sociability and neural response to social threat and social reward*. *Psychopharmacology (Berl)*, 2009. **207**(1): p. 73-83.

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:
**~~A Randomized, Active Placebo-controlled~~ Double-Blind, Dose Comparison Phase 2
Pilot Study of Manualized
3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12
Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-
Canada
Amendment 1 Version 2**
Sponsor: Multidisciplinary Association for Psychedelic Studies
Principal Investigator: Dr. Ingrid Pacey MB,BS, FRCP[C], Research Affiliate,
CARBC, University of Victoria
Study Number: M-P4
Control # 167090 Parent CTA Control # 127822

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Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title:

A Randomized, Active-Placebo-controlled Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB-BS FRCP[C], Research Affiliate, CARBC, University of Victoria

Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD;

Expected Study Dates ~~Jan 2009–April 2010~~ Sept 15, 2013 – May 2016

Approved by: IRB Services, BC Ontario Committee, ~~November 21, 2008~~ July 12, 2013

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 12.5 mg (full dose-initial dose), 100 mg (active placebo-dose Stage 2-initial dose), 62.5 (full dose-supplemental dose), 2550 mg (comparator-initial dose; also active placebo-initial dose), 62.5 (experimental-dose Stage 2-supplemental dose), 125 mg (experimental-comparator- supplemental dose-, and optional titration initial dose)-, 12.5 mg (optional titration supplemental dose, Stage 2), [Full dose strength capsules are used in Stage 1. Supplemental doses are used in both stages and are administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose; Titration dosing occurs in Stage 2. See Table 1 and 2 for dosage by visit.]

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Table 1. Stage 1 Drug Doses

<u>Experimental Session</u>	<u>Dose</u>	<u>Initial Dose</u>	<u>Optional Supplemental Dose</u>	<u>Min-Max Cumulative Dose</u>
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

Table 2. Stage 2 Drug Doses

<u>Experimental Session</u>	<u>Dose</u>	<u>Initial Dose</u>	<u>Optional Supplemental Dose</u>	<u>Min-Max Cumulative Dose</u>	<u>Min-Max Cumulative Dose with Titration</u>
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

Primary Efficacy and Safety Objectives: The primary objective of this study is to assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline 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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks (the primary endpoint, one month after the third experimental (blinded) session).

The investigators will also gather information on physiological effects and side effects after MDMA. *Safety Objectives:* The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.~~

- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (CSSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.
- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

Secondary Objectives:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.
- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint

In specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

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Study Design and Duration

The proposed 3.5 Purpose

~~This Phase 2 pilot study will employ is a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three comparison study in~~

~~12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be hours and scheduled three to five weeks after the previous session. Participants will undergo one apart, within a moderate course of non-drug psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. The study will be unblinded one month after the second~~

~~Symptoms of PTSD and depression will be experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment.~~

~~After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining~~

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~~neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.~~

~~The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.~~

~~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~~ used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

~~A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.~~

~~A therapy team will conduct psychotherapy visits according the treatment manual provided. The team will include two licensed therapists who will work together as cotherapists.~~

~~Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy experimental session, for a total of about 8 months.~~

- ~~• Full dose subjects completing Stage 1 only: 15 months~~
- ~~• Comparator dose subjects who complete Stage 2: 18 months.~~

Number of Centres

~~The study will take place at one center:~~

~~Dr. Ingrid Pacey. Assessments of PTSD symptoms and neurocognitive function will also be performed in the offices of the independent rater, Dr.~~

~~Karen Tallman, located at the same street address as the offices of the principal investigator~~
Principal Investigator.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the primary study endpoint.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with chronic, treatment-resistant PTSD and with a CAPS score of ~~50~~60 or higher. Treatment resistance is defined as being unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to inability to tolerate psychotherapy and/or pharmacotherapy. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all of the inclusion criteria ~~listed below~~ without meeting any of the exclusion criteria. Participants must reside in Canada.

Drug Formulation

Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 50, 62.5, 100 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. The initial full dose of MDMA is 125 mg and the supplemental full dose is 62.5 mg. The initial comparator dose is 50 mg, and the supplemental comparator dose is 25 mg. The initial active dose for the first Stage 2 session consists of an initial dose of 100 mg and a supplemental dose of 50 mg, with optional titration doses of 25 mg initial and 12.5 mg supplemental dose available in the second and third open-label experimental sessions of Stage 2. MDMA will be has been obtained from Lipomed AG. Active placebo~~ All doses of MDMA will also contain be compounded with the inactive substance lactose to ensure that ~~experimental dose and active placebo dose~~ all the blinded capsules weigh the same amount.

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the ~~experimental full dose condition~~ are identical to those in use in other MAPS sponsor-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.~~ Previous researchers have also used doses within this range [1-3][1-6]. The supplemental dose is also identical to the one used in the US study. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [3, 11, 12]. The initial full 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 drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25 mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions. The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [4, 5] 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 [5]. The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

As described above, capsules Capsules containing the initial dose of MDMA will be administered at approximately 10:00 AM. Supplemental doses will be administered upon mutual agreement by the investigators and participant one and a half 1.5 to two and a half 2.5 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. the supplemental dose of MDMA is contraindicated or not necessary.

There will be not be any changes in dose regimen across the three MDMA-assisted first two blinded sessions. If the participant experienced hypertension that required clinical intervention or had a serious adverse event during an experimental session Full dose participants will receive the same dose regimen during a third session in an open-label context after unblinding per protocol. Subjects in the comparator dose condition will not complete Stage 1, but will continue to Stage 2. In Stage 2, they will receive the active dose for the first Stage 2 session, and they can receive the active or full dose during the second and third sessions via a clinical titration dosing strategy.

If the participant experiences hypertension that required clinical intervention or had a serious adverse event that is possibly or probably related to study drug, then no further doses of MDMA will be administered.

S Drug Substance

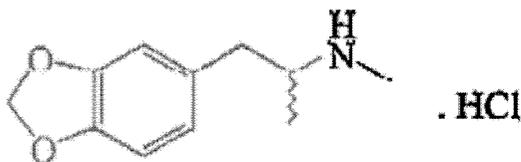
S.1 General Information

The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N, -alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by [redacted]. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. [redacted] with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually by [redacted] between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials

have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report submitted for in Modules 2 and 3 of the CTA approved on March 17, 2009, control # 127822).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.

Step 2: MDA-nitrostyrol + LiAlH₄ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [REDACTED]

Specifications of manufacture, including solvent and procedures, are translated in the second report of [REDACTED] in Modules 2 and 3 for CTA approved on March 17, 2009, control # 127822.

S.2.3 Control of Materials

See above and contained in report by [REDACTED] p. 1

S.3 Characterization:

Batch number is MDM-94-HC/94.1B5.5

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]. One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: [REDACTED] performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2 of report supplied in Modules 2 and 3 of CTA approved March 17, 2009, control # 127822).

Validation: From manufacturer, data available upon request ([REDACTED]).

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] (see attachment and listed above reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(Max)}$ = 1 234 +/- 1 nm

ϵ_{mol} = 3800 +/- 500

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by [REDACTED]

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase: H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

Injection: 250 C, splitless 1 μL

Detection: full scan

Identity (HPLC-DAD): TR = 75.8 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA) 154 (basepeak) 162, 289 (M⁺) MDMA-TFA

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from [REDACTED]

S.4.4 Batch Analysis:

As listed above, the batch is MDM-94-HC/94.1B5.5.

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

UV, in distilled water, $\lambda_{(\text{MAX})}.1 = 234.0 \text{ nm}$

$\epsilon_{\text{mol}.1} = 3939$

$\lambda_{(\text{MAX})}.2 = 285.0 \text{ nm}$

$\epsilon_{\text{mol}.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%

Freebase content: 83.51%

Water content: 055%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 100 ppm

Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: **Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%**

Tests for presence of heavy metals: **Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm**

More details are presented in the attached report (in German).

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S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED] and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [REDACTED] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment number 4, listed below) in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

Brenneisen reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

In an analysis performed in February 2010, the material was 99.9% pure and there was no evidence of decomposition products (see attached document). Heavy metals were < 100 ppm, and residues below 1%.

P. Drug Product

The drug product will consist of 00-opaque03 clear gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: ~~Experimental dose initial Stage 1 full dose of 125 mg; supplemental Stage 1 full dose 125 mg MDMA per capsule; experimental of 62.5 mg; initial Stage 1 comparator dose of 50 mg, supplemental Stage 1 comparator dose 62.5 mg MDMA per capsule; of 25 mg; initial Stage 2 active placebo initial dose 25 mg MDMA plus lactose to reach equivalent weight of 125 mg capsule per capsule; of 100 mg; supplemental Stage 2 active placebo supplemental dose of 50 mg; optional initial Stage 2 titration dose of 25 mg; optional supplemental Stage 2 titration dose of 12.5 mg MDMA, plus lactose to reach equivalent weight of 62236.5 ± 1.5mg per capsule. for all blinded doses.~~ There are no other ingredients in these capsules. The capsules ~~will be~~ prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but ~~will be~~ have been compounded by ~~Kerrisdale Pharmacy, a in Vancouver-area pharmacist, BC.~~ The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies (2,4)[1, 8, 11, 13-15] and on narrative reports of MDMA-assisted therapist (as Adamson and Metzner 1980; Stolaroff 2004). A therapy [12, 16]. The dose of 125 mgmg from the same supply has been used in a previous sponsor-supported research study conducted in the US (3).Switzerland [15]. The sponsor chose the active placebo comparator dose on the basis of a previous research study (4); in people with 25PTSD and in healthy controls [4, 8, 13, 15], with 50 mg expected to produce very few exhibit some activity without producing the same degree of effects. The active dose or doses close to it have been used in studies in healthy controls and is expected to produce most but possibly not all of the effects produced by the full dose[6, 17-20]. The sponsor selected an inactive material to help maintain the blind by ensuring that all blinded doses are of equivalent weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

~~The principal investigator will transport the MDMA to Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk will encapsulate experimental and active placebo doses of MDMA at Kerrisdale Pharmacy, Vancouver BC.~~

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The encapsulation has been performed by a compounding pharmacist who has the appropriate skills. The pharmacy will supply the capsules and lactose. MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all 408 blinded capsules have equivalent similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of blinded full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed in Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk, the licensed dealer, has encapsulated all doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy supplied the capsules and lactose. Compounded MDMA was weighed to the appropriate dose and placed in clear gelatin capsules, one dose per capsule. All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A "packing stat" was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. All 108 capsules are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X39) 23 capsules), 50 mg (27 capsules), 62.5 mg (23 capsules), 25 mg (22 capsules), 12.5 mg (10 capsules) and a varying amount of lactose to maintain equal weights/weight for all blinded doses.

The lactose will be lactose monohydrate (chemical formula = $C_{12}H_{22}O_{11} \cdot H_2O$) was manufactured by

The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses. The IP for each experimental session will be packaged in one primary container, labeled

The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary

container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization monitor selects a number from amongst a set of cards based on the list, and that number is the bottle number used for that participant. This list will not be shared with any blinded site or sponsor staff.

The pharmacist and randomization monitor will be the only staff who are unblinded.

Randomization will be performed via the use of a web-based randomization program. An unblinded randomization monitor will generate the randomization list at the beginning of the study. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions.

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P.3.3 Batch Formula

The batch analyses for [REDACTED] lactose monohydrate are provided in the reports supplied by the manufacturer. [REDACTED] passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Opaque-00Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA.

ExperimentalFull initial dose: 125 mg + 113.5 mg lactose

ExperimentalFull supplemental dose: 62.5 mg + 174.1 mg lactose

Active PlaceboStage 2 initial dose: 25 mg + approximately 100 mg + 143.0 mg lactose or appropriate amount so that full weight = 125 mg

Active placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg

Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose

Comparator initial dose: 50 mg + 184.9 mg lactose

Comparator supplemental dose: 25 mg + 211.0 mg lactose

Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose

Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose

Capsules placed in individual inner envelopes, which are placed in a numbered bottlesprimary container.

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all “active placebo” doses capsules of the product. Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA blinded capsules are of equal equivalent weight.

The lactose used will be Lactose Monohydrate

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, issued by the manufacturer, lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of < = 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of opaque clear capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and will be stored with the rest of the capsules in a separate closed bottle. will bring them to the pharmacist every six months Kerrisdale Pharmacy. Pharmacist Colin Holyk will test these capsules for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

P.7 Container Closure System

All doses of MDMA will be in the form of opaque clear capsules. The MDMA capsules will be stored in amber glass bottles (vials) containing one 3 gram silica gel desiccant in each bottle. clear cellophane packages. Each bottle package (primary container) will be assigned a container number intended for use in the randomization process so as to maintain the double blind. All bottle packages will be appropriately stored in the offices of the principal investigator. Kerrisdale Pharmacy.

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

A Attachments:

1. ~~Lipomed manufacturer's specification and batch analysisAttachments containing manufacturer sheets, requested analyses and certificates of suitability contained in Modules 2 and 3 submitted in CTA approved March 17, 2009, control # 127822~~
2. ~~Quality Analysis of R Brenneisen; pp. 1-2 concern this batch of MDMA and p. 3 concerns capsules produced for a sponsor-supported study in Switzerland~~
3. ~~Additional details of manufacture provided by Lipomed and translated by [redacted] and additional tests performed by Interlab Belp~~
4. ~~Original reports from Interlab Belp and Lipomed (German)~~
5. ~~Stability report of [redacted] referring to different source and batch of MDMA but supporting long-term stability~~
6. ~~Certificate of suitability for capsules~~
7. ~~Letter associated with certificate of suitability for capsules to be used in this study~~
8. ~~Product description for lactose ordered in this study~~
9. ~~Certificate of suitability of lactose ordered for study~~
10. ~~Batch analyses for the lactose used in this study~~
11. ~~Certification that the lactose is BSE/TSE free~~

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation]*. *J Clin Psychopharmacol*, 2000. **20**: 455-66.
2. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. *J Psychoactive Drugs*, 1986. **18**: 319-27.
3. Mithoefer, M., *MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): Eleventh update on study progress*. *MAPS Bulletin*, 2008. **17**: 11-12.
4. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
5. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. *Psychopharmacology (Berl)*, 2002. **162**: 396-405.
1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects*. *J Clin Psychopharmacol*, 2000. **20**(4): p. 455-66.
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4. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**(4): p. 396-405.
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Rick Doblin, PhD
MAPS
10424 Love Creek Road
Ben Lomond, CA 95005
United States

Bern, Febr. 2, 2010 /mdma/maps-cmc_6

MDMA PTSD Studies / CMC / Update 26022010

1. *Name, address of MDMA manufacturer*

Lipomed AG, Fabrikmattenweg 4, CH-4144 Arlesheim, Switzerland
www.lipomed.com/

2. *Method of manufacturing (based on document Lipomed 94.1B5.5, Original in German)*

Step 1: 3,4-Methylenedioxybenzaldehyde + nitroethane → d,l-MDA-nitrostyrol

Solvent: acetic acid; reaction: 4 h, refluxing; cristallization: from methanol.

Step 2: d,l-MDA-nitrostyrol + LiAlH₄ → d,l-MDA

Solvent: tetrahydrofuran (dried); reaction: 2 h, refluxing;
reprocessing: isopropanol, methyl tert-butyl ether; distillation of free base under vacuum.

Step 3: d,l-MDA + formic acid → d,l-MDA-formamide

Solvent: benzene; reaction: water separator, 24 h, refluxing;
reprocessing: ethyl acetate; cristallization: from diisopropyl ether.

Step 4: d,l-MDA-formamide + LiAlH₄ → d,l-MDMA-HCl

Solvent: tetrahydrofuran (dried); reaction: 3 h, refluxing;
reprocessing: isopropanol, methyl tert-butyl ether; distillation of free base under vacuum; cristallization: from ethanol/hydrochloric acid

and diisopropyl ether; recrystallization: from isopropanol/ diisopropyl ether.

3. Methods of CoA

- Manufacturer:

➔ HPLC, GC, IR, UV, MP etc.: experimental details on request.

- DCR:

➔ HPLC (HP 1090-DAD):

- Column: Spherisorb ODS-1, 3 μ m, 125 x 4 mm i.d.; mobile phase: H₂O:acetonitrile:H₃PO₄ 85%:hexylamine = 928:72:5:0.28 mL; isocratic; flow 0.8 mL/min; 40°C
- Inj.vol.: 10 μ L
- Detection: 198 nm
- Identification: DAD spectrum 192-350 nm vs. standard
- Validation data on request.

➔ GC/MS:

- Column: DB-5ms, 25 m x 0.2 mm i.d., film 0.33 μ m
- Temperature program: 60°C (2 min hold) - 250°C @ 20°C/min, 250°C (5 min hold)
- Carrier gas: He 1.2 mL/min
- Derivatization: MBTFA
- Injection: 250°C, splitless, 1 μ L
- Detection: full scan.

4. CoA of clinical test substance

- Manufacturer:

- ➔ Test substance: d,l-MDMA-HCl (\pm 3,4-methylenedioxymethamphetamine hydrochloride)
- ➔ Art./batch #: MDM-94-HC/94.1B5.5
- ➔ Specifications/QC data: Lipomed "Analysis Data Sheet"

- DCR:

- ➔ Identity (HPLC-DAD): t_R = 5.8 min; GC/MS: t_R = 10.6 min (MDMA-TFA); m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA)
- ➔ Purity (HPLC): 99.9%, no decomposition products detected.

- Interlabor Belp (based on document 0901-00345, Original in German):

- ➔ Heavy metals, according to Ph.Eur. 6.3, 2.4.8: <100 ppm
- ➔ Ignition residue, according to Ph.Eur. 6.3, 2.4.16: <1%

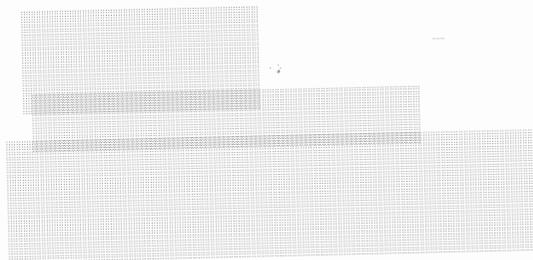
5. *Stability data*

➔ Purity (HPLC) update: measured at DCR on Febr. 25, 2010: 99.9%, no decomposition products detected.

6. *Container*

➔ The clinical test substance is stored and shipped in a brown-glass bottle for pharmaceutical purposes with white, tightly closing screw cap.

Bern, Febr. 26, 2010



- Content uniformity:

Target [mg]	Measured Mean \pm s.d. [N = 3, mg]	Deviation from target [\pm %]
12.5	11.76 \pm 0.51	- 5.93
25.0	23.65 \pm 1.55	- 5.40
62.5	66.55 \pm 1.85	+ 6.47
125.0	125.96 \pm 5.55	+ 0.77

- Identity, purity:

MDMA confirmed by HPLC and GC/MS, >99%, no impurities detected

8. *Container*

Every single capsule is kept in a 10-mL plastic, white, photoresistant, tightly capped container (Aponorm®) and stored at room temperature

9. *Stability of clinical test preparation*

No decrease of MDMA purity and decomposition expected for study duration; however, stability data not yet available

10. *Conformity decision, release for clinical trial*

Based on CoA's of manufacturer (Lipomed) and of second, independent laboratory (DCR, Univ. of Bern) d,l-MDMA-HCl was approved by Swissmedic on June 2, 2006 (notification no. 2006 DR 2157) as clinical test substance and in form of capsules (4 dosages) as clinical test preparation.

Bern, February 23, 2007

Attachment: CoA Lipomed

General Table of Contents

Module 1

1.1 Table of Contents

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1.2.1 HC 3011

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1.2.3 Investigators' Brochure

1.2.4 Protocol Synopsis (PSEAT-CTA)

1.2.5 Study Protocol

1.2.6 Informed Consents

1.2.6.1 REB Attestation

1.2.7 Clinical Trial Site Information

1.3 Electronic Review Documents

Form HC 3011
Investigator's Brochure
Protocol Synopsis (PSEAT)
Study Protocol
Informed Consent Forms

Module 2/3

2.3 Overall Clinical Summary

Attached documents

2.4 Electronic Review Documents

Quality Overall Summary
Attached Documents



Feb 5, 2009

Dr. John Patrick Stewart
Acting Director,
Office of Clinical Trials
Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator: 3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9

Re: MAPS MDMA/PTSD Protocol # MP-4, Control Number: 126833

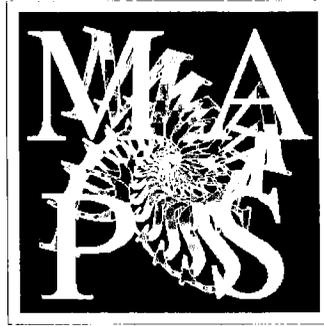
Dear Dr. Stewart,

Enclosed is a resubmission of a Clinical Trial Application (CTA) for a Phase 2 study entitled, "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." We originally submitted this protocol on December 18, 2008. We withdrew the application on January 23, 2009, due to the need to wait for some requested chemistry information which we have obtained and are now submitting. On February 3, 2009, Dr. Beata Wiatrowska, M.D., FRCP(C), called to say that she'd accepted our January 20, 2009, responses to her January 16, 2009 Clarifax about protocol design issues.

The principal investigator for the study is Dr. Ingrid Pacey MB BS FRCP[C], Vancouver, British Columbia. The enclosed forms, investigator's brochure, protocol, consent materials and chemistry information are presented for review for this CTA. This protocol and associated informed consent have already been reviewed and approved by IRB Services, Aurora, Ontario, Canada.

The sponsor of the study is the Multidisciplinary Association for Psychedelic Studies (MAPS), a US-based non-profit research and educational organization working to develop MDMA into a prescription medicine for use in combination with psychotherapy. The enclosed application is for an investigation that is part of an international series of Phase 2 studies, the protocols of which

Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org

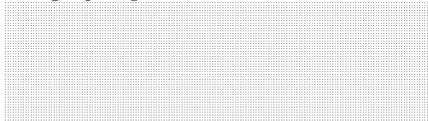


have all been submitted to FDA as part of MAPS IND #63-384. MAPS has successfully completed an MDMA/PTSD pilot study in the US in 21 subjects and is sponsoring ongoing MDMA/PTSD studies in Switzerland and Israel, each to enroll 12 subjects and estimated to be completed around the end of 2009. Our Canadian MDMA/PTSD is an attempt to replicate our US results.

MAPS has also helped to initiate a study of MDMA-assisted psychotherapy for people with anxiety related to a cancer diagnosis, taking place at McLean Hospital, Harvard Medical School.

I look forward to hearing from you regarding the results of your review.

Sincerely



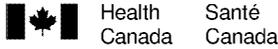
Rick Doblin PhD
President, MAPS

Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org



DRUG SUBMISSION APPLICATION						
PART 1 - Manufacturer/Sponsor and Drug Product Information						
HC Use Only:	1. Submission No.	2. Responsible Area	3. File No.	4. Date of Receipt		
				MM	DD	YYYY
5. Type of Submission: CTA		6. Number of Volumes: 2, 0 (no duplicates)		7. Schedule: Schedule III		
8. Brand or Proprietary Name: None: see below						
9. Proper, Common or Non-Proprietary Name: N-Methyl-3,4-methylenedioxyamphetamine; (+/-)-3,4-methylenedioxymethamphetamine (MDMA)						
A) Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this will be the DIN/NOC OWNER) (For CTA and CTA-A, refer to attached Guidance)						
10. Company Code	11. Manufacturer/Sponsor Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies					
12. Street/Suite/PO Box 3 Francis St.	13. City/Town : Belmont	14. Prov./State MA	15. Country USA	16. Postal/ZIP Code 02478-2218		
Contact Person for Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this is the DIN/NOC OWNER contact)						
17. Name Rick Doblin PhD	18. Telephone No. 617-484-8711	19. Fax No. 617-484-8427	20. Language Preferred / English 9 French			
21. Title: President, MAPS	22. E-mail Rick@maps.org					
B) Contact for THIS Drug Submission						
23. Company Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies						
24. Street/Suite/PO Box 3 Francis St.	25. City/Town Belmont	26. Prov./State MA	27. Country USA	28. Postal/ZIP Code 02478-2218		
29. Name Rick Doblin PhD	30. Telephone No. 617-484-8711	31. Fax No. 617-484-8427	32. Language Preferred / English 9 French			
33. Title : President, MAPS	34. E-mail: Rick@maps.org					
C) Regulatory Mailing Address (Complete where a DIN is to be issued, see attached Guidance) Same as A Above 9						
35. Company Name (Full Name - No Abbreviations) Same as above						
36. Street/Suite/PO Box	37. City/Town	38. Prov./State	39. Country	40. Postal/ZIP Code		
Regulatory Mailing Contact Same as A Above 9						
41. Name	42. Telephone No.	43. Fax No.	44. Language Preferred 9 English 9 French			
45. Title	46. E-mail					
D) Canadian Importer/Distributor (ONLY where Address in A is not in Canada)¹ Same as C Above 9						
47. Name of Importer (Full Name - No Abbreviations) Dr. Ingrid Pacey MBBS FRCP[C]						
48. Street/Suite/PO Box 3369 West 4th Ave.	49. City/Town Vancouver	50. Prov./State BC	51. Country Canada	52. Postal/ZIP Code V6R 1N6		

¹ FOR CLINICAL TRIAL APPLICATIONS (HUMAN DRUGS): WHERE THE SPONSOR IS LOCATED OUTSIDE OF CANADA, APPENDIX 1 MUST BE COMPLETED AND SUBMITTED FOR EACH IMPORTER ACTING AS THE SPONSOR'S AGENT IN CANADA. REFER TO THE ATTACHED GUIDANCE AND THE "GUIDANCE FOR CLINICAL TRIAL SPONSORS" FOR ROLES AND RESPONSIBILITIES.



E) Address to which the Drug Notification Form (DIN)/ Notice of Compliance (NOC) are to be sent: As Above: A: 9 B: 9 C: 9 D: 9
Not Applicable: 9

53. Related Submissions (referred to in this submission):

A) Type	Control No.	Brand Name	Manufacturer/Sponsor Name	File No.	Date Cleared
_____	_____	_____	_____	_____	_____
Reason for Submission:					
B) Type	Control No.	Brand Name	Manufacturer/Sponsor Name	File No.	Date Cleared
_____	_____	_____	_____	_____	_____
Reason for Submission:					
C) Type	Control No.	Brand Name	Manufacturer/Sponsor Name	File No.	Date Cleared
_____	_____	_____	_____	_____	_____
Reason for Submission:					

Attach separate sheets (same format) if necessary. Number of pages attached: _____

PART 2 - Drug Product Formulation Information

54. Proposed Shelf Life 20 years 0 months at _____ EC .

55. Medicinal (Active) Ingredient(s)

Ingredient Name	Standard	Strength	Units	Per	Calculated as Base?
<u>3,4-methylenedioxymethamphetamine (MDMA)</u>	<u>USP</u>	<u>125</u>	<u>mg</u>	<u>Capsule</u>	<u>Yes</u>
<u>Same as above</u>	<u>USP</u>	<u>62.5</u>	<u>mg</u>	<u>Capsule</u>	<u>Yes</u>
<u>Same as above</u>	<u>USP</u>	<u>20 mg</u>	<u>mg</u>	<u>Capsule</u>	<u>Yes</u>
<u>Same as above</u>	<u>USP</u>	<u>12.5 mg</u>	<u>mg</u>	<u>Capsule</u>	<u>Yes</u>
_____	_____	_____	_____	_____	<u>9 Yes 9 No</u>
_____	_____	_____	_____	_____	<u>9 Yes 9 No</u>
_____	_____	_____	_____	_____	<u>9 Yes 9 No</u>

Attach separate sheets (same format) if necessary. Number of pages attached: _____

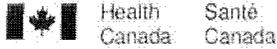
56. Non-medicinal ingredient(s) (include colouring agents)

A) Preservative(s)	Ingredient Name	Standard	Strength	Units	Per
<u>None</u>	_____	<u>NA</u>	<u>N/A</u>	<u>NA</u>	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
B) Colouring Agents	_____	<u>NA</u>	<u>NA</u>	<u>NA</u>	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
C) Other	_____	_____	_____	_____	_____
<u>Lactose (to maintain identical capsule weights)</u>	_____	_____	<u>Approx 100</u>	<u>mg</u>	<u>capsule</u>
<u>Same as above</u>	_____	_____	<u>Approx. 50</u>	<u>mg</u>	<u>capsule</u>
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Attach separate sheets (same format) if necessary. Number of pages attached: _____

D) For Biological drugs (human) containing non-medicinal ingredients of biological origin, **indicate on a separate sheet** the manufacturer and product name for each non-medicinal ingredient of biological origin.

57. Dosage Form: **Opaque capsule**

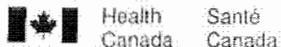


58. Container Type: 36 individual bottles containing initial and supplemental dose; no take-home doses Package Size: Bottle w/two capsules	
59. Therapeutic/Pharmacological Classification : Monoamine releaser and uptake inhibitor, entactogen	
60. Route(s) of Administration: Oral	
61. Drug Product <input checked="" type="checkbox"/> Biologic/Radiopharmaceutical <input checked="" type="checkbox"/> Pharmaceutical <input checked="" type="checkbox"/> Natural Health Product <input checked="" type="checkbox"/> Drug & Medical Device	
62. Drug Use <input checked="" type="checkbox"/> Human	
63. Proposed Indication/Use: For use as an adjunct to psychotherapy for people with posttraumatic stress disorder, to be administered within the context of an extended psychotherapy session.	
64. Proposed Dosage (include maximum daily dose): One initial dose (experimental dose = 125 mg, active placebo = 25 mg) possibly followed by one supplemental dose (experimental dose = 62.5 mg, active placebo = 12.5 mg). Maximum dose per session = 187.5 mg). No take-home or daily doses.	
65. Draft of Proposed Canadian Labels enclosed? <input checked="" type="checkbox"/> No - Package Insert enclosed? <input checked="" type="checkbox"/> No Approved foreign labelling enclosed? <input checked="" type="checkbox"/> No <small>*For CTAs and CTA-As labels should not be submitted unless requested by the appropriate Directorate.</small>	
66. Rationale for all SNDS, SANDS (all human drug types), SABNDS (veterinary drugs), or for biological drug/DIN submissions	
67. Type of Notifiable Change (NC) submission (if applicable) - human drugs only	
<input checked="" type="checkbox"/> Change in expiry period/storage conditions	<input checked="" type="checkbox"/> Change in packaging material composition
<input checked="" type="checkbox"/> Change in formulation	<input checked="" type="checkbox"/> Change in packaging specifications for parenteral/inhalation drug
<input checked="" type="checkbox"/> Change in manufacturing method	<input checked="" type="checkbox"/> Change in container size for parenteral drug
<input checked="" type="checkbox"/> Change in manufacturing site	<input checked="" type="checkbox"/> Change in specifications (medicinal or non-medicinal ingredient, pharmaceutical form, analytical method)
<input checked="" type="checkbox"/> Change in text of labelling	<input checked="" type="checkbox"/> Other (specify)
<input checked="" type="checkbox"/> Change in drug substance (source, synthesis)	
Complete Sections 68 - 70 for Veterinary Products only	
68. Species and Subtypes Recommended for use _____ _____ _____ _____	69. Used for treatment of food-producing animals? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	70. Withdrawal Time
	Species Days Hours

I, the undersigned, certify that the information and material included in this drug submission application is accurate and complete².

71. Name of Authorized Signing Official Rick Doblin PhD		73. Date		
		YYYY	MM	DD
		2008	12	12
74. Title: President, MAPS	75. Telephone No. 617 484-8711	76. Fax No. 617 484-8427		
77. Name of Company to which the Authorized Signing Official Belongs: Multidisciplinary Association for Psychedelic Studies (MAPS)				

² IF THE SIGNING OFFICIAL IS A THIRD PARTY ACTING ON BEHALF OF THE MANUFACTURER/SPONSOR COMPANY IDENTIFIED IN SECTION 11, A LETTER OF AUTHORIZATION, SIGNED BY THE MANUFACTURER/SPONSOR COMPANY (SECTION 11), MUST BE FILED WITH THE COMPLETED SUBMISSION APPLICATION FORM, E.G. APPENDIX 2.



APPENDIX 1 - for Clinical Trial Applications and Amendments only

TEMPLATE AUTHORISATION FOR A THIRD PARTY TO IMPORT THE
NEW DRUG DESCRIBED IN THIS CLINICAL TRIAL APPLICATION OR AMENDMENT³

I, Rick Doblin Ph.D authorize Ingrid Pacey MB.BS, FRCPC

to import the new drug for the purposes of the clinical trial described within this application.

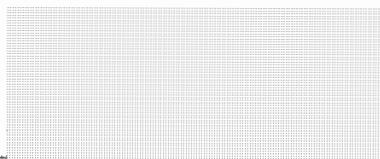
Signed:

Print name:

Title:

Clinical Trial Sponsor:

Date:



Rick Doblin

President, MAPS

Multidisciplinary Association for Psychedelic Studies

12/12/08

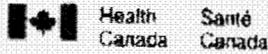
³ SUBMIT WITH APPLICATION ONLY IF THE CLINICAL TRIAL SPONSOR IS LOCATED OUTSIDE OF CANADA AND IS AUTHORIZING ONE OR MORE THIRD PARTIES TO IMPORT THE NEW DRUG FOR THE PURPOSES OF THE CLINICAL TRIAL DESCRIBED WITHIN THIS APPLICATION. A SEPARATE AUTHORISATION IS REQUIRED FOR EACH CLINICAL TRIAL APPLICATION. AS ADDITIONAL IMPORTERS ARE IDENTIFIED, ADDITIONAL COPIES OF APPENDIX 1 SHOULD BE PROVIDED TO HEALTH CANADA. IF THE IMPORTER HAS NOT CHANGED WHEN A CLINICAL TRIAL APPLICATION AMENDMENT IS FILED, APPENDIX 1 DOES NOT NEED TO BE RE-SUBMITTED.

01/14/1999 09:04

6047328066

LOUIE MYERS PACEY

PAGE 02/02



APPENDIX 3 - CLINICAL TRIAL APPLICATION INFORMATION
(for clinical trial applications for human drugs only)

78. Clinical Trial Protocol Number (if assigned) M-P4	79. Clinical Trial Protocol Title: 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
80. Anticipated Clinical Trial Composition (check all that apply): <input checked="" type="checkbox"/> Pediatric population (0-18 years of age) / Females / Males	81. Phase of Clinical Trial (check appropriate box): <input checked="" type="checkbox"/> Phase I - bioequivalency study (7 day administrative target) <input checked="" type="checkbox"/> Phase I - study in healthy humans (7 day administrative target) <input checked="" type="checkbox"/> Phase I - other (30 day default) / Phase II (30 day default) <input checked="" type="checkbox"/> Phase III (30 day default) <input type="checkbox"/> Other - specify:
82. Information regarding Research Ethics Board that has refused to approve the protocol and/or informed consent form enclosed? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No / Not Applicable <input checked="" type="checkbox"/> Not known at this time	
83. Clinical Trial Site Information Form enclosed for all sites known at time of application? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> No sites are known at this time	
84. Investigator's brochure enclosed? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
85. Information regarding human- and/or animal-sourced excipients enclosed? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Not Applicable	
86. Quality (chemistry & manufacturing) information enclosed? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Not Applicable - product has received Notice of Compliance and/or Drug Identification Number (DIN)	

In respect of the clinical trial identified in Appendix 3 of this form we certify that:

- The information and material contained in, or referenced by, this application are complete and accurate and are not false or misleading.
- If requested by Health Canada, additional information or samples required to assess this application will be provided within two days following receipt of the request from Health Canada.
- The clinical trial will be conducted and the drug used in accordance with the protocol and the requirements set out in Division 5 of the *Food and Drug Regulations*. The clinical trial will be conducted in accordance with good clinical practices.
- The trial will not commence at any site until receipt of a No Objection Letter from the Therapeutic Products Directorate or the Biologics and Genetic Therapies Directorate of Health Canada, or 30 calendar days following receipt of the application by Health Canada, whichever comes first.
- Records will be maintained for a period of 25 years and will be accessible for on-site inspection by Health Canada Inspectors.

87. Senior Medical Officer or Scientific Officer in Canada Ingrid Pacey MBBS FRCP(C)	88. Tel. No. 604-732-9309	89. Signature 	90. Date YYYY MM DD 2008 12 16
91. Senior Executive Officer Rick Doblin PhD	92. Tel. No. 617-484-8711	93. Signature 	94. Date YYYY MM DD 2008 11 21

HC/SC 3041 (1-02)



Health Canada / Santé Canada

QUALIFIED INVESTIGATOR UNDERTAKING

An undertaking must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified below. The completed undertaking must be retained by the clinical trial sponsor for a period of 25 years.

Please note that the Qualified Investigator Undertaking should not be submitted to Health Canada unless requested.

PART 1 - Clinical Trial Protocol Information				
Please check one of the following: Clinical Trial Application (CTA) / Clinical Trial Application Amendment (CTA-A) 9				
1. Clinical Trial Protocol Title: 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			2. Clinical Trial Protocol Number (If Applicable) M-P4	
PART 2 - Drug Product / Sponsor Information				
A) Drug Product Information				
3. Brand Name None: see below				
4. Proper or Common Name: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)				
B) Sponsor of Clinical Trial				
5. Company Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies				
6. Street / Suite / PO Box 3 Francis St.	7. City / Town Belmont	8. Prov. / State MA	9. Country USA	10. Postal/ZIP Code 02478-2218
C) Contact for THIS Clinical Trial				
11. Contact Name: Rick Doblin Ph.D			12. E-mail: Rick@maps.org	
13. Company Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies				
14. Street / Suite / PO Box 3 Francis St.	15. City / Town Belmont	16. Prov. / State MA	17. Country USA	
18. Telephone No. 617-484-8711	19. Fax No. 617-484-8427		20. Postal/ZIP Code 02478-2218	



PART 3 - Qualified Investigator Information

A) Clinical Trial Site

21. Name of Site (Full Name - No Abbreviations)

22. Street / Suite / PO Box

23. City / Town:
Vancouver

24. Province
BC

25. Postal Code

B) Qualified Investigator

26. Name:
Ingrid Pacey MBBS FRCP(C)

27. Title
Psychiatrist

28. Language Preferred
/ English French

29. Street / Suite / PO Box
3369 West 4th Ave.

30. City / Town
Vancouver

31. Province
BC

32. Postal Code
V6R 1N6

33. E-mail

34. Tel. No.
604-732-9309

35. Fax No.
604-733-6951

In respect of the identified clinical trial, I certify, as the qualified investigator for this site that:

1. I am a physician or dentist and a member in good standing of a professional medical or dental association as defined in Part C Division 5 of the *Food and Drug Regulations*;
2. I will supervise the medical care and medical decisions respecting this clinical trial at this site;
3. I will conduct this clinical trial in accordance with Good Clinical Practices; and
4. I will immediately on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the Research Ethics Board for this site of the discontinuance, provide them with the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons.

36. Signature of Qualified Investigator

37. Date

YYYY	M	D
08	12	16

Investigator's Brochure: MDMA

MAPS: 12/2007

(+/-)-3,4-methylenedioxymethamphetamine
(MDMA, "Ecstasy")
Investigator's Brochure

Lisa Jerome Ph.D
December 2007

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Preface

In 2001, Baggott, Jerome and Stuart collaborated on a comprehensive review of the literature concerning 3,4-methylenedioxymethamphetamine, or MDMA (Baggott et al. 2001). After writing this monumental work, three additional reviews were created to assist and support the Multidisciplinary Association for Psychedelic Studies (MAPS), first by Jerome and Baggott in 2003, and then Jerome in 2004 and 2005 (Jerome 2004; 2005; Jerome and Baggott 2003). As the amount and pace of research accelerated, and after gaining more knowledge about investigator's brochures, the present author (Jerome) concluded that information on MDMA should be presented in a more accessible and compact format. Fortunately, a number of excellent reviews of nearly all aspects of MDMA have appeared in the past four years, making the task of summarizing and presenting this research easier. As in all previous documents, this brochure is based on literature located through the electronic database PubMed, examining relevant journals and communication with researchers. With the exception of some information on ongoing studies and conference presentations, most of the information has been drawn from reports appearing in print or electronic editions of relevant journals.

This document is intended to encapsulate the current state of our knowledge concerning MDMA, especially as it pertains to humans. Rather than follow the format of its predecessors, this document will follow the outline used for recently created investigator's brochures for LSD and psilocybin. There will be a greater focus on proposed mechanisms of action, cataloguing acute physiological, behavioral and therapeutic effects in humans, and information on planned or ongoing use in medical settings. Readers interested learning more about MDMA or specific areas are strongly encouraged to read reviews by Cole and Sumnall, Dumont and Verkes, Laws and Kokkalis, Zakzanis and others on the pharmacology, acute and potential long-term effects and risks of MDMA and ecstasy, with ecstasy defined here as material represented as containing MDMA (Baylen and Rosenberg 2006; Cole and Sumnall 2003a; b; Dumont and Verkes 2006; Green et al. 2003; Guillot 2007; Laws and Kokkalis 2007; Sumnall and Cole 2005; Zakzanis et al. 2007).

New Developments

Three major developments have transformed our understanding of previous and current findings in the area of MDMA research since the last update of the literature review. The first development affects interpretation of nonhuman animal studies, and the second development relates to our understanding of the presence and degree of long-term effects of ecstasy use. The third development relates to primate studies examining the impact of ambient temperature on the effects of MDMA on body temperature.

MDMA research and Interspecies Scaling

Up until as recently as 2006, investigations of the pharmacology, functional effects or toxicity of MDMA in nonhuman animals injected large and often repeated doses of MDMA (see Baggott et al. 2001). Some of the earliest research used high doses in order to study mechanisms of neurotoxicity. Most researchers continued to employ these doses, and some later explained these dosing regimens in terms of using interspecies scaling to

arrive at human-equivalent doses. Interspecies scaling is a pharmacological model intended to account for species-specific differences in metabolism (Mahmood and Balian 1996; Mordenti and Chappell 1989). However, interspecies scaling assumes that the target compound has linear pharmacokinetics, and requires data from at least two species to arrive at human-equivalent doses. Findings first reported in humans and later in monkeys (de la Torre et al. 2000; Mechan et al. 2006) demonstrate that MDMA has nonlinear pharmacokinetics, with larger doses producing greater increases in blood MDMA levels than would be expected from linear pharmacokinetics. Furthermore, contrary to earlier reports that found that route of administration had no impact on plasma MDMA levels (Finnegan et al. 1988; Ricaurte et al. 1988), a recent study of MDMA in monkeys found that sub-cutaneous doses produced higher peak plasma MDMA levels than intra-gastric administrations (Mechan et al. 2006). Some recent reports describe findings suggesting that even the doses of MDMA employed in rodent studies are inappropriately high (Baumann et al. 2006; Wang et al. 2005), though see work by Xie and colleagues (Xie et al. 2006). After examining these recent findings, it appears that much of the previous research in nonhuman animals has used inappropriately high doses of MDMA, and this occurred not only in studies of MDMA neurotoxicity, but also in studies of behavioral or pharmacological effects. Studies conducted subsequent to the discovery began employing mg/kg doses similar or identical to those used by humans (e.g. Taffe et al. 2006; Von Huben et al. 2006). Most drug-discrimination and self-administration studies in rodents (De La Garza et al. 2007) have employed and continue to employ doses identical or similar to those used by humans. However, the discoveries concerning the inadequacy of interspecies scaling mean that findings from the majority of previous studies must be considered with caution.

The Netherlands XTC Toxicity (NeXT) Studies

A team of researchers in the Netherlands embarked upon an ambitious program of research that included prospective studies of people who planned on using ecstasy in the future (De Win et al. 2005). Participants expressing interest in using ecstasy were assessed prior to use. After some reported their first use of ecstasy or soon afterwards, the team assessed these participants as well as another group that had not yet used ecstasy. The researchers studied brain activity, estimated brain serotonin transporter (SERT) sites, neurochemical markers of brain injury, working memory, and cognitive function including verbal memory. These studies are unique in their examination of people before and after drug self-administration rather than making cross-group comparisons between ecstasy users and non-user controls. Hence findings from these prospective studies far more relevant to examining risks and benefits in human MDMA studies than the majority of previous work. In general, studies from this research program failed to find any long-term effects of low to moderate ecstasy use. They did not find any changes in serotonin uptake sites nor chemical markers of brain injury, and they found only minor region-specific changes in cerebral blood volume (de Win et al. 2007; de Win et al. 2006; Jager et al. 2007b). While an examination of change scores before and after use indicated greater improvement in non-users than in ecstasy users, they failed to find impaired working memory after low ecstasy use (Jager et al. 2007b; Schilt et al. 2007). There are a number of problems with this research, including use of change scores and the inclusion of an individual whose ecstasy use was considerably greater than others in the cognitive

function assessment. However, despite these findings, the general picture from the NeXT studies is that low to moderate ecstasy use produces very few long-term effects and is not comparable to effects found after heavy use of ecstasy and other drugs.

No Interaction between MDMA and Ambient Temperature on Human Body Temperature

To date, the only novel and relevant finding from human MDMA studies is a study that sought to detect an interaction between MDMA and ambient temperature on human body temperature after 2 mg/kg MDMA (Freedman et al. 2005). Freedman and colleagues found that human body temperature was unaffected by the combination of MDMA and ambient temperature, and that the desirable effects of MDMA are not increased by warm ambient temperature (Freedman et al. 2005). One of two research teams reached similar conclusions in rhesus monkeys (Crean et al. 2006; Von Huben et al. 2006).

1. Drug Substance and Formulation

(+/-) 3,4-methylenedioxymethamphetamine (MDMA, 3,4-methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyamphetamine,) has the chemical formula of $C_{11}H_{15}NO_2$. It is a phenylisopropylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in 1912 as an intermediate chemical involved in the production of the stytic hydrastinine (Freudenmann et al. 2006). No significant investigations examined the pharmacological, physiological or psychological effects of MDMA until the 1950s, when the US Army administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991), and there are records of a police seizure of MDMA in the early 1970s that suggests either intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Some have estimated that up to 4000 people underwent MDMA-assisted psychotherapy in North America prior to its placement in Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001). However, none of the therapists conducted controlled studies or published any formal descriptions or analyses of MDMA-assisted therapy at this time. Therapeutic use continued up until its placement in US Schedule 1 in 1986 (Adamson 1985; Greer and Tolbert 1998; Stolaroff 1997). During the early 1980s, increasing numbers of people began using MDMA outside the therapeutic context (Beck and Rosenbaum 1994). The first wave of non-medical use occurred not only in dance clubs but in small groups of people, in a self-exploratory or spiritual context or while attending concerts. Non-medical use continues today in the same contexts (Carlson et al. 2004; Sumnall et al. 2006).

A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986; Greer and Tolbert 1986), including Greer and Tolbert's study of MDMA in a

psychotherapeutic context. However, controlled human studies of MDMA did not commence until early to mid-1990s, with the publication of research conducted by Grob and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006; Mithoefer 2006; Oehen 2006).

Many researchers categorize MDMA as belonging to a unique class of drugs, the entactogens (Nichols 1986; Vollenweider et al. 1998a), of which it is considered the first identified member, and perhaps a prototype of the class. Entactogens are reported to produce changes in mood, social interactions or feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens (Cami et al. 2000; Gouzoulis-Mayfrank et al. 1999; Liechti et al. 2001b; Tancer and Johanson 2003), but it also appears to possess qualities it shares in common with a small number of related compounds, as methylenedioxyethylamphetamine (MDE) (Gouzoulis-Mayfrank et al. 1999). Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy (Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). To date only two controlled studies have sought to measure these effects (Farre et al. 2007; Harris et al. 2002). Although researchers have offered several models and explanations for the source of entactogenic effects, it appears that release of serotonin plays a significant role in producing at least some of these effects. Indirect action on 5HT_{1A} or 5HT_{2A} receptors, and neuroendocrine responses, as increases in the hormones oxytocin, vasopressin and cortisol may also play a role in producing the unique effects of MDMA.

2. Pharmacological and toxicological effects

Overview

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear.

MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture. The

nature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978), and an a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al. 2003). Typically, human trials have used doses between 1 and 2 mg/kg.

MDMA and Monoamines

While the pharmacology of MDMA is complex, its chief effect is the release of monoamines, particularly serotonin. MDMA also releases norepinephrine and dopamine (Cole and Sumnall 2003b) and prevents uptake of all three monoamines. Recent in vitro studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake (Mlinar and Corradetti 2003; Verrico et al. 2007) and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine (Han and Gu 2006). MDMA appears to alter the configuration of the serotonin transporter so that it works in reverse of its usual mode, transporting serotonin outside of neurons rather than shuttling extracellular serotonin into these neurons (Cole and Sumnall 2003b; Johnson et al. 1986; see also Rudnick and Wall 1992). While MDMA has some affinity for some serotonin, norepinephrine, acetylcholine and histamine receptors, its direct activity at these receptors is weaker than its activity on monoamine transporters.

Early studies of the pharmacological affinity of MDMA reported after detecting strong affinity for serotonin, norepinephrine and dopamine transporters, binding at $\alpha 1$, 5HT₂, $\alpha 2$ adrenergic receptors, H₁ histamine receptors and acetylcholine muscarinic M₁ receptors, β adrenergic receptors, dopamine D₂ and D₁ dopamine receptors, roughly in that order (Battaglia et al. 1988). This study failed to detect any direct pharmacological effects on GABA, glutamate or opioid receptors. Later reports and investigations have clarified and for the most part supported this data (e.g. Jones et al. 2004, see also NIMH PDSP database; Setola et al. 2003), providing more specific affinity assays and with only one significant disagreement, concerning the muscarinic M₁ receptor. However, it appears that the effects of MDMA at all receptors investigated to date is considerably lower than its activity at any of the monoamine transporters, suggesting that any receptor-mediated effects reported in humans or nonhuman animals arise indirectly from monoamine release or inhibition of reuptake. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release activating 5HT₄ receptors (Nair and Gudelsky 2005; 2006). Indirect effects of monoamine are likely involved in producing therapeutic effects, as facilitated recall and changed meaning of perceptions and events, increased positive mood and increased interpersonal closeness, empathy or compassion for the self and others.

Table 1: Affinity assays from Battaglia et al. 1988: Affinities of MDMA at receptors wherein K₁ is below 500 mcM. Male rat brain samples used in assays.

Transporter/Receptor	K _i (mcM)	Hot Ligand	Species	Source	Reference
Serotonin Transporter	0.61 +/- 0.05	3H-paroxetine	Rat	Fr. Cortex	(Battaglia et al. 1988)
Norepinephrine Transporter	15.8 +/- 1.7	3H-Mazindol	Rat	Fr. Cortex	(Battaglia et al. 1988)
Dopamine Transporter	24.4 +/- 1.9	3H-GBR-12935	Rat	Striatum	(Battaglia et al. 1988)
α ₂	3.6 +/- 0.8	3H-aminoclonidine	Rat	Fr. cortex	(Battaglia et al. 1988)
5HT ₂	5.1 +/- 0.3	3H-ketanserin	Rat	Fr. Cortex	(Battaglia et al. 1988)
H ₁	5.7 +/- 2.4	3H-mepyramine	Rat	Fr. Cortex	(Battaglia et al. 1988)
M ₁	5.8 +/- 0.3	3H-QNB	Rat	Fr. Cortex	(Battaglia et al. 1988)
M ₂	15.1 +/- 0.1	3H-QNB	Rat	Brainstem	(Battaglia et al. 1988)
α ₁	18.4 +/- 1.2	3H-prazosin	Rat	Fr. Cortex	(Battaglia et al. 1988)
B	19.2 +/- 2.1	3H-dihydroalprenolol	Rat	Fr. Cortex	(Battaglia et al. 1988)
5HT ₁	23 +/- 1.5	3H-serotonin	Rat	Fr. Cortex	(Battaglia et al. 1988)
D ₂	95 +/- 15	3H-Spiperone	Rat	Striatum	(Battaglia et al. 1988)
D ₁	148 +/- 14	3H-SCH-23390	Rat	Striatum	(Battaglia et al. 1988)

Fr. Cortex = Frontal cortex

Table 2: Receptor binding profiles for MDMA recorded from the NIMH Psychoactive Drug Screening Program Database (PDSP)

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

Human MDMA studies suggest that serotonin release plays a prominent role in producing the effects of MDMA. Preventing serotonin release through administration of selective serotonin reuptake inhibitors (SSRIs) appears to attenuate or eliminate most subjective, physiological and immunological effects of MDMA (Farre et al. 2007; Liechti et al. 2000a; Liechti and Vollenweider 2000b; Pacifici et al. 2004; Tancer and Johanson 2007). Pre-treatment or coadministration with SSRIs attenuated the effects of MDMA on mood and perception, though leaving intact specific effects, as nervousness or excitability (Liechti et al. 2000a). Some researchers reported that SSRIs attenuated MDMA-induced increases in heart rate and blood pressure (Farre et al. 2007; Liechti and Vollenweider 2000b) while others only reported that SSRIs attenuated elevated heart rate only (Tancer and Johanson 2007). All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but that this combination prevents or

significantly reduces the appearance of the subjective effects of MDMA. The perceptual effects of MDMA appear to be the result of direct or indirect action on 5HT_{2A} receptors, as coadministration of the 5HT_{2A} antagonist ketanserin reduced reported perceptual alterations after 1.5 mg/kg MDMA and eliminated slight elevation in body temperature (Liechti et al. 2000b). At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D₂ receptors, as administering the D₂ antagonist haloperidol diminished positive mood and increased anxiety in humans (Liechti and Vollenweider 2000a). There are no reports examining the contribution of norepinephrine release to MDMA effects in humans. Investigations in rodents suggest that norepinephrine plays a role in cardiovascular effects (Quinn et al. 2006).

In rats, relatively large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin (Connor et al. 2000; Nash et al. 1988), with elevation lasting up to four hours after dosing, and attenuated by a 5HT₂ receptor antagonist. Given the large dosage used, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. A study of isolated rat hypothalamus reported arginine vasopressin and oxytocin release after MDMA and the MDMA metabolite HMMA (Fallon et al. 2002).

Receptor Affinity and Direct and Indirect Actions on Receptors

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. MDMA probably stimulates 5HT_{1A} receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial 5HT_{1A} antagonist in some brain areas (Giannaccini et al. 2007). Early studies in rodents suggest that 5HT_{1A} receptors reduce anxiety and aggression (Brunner and Hen 1997; Graeff et al. 1996), and some drug discrimination studies suggest that the 5HT_{1A} agonist 8-OH-DPAT partially or fully substitutes for MDMA (Glennon and Young 2000; Glennon et al. 2007; Schechter 1986). Administering a 5HT_{1A} antagonist attenuates the prosocial behavior of adjacent lying in rats given MDMA, possibly because it prevents elevation in oxytocin (Morley et al. 2005; Thompson et al. 2007). To date there are no human studies investigating the contribution of 5HT_{1A} receptors to MDMA effects.

MDMA exhibits affinity for two of three 5HT₂ family receptors, 5HT_{2B} and 5HT_{2A}, and for α_{2B} , α_{2C} , histamine H₁ and muscarinic M₃ receptors, with strongest affinity recorded for 5HT_{2B}, α_{2B} , α_{2C} and muscarinic M₃ receptors (Battaglia et al. 1988; Lavelle et al. 1999; Lyon et al. 1986; Setola et al. 2003), additional data from PDSP database. A pair of reports suggests MDMA may have some affinity for the trace amine receptor (TAR). In contrast with Battaglia's work, later investigations did not find high affinity for M₁ receptors. It is possible but not yet demonstrated that MDMA agonism at 5HT_{2B} and α_2 receptors might play a role in producing some of the subjective or psychological effects of MDMA. Most 5HT_{2B} receptors are found on tissues outside the brain (Setola et al. 2003). However, 5HT_{2B} receptors are also present within the amygdala (Duxon et al. 1997), and so it is possible that these receptors may be involved in regulating emotional reactivity or other amygdalar responses. For example, MDMA and fenfluramine can produce increased or decreased anxiety, or both at once, and feelings of dreaminess, suggesting a few commonalities between the two serotonin releasers and 5HT_{2B} agonists

(Bond et al. 1995; Mortimore and Anderson 2000). Clonidine and other α_2 agonists are associated with increased feelings of calmness and relaxation, and it is possible that, like these compounds, MDMA also induces a calm or relaxed state via α_2 agonism. To date there are no behavioral studies examining the role of 5HT_{2B} or α_2 adrenergic receptors in the subjective or therapeutic effects of MDMA. Even less is known about the significance of MDMA activity at histamine and muscarinic receptors.

At least some direct or indirect effects of MDMA on serotonin receptors may in turn produce additional effects, as changes in GABA uptake in the ventral tegmental area of rats (Bankson and Yamamoto 2004). However, very few publications investigate direct effects of MDMA upon receptors, and it is likely that most effects on serotonin or dopamine receptors result from monoamine release and not direct receptor activation or antagonism.

MDMA and Gene Expression

A number of research teams have studied the effects of MDMA on gene expression in rodents over the past seven years. However, many of these reports used 10 to 20 mg/kg MDMA, leaving it uncertain whether these changes can be generalized to humans given lower doses. These studies reported an increase in transcripts for genes that regulate the GABA transporter (Peng et al. 2002; Thiriet et al. 2002). Some of the increased gene transcriptions are associated with monoamine release (Peng et al. 2002). Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release. A recent publication found that repeated administration with 1 or 5 mg/kg weekly for four weeks increased transcripts for 5HT_{1B} receptors in various brain regions and 5HT_{2C} receptors in the cortex and hypothalamus after MDMA (Kindlundh-Hogberg et al. 2006). However, because transcription was assessed ten hours after the last MDMA administration, it is not clear whether these changes reflect residual acute effects of MDMA or changes related to repeated administration. However, generally speaking it appears that serotonin plays more of a significant role than dopamine in changing gene transcription. Future studies will need to separate direct and indirect effects of MDMA on gene expression or transcription.

Physiological Effects

Moderate to high doses of MDMA elevate body temperature in rodents, often producing hyperthermia (Cole and Sumnall 2003b), and doses of MDMA closer to those used by humans still produce at least a slight increase in body temperature (Reveron et al. 2006), suggesting that this effect may occur only at higher doses. Ambient temperature and MDMA interact on body temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperature and MDMA producing hypothermia rather than hyperthermia (Dafters 1994; Fantegrossi et al. 2003; Malberg and Seiden 1998).

High doses of MDMA produce significant elevations in body temperature in primates (Bowyer et al. 2003; Mechan et al. 2006), but when they receive doses closer to those humans ingest, monkeys exhibit only slight to moderate elevation in body temperature

(Crean et al. 2007; Crean et al. 2006). In contrast to findings in rodents, human and nonhuman primates are not subject to interactions between ambient temperature and MDMA, exhibiting slight to moderate increases in body temperature in cool, room temperature and warm environments (Crean et al. 2007; Crean et al. 2006; Freedman et al. 2005), though one paper examining monkeys in restraining chairs detected an interaction between MDMA and ambient temperature on monkey body temperature (Banks et al. 2007). The difference between rodent and primate response to MDMA in different ambient temperatures may result from interspecies differences in means of body heat reduction, including differences relating to body mass (Gordon 2007).

While there are few *in vivo* assessments of cardiovascular effects of MDMA in nonhuman animals, Cole and Sumnall noted in their review that previous findings detected increased sympathetic activity, as seen in humans (Cole and Sumnall 2003b). A team of researchers based in Dublin, Ireland conducted a number of *in vitro* studies with rat vascular tissue demonstrating that MDMA has both pressor and depressor effects, acting through adrenergic receptors. They reported elevations in blood pressure (Bexis and Docherty 2005; 2006).

A large body of research has examined the neurotoxic potential of MDMA, with the general consensus being that MDMA may be neurotoxic to the axons of serotonergic cells at high or repeated doses (Baumann et al. 2007; Cole and Sumnall 2003b). Studies in rodents and nonhuman primates have found that high and repeated doses of MDMA reduce brain serotonin levels and may damage the axons of serotonergic neurons (Cole and Sumnall 2003b). However, lower doses do not appear to do this (Mechan et al. 2006; Wang et al. 2005), and it is not likely that the dosages and regimens found in controlled studies produce these effects. The issue of MDMA neurotoxicity is addressed further under "Possible Risks" below.

Studies in mice found increased limbic excitability after repeated moderate or high doses of MDMA and increased activity after each dose without reducing brain serotonin or dopamine levels (Frenzilli et al. 2007; Giorgi et al. 2005). The significance of this finding for humans remains unclear, as animals received daily doses of MDMA. However, such changes might be related to increased tolerance to MDMA effects after frequent, repeated doses.

Humans

Onset of MDMA effects occurs 30 to 60 minutes after administration (Cami et al. 2000; Mas et al. 1999), peak effects appear 75 to 120 minutes post-drug (Liechti et al. 2001b; Tancer and Johanson 2003), and duration of effects lasts from three to six hours (Harris et al. 2002; Liechti et al. 2001a; Vollenweider et al. 1998a), with most effects returning to baseline or near-baseline levels six hours after drug administration. MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing (Downing 1986) and replicated by other research teams in the US and Europe (Lester et al. 2000; Liechti et al. 2001a; Mas et al. 1999; Tancer and Johanson 2001). Elevation in blood pressure met diagnosis for hypertension in approximately 5% of research participants receiving at least 100 mg MDMA in research

studies (Mas et al. 1999; Vollenweider et al. 1998a), but none of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned. Most people do not experience elevations that are greater than seen after moderate exercise. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration (Downing 1986) and peak between 1 and 2 hours post-drug, with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure, and they also exhibited a greater elevation in heart rate than women, as reported in a study summarizing and pooling data from a series of human MDMA studies (Liechti et al. 2001a). These studies did not report any discomfort or increased stress accompanying cardiovascular effects.

As previously noted, MDMA produces only a slight elevation in body temperature (Liechti et al. 2001a) and this elevation is unaffected by ambient temperature (Freedman et al. 2005). Doses between 1.5 and 2 mg/kg MDMA (approximately 100-150 mg) fail to produce any clinically significant elevation in body temperature (Freedman et al. 2005; Liechti et al. 2001b). Men seem to exhibit a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram (Liechti et al. 2001a). However, it is notable that participants in controlled studies have not engaged in vigorous exercise and either remained sitting or lying down throughout most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings. One of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while the other failed to find any significant differences in ecstasy-user body temperature at a club (Cole et al. 2005; Irvine et al. 2006). In the study of Irvine and colleagues, average blood MDMA was 0.31 +/- 0.21 ng/L, though five participants had significantly higher blood MDMA levels.

MDMA and Brain Activity

Gamma and colleagues performed positron emission tomography (PET) brain scans 75 minutes after administering 1.7 mg/kg MDMA, finding increased regional blood flow (rCBF) in prefrontal, inferior temporal and cerebellar areas and decreased rCBF in the left amygdala (Gamma et al. 2000). Decreased amygdalar activity may be indicative of reduced reactivity to potential threats (Phelps et al. 2001). Ecstasy user participants receiving two doses of MDMA exhibited decreases in bilateral visual cortex, caudate, superior parietal, and dorsolateral frontal regions (Chang et al. 2000) ten to 21 days later, with increased rCBF measured in two participants at a later time point. However, a comparison between heavy ecstasy users and non-user controls failed to find differences in rCBF (Gamma et al. 2001), and a report assessing changes before and after initial use found only increase in one area of prefrontal cortex (de Win et al. 2007), suggesting that the changes seen by Chang and colleagues are a transient effect. Electroencephalography recorded after MDMA showed the following changes EEG activity; overall increase in beta activity, reduction in alpha activity, and specific decreases in alpha and delta in frontal areas and increased frontotemporal beta signal (Frei et al. 2001), EEG patterns the authors reported as being similar to those seen with serotonergic and noradrenergic drugs, and to a lesser extent, dopaminergic drugs.

Neuroendocrine Effects of MDMA

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotrophic hormone concentrations (Farre et al. 2004; Grob 2001; Grob et al. 1996; Harris et al. 2002; Mas et al. 1999), while growth hormone was unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peaked at about 2 hours after MDMA administration. A second dose of 100 mg MDMA given four hours after an initial 100 mg produced a second increase in cortisol during an interval when cortisol levels were declining (Pacifici et al. 2001), and a dose of 100 mg MDMA given 24 hours after an initial dose stimulated a greater release of cortisol, but not prolactin (Farre et al. 2004). In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug (Harris et al. 2002). Along with these findings from controlled studies, a naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared with clubgoers without any detectable levels of MDMA. It is likely that all neuroendocrine changes result from monoamine release, and it is currently unknown what role, if any, they play in producing the effects of MDMA. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol in some circumstances may serve as a signal to seek affiliation or to increase positive mood (Bartz and Hollander 2006; Domes et al. 2007; Kirsch et al. 2005; Wirth and Schultheiss 2006).

Immunological Effects of MDMA

Humans exhibit transient immunological changes after a dose of 100 mg (Pacifici et al. 2004; Pacifici et al. 2000; Pacifici et al. 1999; Pacifici et al. 2002), including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. Pacifici and colleagues report that in several respects, these effects are similar to those that occur with other psychoactive substances and are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release (Pacifici et al. 2004). The significance of these immunological effects remains unclear. However, we expect the impact of these effects to be modest in most cases.

Behavioral and psychological effects

Researchers investigating how MDMA produces its behavioral and psychological effects on humans and nonhuman animals are only just beginning to approach this topic, and the first controlled studies into the therapeutic potential of this compound are only just reaching completion now. In rodents, doses of MDMA equivalent or only slightly greater in size than human doses produce little to no behavioral effects. However, doses of 5 mg/kg or greater possess several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses and decreased anxiety at higher doses (Cole and Sumnall 2003b; Green et al. 2003). Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze (Ho et al. 2004), while higher doses exhibited reduced anxiety on the plus maze. Rats given higher doses also reduced aggressive behavior, but they also reduced social investigation. Rodents

responded to high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail") (Green et al. 2003), all signs of rodent "serotonin syndrome." MDMA produces some repetitive behavior, but not to the same degree as do psychostimulants. MDMA increased locomotor activity in rats, leading them to walk around a cage perimeter, interpreted as an indicator of thigmotaxis, a sign of anxiety (Cole and Sumnall 2003b). However, it is notable that a recent in-press publication failed to find thigmotaxis in rats given 5 mg/kg MDMA (Selken and Nichols 2007). By contrast, rhesus monkeys do not exhibit increased locomotor activity after up to 2.4 mg/kg MDMA (Crean et al. 2006). To date, no one has performed empirical investigations of the effects of MDMA on social interaction in human or nonhuman primates.

Morley and colleagues observed rat behavior after 5 mg/kg MDMA, noting that this dose increased likelihood of prosocial behavior, such as lying next to each other (Morley et al. 2005). Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through 5HT_{1A} receptor agonism (Thompson et al. 2007), with the oxytocin increase arising from indirect effects of MDMA on 5HT_{1A} receptors. To date, there have been no human pharmacological challenge studies combining MDMA with 5HT_{1A} agonists or antagonists, and it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA (Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992; Vollenweider et al. 1998).

Humans

MDMA alters mood, perception and cognition. These effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later (Lamers et al. 2003; Tancer and Johanson 2001; Vollenweider et al. 1998a). Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later (Harris et al. 2002; see also Huxster et al. 2006). Most of the therapeutic effects of MDMA result from changes in affect, cognition and social interaction. When combined with psychotherapy that supports one or more of these effects, MDMA permits people to confront and consider emotionally intense memories, thoughts or feelings, and perhaps through changes in mood and perception, increases empathy and compassion for others and the self. MDMA may also increase accuracy of assessing at least some emotional expressions.

Active doses of MDMA alter mood and cognition and produce slight alterations in perception (Dumont and Verkes 2006; Liechti et al. 2001a). Changes in mood include increased positive mood and anxiety (Cami et al. 2000; Harris et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2003). People reported feeling more talkative and friendly after receiving MDMA, and at least one research team informally reported increased feelings of closeness to others (Vollenweider et al. 1998). Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA (Harris et al. 2002), possibly due to the low sensitivity of this measure. However,

a recent investigation into the effects of pretreatment with the SSRI paroxetine on MDMA effects in humans reported MDMA increased feelings of sociality and closeness to others, and that the SSRI paroxetine reduced these effects (Farre et al. 2007). People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety in relation to loss of control, and experiences of racing or blocked thoughts after MDMA (Cami et al. 2000; Liechti et al. 2001; Vollenweider et al. 1998). Study participants experienced slight changes in visual or auditory perception, including changes in the brightness of the room or colors, sounds seeming closer or farther away, and simple visual distortions. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA (Vollenweider et al. 1998). People maintained insight as to their experience, and there was little indication that MDMA produced any strong alterations to the sense of self or control over the experience (Harris et al. 2002; Tancer and Johanson 2003). Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes (Liechti et al. 2001a). Though some researchers had hypothesized that MDMA would produce more positive or rewarding effects when taken in a warm environment (Parrott 2004), researchers comparing the effects of MDMA in a warm and a cool room failed to support this hypothesis (Freedman et al. 2005).

People receiving active doses of MDMA experienced euphoria, positive mood, vigor and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension and dysphoria, as concern over losing control over the self (Cami et al. 2000; Harris et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2003). It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects, though there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood (Liechti and Vollenweider 2000a; Tancer and Johanson 2003).

MDMA produces modest acute changes in attention and cognition, with previous reports indicating impaired performance on some tasks, as digit-symbol substitution, and not others, as the Stroop task (Cami et al. 2000; Gamma et al. 2000; Vollenweider et al. 1998b). Larger doses of MDMA attenuated prepulse inhibition in rats, defined as a reduced startle response to an intense stimulus when it is preceded by a less intense cue. However, in humans, MDMA enhances PPI (Vollenweider et al. 1999). A recent series of studies conducted in the Netherlands that examined the effects of MDMA on skills needed for driving cars reported transient and selective changes in verbal and visual attention and memory after 75 or 100 mg MDMA (Kuypers and Ramaekers 2005; 2007; Ramaekers and Kuypers 2006). Changes included difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects, but without any impairment in spotting scene changes, reduced weaving in a driving simulation, but excessively cautious response to the actions of another car in an assessment of actual driving. MDMA acutely improved performance on one measure of impulsivity while failing to improve or impair performance on other impulsivity measures (Ramaekers and Kuypers 2006). The cause or causes behind these changes are unclear but may relate to changes in attention, salience of visual objects and altered time

perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug methylphenidate (Ritalin) did not produce similar changes. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

Retrospective surveys of people who had used MDMA or ecstasy offered similar accounts of MDMA effects to those observed and reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents reported experiencing stimulant-like effects, as greater energy or talkativeness, and hallucinogen-like effects, as perceptual changes or poor concentration. They also reported that MDMA/ecstasy increased feelings of closeness, compassion or empathy toward the self or others (Cohen 1995; Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). The disparity in detection of entactogenic findings in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness.

3. Pharmacokinetics and biological disposition

MDMA is metabolized in the liver and has a half-life of seven to nine hours (de la Torre et al. 2004), though a half-life of 11 hours has been reported (Pizarro et al. 2004) and is distributed throughout the body (De Letter et al. 2004), though a study in rats reported greater disposition in brain than in plasma (Chu et al. 1996). After 100 mg MDMA, T_{max} is reached at 2 hours, at a time close to peak physiological and subjective effects, and urinary recovery over a 24 hour period is 15% (de la Torre et al. 2004). The pharmacokinetics of MDMA have been primarily characterized by a group of Spanish researchers, with the exception of one publication from researchers in the Netherlands. The Spanish team first reported nonlinear pharmacokinetics for MDMA, findings that are confirmed in recent studies in nonhuman primates (Mechan et al. 2006). MDMA is metabolized by several CYPD enzymes, including but not limited to CYP2D6, CYP1A2 and CYP3A4. Monoamine oxidase and catechol-O-methyltransferase (COMT) also metabolize MDMA.

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called α -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999).

Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). By contrast, urinary recovery of the major metabolite HMA after 100 mg was 40% (de la Torre et al. 2004). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

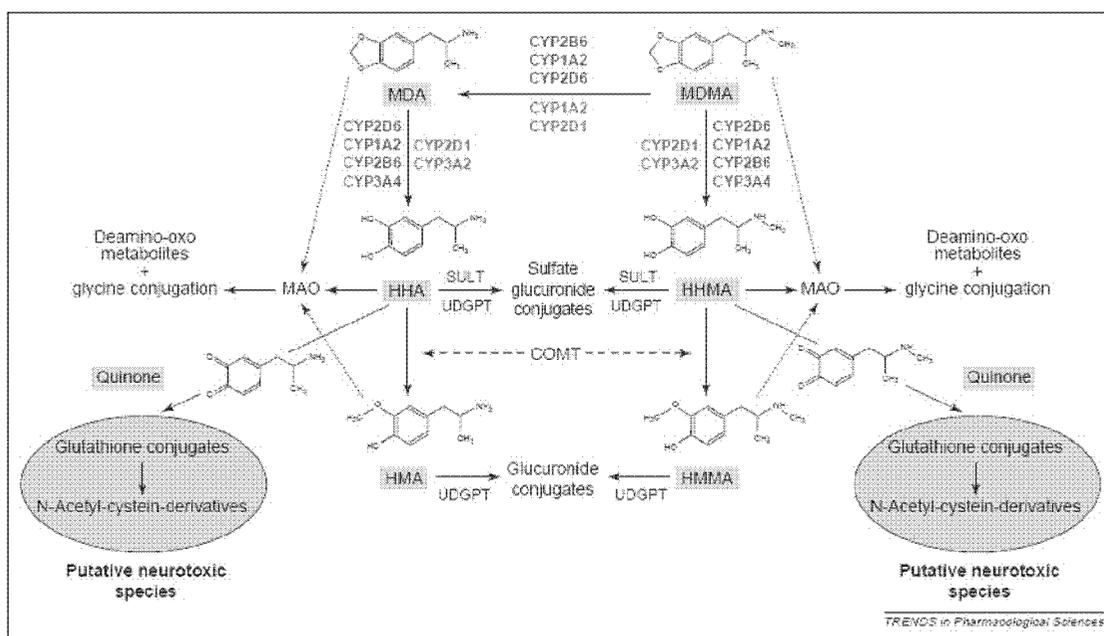


Figure 1: Metabolism of MDMA in rats and humans; enzymes involved in human metabolism in red ink. Reproduced with permission of R de la Torre.

4. Safety and effectiveness in humans obtained from prior clinical studies

When Merck first patented MDMA, it was solely as an intermediate step toward the production of another compound (Freudenmann et al. 2006), and there were no early clinical investigations of MDMA. Published accounts of MDMA-assisted psychotherapy first appeared during the time of hearings for the scheduling of MDMA (Adamson 1985). Shortly afterwards, the only published study of MDMA-assisted therapy appeared, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986). These accounts suggested that, when combined with psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a life-threatening illness. The Swiss government permitted psychotherapists to conduct MDMA-assisted psychotherapy between 1988 and 1993 (Gasser 1994; Widmer 1998). These therapists reported that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration. The Swiss

psychotherapists did not publish any formal analyses of the treatment. Permission to conduct MDMA-assisted psychotherapy in Switzerland was revoked due to events unrelated to the safety or efficacy of MDMA and due to the lack of any published research results.

Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001). A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway to study the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006). Three planned or ongoing investigations to date are sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a member-based nonprofit organization dedicated to supporting and developing research into the therapeutic potential of MDMA and psychedelic drugs. The fourth is sponsored by John Halpern MD.

MDMA-assisted psychotherapy for PTSD

Two studies of MDMA-assisted psychotherapy in people with PTSD are underway, one in South Carolina and the other in Switzerland. A third study is nearly underway in Israel. None of these studies are complete as of yet. The first study has enrolled all or nearly all study participants, and the second has enrolled approximately half of the planned participants.

Michael Mithoefer MD has enrolled nineteen participants in a randomized, placebo-controlled study of MDMA-assisted psychotherapy in 20 people with PTSD symptoms that have not responded to psychotherapy or pharmacotherapy, and a 21st subject who will be a veteran with PTSD who has not been willing or able to receive these treatments. He has enrolled all participants, but to date only 16 participants have completed the study. The study includes an open-label continuation for participants who received placebo during the course of the study. MDMA-assisted psychotherapy is conducted during two extended sessions as part of a course of psychotherapy (Mithoefer 2006). Participants who received MDMA during the course of the study are eligible for a third open-label session as well. An independent rater assesses psychotherapy symptoms at the start of the study and two months after participants have had their second MDMA-assisted therapy session. The original study design involved the administration of 125 mg MDMA, and the current design allows for a supplemental administration of 62.5 mg approximately 2.5 hours after the initial dose. MDMA has been tolerated in participants, and there have been no drug-related serious adverse events to date. An informal analysis of preliminary data suggests that participants assigned to receive MDMA experience fewer PTSD symptoms two months after the second MDMA or placebo-assisted session.

There is no indication that receiving MDMA is associated with any changes in cognitive function.

Peter Oehen MD, the principal investigator for the study underway in Switzerland, is assessing the effects of MDMA-assisted psychotherapy in twelve people with PTSD. So far, he has enrolled up to seven participants in this study, and five have undergone at least one MDMA-assisted psychotherapy session. This study is nearly identical to the investigation underway in the US except that it is active placebo controlled, with 25 mg MDMA as the active placebo and a booster dose of 62.5 or 12.5mg respectively after 2.5 hours, and participants undergo three instead of two MDMA-assisted psychotherapy sessions. One individual dropped out of the study owing to distress during the first of three MDMA-assisted sessions, the previous pharmacological treatment was then reinstalled immediately.

A study of MDMA-assisted psychotherapy in twelve people with war or terrorism-related PTSD is recruiting participants and will take place in Israel sometime in early 2008. The study will follow procedures similar to those described in the US and Swiss studies. To date, no one has undergone an MDMA-assisted session in this study.

MDMA for anxiety arising from diagnosis with a potentially life-threatening illness

A randomized, active placebo controlled dose-response study of MDMA-assisted psychotherapy in twelve people with anxiety arising from diagnosis with advanced stage cancer is underway at McLean Hospital, affiliated with Harvard Medical School. John Halpern, MD is currently recruiting participants for this study involving two MDMA-assisted sessions, and will include introductory sessions beforehand and integrative sessions after each MDMA-assisted session. This study also employs 25 mg MDMA followed by 12.5 mg, administered during both occasions, as an active placebo. Participants in the active dose condition will receive 83.3 mg and 41.7 mg during their first MDMA-assisted session, producing a cumulative dose of 125 mg, and 125 mg followed by 62.5 mg during the second session. No participants are enrolled in this study to date.

MDMA and Parkinson's disease

Studies in rodents and nonhuman primates have examined the effects of MDMA and related compounds in alleviating the symptoms of Parkinson's disease (PD), which include slow, halting movements, or in treating dyskinesia, involuntary movements and twitches that can arise from using medications to treat the condition (Iravani et al. 2003; Lebsanft et al. 2005a; Lebsanft et al. 2005b; Sotnikova et al. 2005). Researchers found that MDMA and other entactogens, such as MDE, could attenuate abnormally slow movements in rodents without functioning dopamine systems (Sotnikova et al. 2005), and that monkeys with dopamine systems damaged by MPTP also improved after treatment with MDMA (Iravani et al. 2003). While this program of research is likely inspired by the account of a former stuntman with young-onset PD, there are no human trials of MDMA or any other entactogenic compound as a possible treatment for PD or PD-related dyskinesias underway. Because of the sympathomimetic effects of MDMA and the potential of MDMA neurotoxicity with daily dosing, it seems unlikely that MDMA

will be developed as a medication for PD. It appears that the anti-Parkinsonian effects of MDMA may be due at least in part to indirect activation of 5HT_{1A} receptors, and perhaps to activation of trace amine receptors (Bishop et al. 2006; Sotnikova et al. 2005).

5. Possible Risks and Side Effects

Overview

MDMA was administered to perhaps thousands of people prior to scheduling, and as of late 2007, it has been administered to approximately 390 people in uncontrolled and controlled studies. People continue to use ecstasy around the world in various non-medical settings (Beck and Rosenbaum 1994; Carlson et al. 2005; Cole and Sumnall 2003a; Solowij et al. 1992; Sumnall et al. 2006), including dance events, large gatherings, concerts and small parties. While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use (Baggott 2002; Gore 1999). Drug-related serious adverse events have not occurred in any of the human MDMA research studies so far. In 2005, the number of MDMA/ecstasy related emergency room visits logged into the Drug Abuse Warning Network (DAWN) was 10,752 of approximately 1,449,154 ED visits related to any form of drug, approximately 0.007% or calculated to be 3.6 per population of 100,000 (Substance Abuse and Mental Health Services Administration 2007). Operating on national survey data on drug use and emergency department admissions in the US and a study of Australian polydrug users, Baggott and colleagues estimated that between 2.9 and 11 emergency department visits might arise from 10,000 uses of ecstasy (Baggott et al. 2001, pp. 148-150).

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

Common Adverse Effects and Side Effects

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies of MDMA are listed in Table 2 and include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance,

dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas (Harris et al. 2002). Other less common side effects include parasthesias (unusual body sensations) such as tingling sensations, or feeling hot or cold. These effects are transient and recede with the waning of drug effects. One study found that women were more likely than men to experience most commonly reported side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating (Liechti et al. 2001b).

Sub-acute effects appearing 24 to 48 hours (1 to 2 days) after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with sub-acute effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006). The possibility of long-term effects is discussed in more detail below.

Table 3: Acute Side Effects of MDMA

	Overall Incidence After Placebo	Overall Incidence After MDMA	Downing 1986	Gamma et al. 2000	Greer & Tolbert 1986	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Vollenweider et al. 1998
N:	13-57	13-112	10	16	29	14	14	16	13
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	1.7 mg/kg	75-150, 200 mg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.7 mg/kg
Measurement Time:	-	-	2-5 h	?	?	?	?	?	0-360 min
Lack Of Appetite	2%	70%	100%	63%	97%	50%	50%	50%	62%
Jaw Clenching	0%	63%	60%	64%	76%	57%	71%	44%	62%
Dry Mouth	Na	57%	na	na	Na	57%	57%	na	na
Thirst	4%	48%	na	50%	Na	57%	57%	38%	38%
Restless Legs	0%	45%	na	na	Na	na	na	44%	46%
Impaired Balance/Gait	0%	44%	70%	na	10%	71%	43%	50%	62%
Difficulty Concentrating	16%	42%	30%	50%	3%	71%	50%	63%	62%
Dizziness	2%	40%	na	na	Na	57%	21%	50%	31%
Restlessness	0%	39%	na	na	Na	50%	29%	44%	31%
Sensitivity To Cold	7%	38%	na	na	Na	na	na	na	38%
Private Worries	23%	38%	na	na	Na	na	na	na	38%
Heavy Legs	0%	38%	na	na	Na	na	na	na	38%
Palpitations	0%	33%	na	38%	Na	43%	21%	na	31%
Feeling Cold	4%	33%	na	na	Na	43%	na	na	23%
Perspiration	0%	30%	na	50%	Na	36%	na	na	0%
Drowsiness	50%	23%	na	na	14%	43%	na	na	na
Nystagmus	Na	23%	80%	na	3%	na	na	na	na
Hot Flashes	0%	23%	na	na	Na	na	na	na	23%
Nausea	4%	21%	10%	na	24%	36%	na	na	8%
Trismus	Na	21%	na	na	3%	57%	na	na	na
Inner Tension	0%	17%	na	na	3%	43%	14%	19%	23%
Insomnia	0%	17%	0%	na	Na	na	na	na	31%
Anxiety	0%	16%	na	na	17%	14%	na	na	na
Weakness	0%	16%	na	na	3%	36%	na	na	23%
Urge To Urinate	8%	15%	na	na	Na	na	na	na	15%
Tremor	0%	14%	na	na	3%	21%	14%	na	31%
Muscle Aches / Tension	Na	14%	na	na	21%	na	na	na	0%
Forgetfulness	0%	14%	na	na	3%	na	na	na	38%
Fatigue	26%	13%	na	na	7%	na	29%	na	8%
Parasthesias	0%	12%	na	na	3%	na	na	na	31%
Lack Of Energy	14%	12%	na	na	3%	29%	na	na	na
Brooding	0%	12%	na	na	3%	29%	na	na	na
Fainting	Na	3%	na	na	3%	na	na	na	na
Blurred Vision	Na	3%	na	na	3%	na	na	na	na
Lip Swelling	Na	2%	na	na	3%	na	na	na	0%
Headaches	Na	2%	0%	na	3%	na	0%	na	na

na: not available

Reproduced from Baggott et al. 2001

Medical Emergencies and Adverse Events in Ecstasy Users

An examination of the literature published up through early 2001 located over 205 published case reports or case series concerning adverse events after ecstasy use. The most frequently reported events were hyperthermia (25.1% of 199 case reports), psychological symptoms or psychosis (22.1% of 199), hepatotoxicity, or liver conditions and problems (16.1% of 199 cases), and hyponatremia (9.5%) accounted for the majority of the serious adverse events after ecstasy use (Baggott et al. 2001). A second examination of the literature in 2004 found that these continued to be the most frequently reported problems reported in literature assessed after the initial examination (Jerome 2004), with only two new conditions reported in the literature, gingivitis from maintaining an ecstasy tablet between the lips and gum (Brazier et al. 2003), and chorioretinopathy, an eye condition sometimes associated with use of sympathomimetic drugs that cleared up after cessation of use (Michael et al. 2003). Set and setting may play a role in the development of some ecstasy-related adverse events, such as rigorous exercise, lack of attention to somatic cues and too little or too much hydration in the case of hyperthermia and hyponatremia (Henry and Rella 2001). Hall and Henry address medical emergencies related to ecstasy use, describing all events mentioned in Baggott and colleagues (Hall and Henry 2006). While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only (Cregg and Tracey 1993; Liechti et al. 2005; Williams et al. 1998). It is notable that none of these events has occurred during a human MDMA study, so that even psychological distress has not required pharmacological intervention or hospitalization.

Other serious adverse events occurring after ecstasy use include cardiac problems (as arrhythmias), cerebrovascular events, hematological, respiratory events (as pneumostadium), dermatological, ophthalmological and dental events (Baggott et al. 2001). As with the four most common serious adverse events, none of these events have occurred in the context of human MDMA research.

In vitro and in vivo investigations of the effects of MDMA on cardiac, hepatic (liver) and kidney tissues or cells have occurred over the past ten years (Baggott et al. 2001; Jerome 2005) (see for example Beitia et al. 2000; Caballero et al. 2002) (Varela-Rey et al. 1999). Researchers conducting in vitro studies often use large doses (in micromoles) that are unlikely to occur after a typical human dose. At these high or extremely high doses, MDMA damages liver cells, particularly under warm ambient temperature, possibly mimicking hyperthermia-related hepatotoxicity in humans. In one case series of postmortem heart tissue, Patel and colleagues determined that 58.3% of the hearts from ecstasy-associated deaths were larger than normal versus 18.7% of the hearts from non-ecstasy related deaths (Patel et al. 2005). Since myocardial hypertrophy (an enlarged heart) is associated with stimulant use, and given the large extent of polydrug use in ecstasy users, this study cannot rule out the possibility that the increase they saw was not a result of psychostimulant use. A recent retrospective comparative study using echocardiograms in 29 heavy ecstasy users (reporting use of 3.6 tablets per week) and 29

age and gender matched undergraduate controls detected abnormalities indicative of potential valvular heart disease (VHD) in eight ecstasy users and none in controls, though less pronounced than abnormalities seen in people taking the anti-Parkinson's disease medication pergolide (Droogmans et al. 2007). The average cumulative dose in people with detectable abnormalities was 943 +/- 1162 tablets versus 242 +/-212 tablets in those without abnormalities). The authors hypothesize that the observed cardiac changes in ecstasy users were less prominent than in people taking pergolide because of weekly rather than daily use, and because drug-induced VHD is reversible. Given the extensive and frequent use in this sample, the risk of similar cardiac abnormalities developing in people taking part in human MDMA studies is very low. However, these findings also suggest that regular use of ecstasy may have some of the same risks as regular use of other 5HT_{2B} agonists, as some migraine medications and the appetite suppressant fenfluramine.

Long-Term Effects

Central Serotonin Function, Cognition and Affect: Retrospective Studies

There is a wealth of research examining the effects of repeated doses of MDMA in nonhuman animals (Cole and Sumnall 2003b; Green et al. 2003). Findings included reduction in brain serotonin, signs of impaired transport of serotonin and some behavioral changes, as increased anxiety (Callahan et al. 2001; Gurtman et al. 2002; Hatzidimitriou et al. 1999). These findings suggested that MDMA could damage serotonin axons, producing a form of neurotoxicity. However, as noted earlier, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses. It now appears that lower doses of MDMA fail to reduce brain serotonin. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin and no chemical markers of neuronal injury (Fantegrossi et al. 2004), and rats receiving lower doses of MDMA do not exhibit signs of neurotoxicity, such as changes in serotonin transporter sites or markers of neuronal injury (Wang et al. 2005). While a recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days (Meyer et al. 2006). However, studies in very moderate ecstasy users failed to see an increase in this marker (de Win et al. 2007), and only one of three studies of this marker in humans detected it in heavy users (Chang et al. 1999; Cowan et al. 2007; Reneman et al. 2002).

Changes in Serotonin Function and Indicators of Neuronal Injury or Repair

Spurred on by nonhuman animal studies that found that repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of ecstasy in humans (see for example Krystal et al. 1992; McCann et al. 1999; McCann et al. 1994; Semple et al. 1999). These studies detected differences in mood and cognition in ecstasy users, and possible changes in brain serotonin uptake sites. Researchers assumed that if MDMA reduced serotonin function, it should produce observable effects, as reduced brain serotonin uptake sites or changes in mood or psychological well-being. These early investigations possessed a number of methodological flaws, including retrospective design and poor matching of

ecstasy users with appropriate controls (Baggott et al. 2001; Gouzoulis-Mayfrank and Daumann 2006a; b). Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactives, including alcohol (Buchert et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Thomasius et al. 2003). Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points (Daumann et al. 2004b; Gouzoulis-Mayfrank et al. 2005); (Buchert et al. 2006; Zakzanis and Campbell 2006; Zakzanis and Young 2001). For the most part, these studies suggested that heavy but not moderate ecstasy users had impaired verbal memory and lower numbers of estimated SERT sites, with heavy use often defined as being at or greater than 50 times or tablets. Estimated SERT sites returned to control levels after sustained abstinence from ecstasy, while cognitive function did not return to control levels (though see Zakzanis and Campbell 2006). These studies failed to find improved cognitive function after abstinence from ecstasy use, and they failed to find further deterioration after continued use. The different pattern of findings for SERT sites and cognitive function suggested that changes in one domain should not be treated as an indicator of changes in another domain.

Impaired Cognitive Function

Two recent findings concerning cognitive function in ecstasy users have appeared in the literature, with one finding measuring a facet of visual perception and the other pertaining to effects of anxiety over confirming others' negative views might have on ecstasy user participants. In a study of "heading," or perceived self-motion, in ecstasy users and cannabis user controls, Rizzo and associated found that both ecstasy and cannabis users had difficulties with "heading" in a simulated visual perception task, with ecstasy users performing less well than cannabis users under angles (Rizzo et al. 2005). Study participants had to a minimum lifetime ecstasy use of at least ten occasions, and average cumulative use was 36.9 +/- 32.1 occasions, with an average period of abstinence of roughly half a year (226.9 +/- 134 days). Hence while cumulative use was lower than in other studies of cognitive function in ecstasy users, it is greater than expected during human MDMA studies. Ecstasy users performing tests of cognitive function may be affected by stereotype threat, the fear of confirming negative beliefs people hold about a specific group membership, as race or gender. When ecstasy users heard from investigators that ecstasy use had no effects on memory, they scored higher on measures of memory than ecstasy users given information stating that ecstasy use impairs memory, while both groups of ecstasy users scored similarly to non-user controls on measures of executive function (Cole et al. 2006). Hence it may be the case that findings of impaired cognitive function in ecstasy users are due in part to the disruptive effects of stereotype threat.¹

Two independent meta-analyses (cross-study statistical analyses) of memory in ecstasy users arrived at somewhat contradictory conclusions (Laws and Kokkalis 2007; Zakzanis et al. 2007). While both analyses detected an association between ecstasy use and impaired performance on at least some measures of memory, one analysis, that of Laws and Kokkalis, reported that this association had a medium to large effect size and found

¹ The author of this document is a coauthor of the paper on the effects of stereotype threat on memory.

no effect of ecstasy dose, while the other, that of Zakzanis and colleagues, reported that the association had a small to medium effect size and found a dose effect. Zakzanis and colleagues also concluded that use of other drugs independently impaired cognitive function, while Laws and Kokkalis failed to find an association between cannabis use and verbal memory performance, relating it instead to visual memory performance. It is unclear why the two analyses reached somewhat different conclusions. Both examined a similar though not identical set of retrospective studies. It is important to note that minimum cumulative use in both analysis was above ten uses, and that average cumulative use was considerably higher (287 tablets in Zakzanis' analysis and 327 in Laws and Kokkalis' paper).

Previous research has established a link between repeated ecstasy use and impaired executive function, defined here as planning, decision-making, and inhibiting a well-learned response (Baggott et al. 2001; Cole and Sumnall 2003; Jerome 2005). The nature and strength of the association between regular ecstasy use and impaired executive function remains inconclusive, with some reports finding impaired executive function in ecstasy users, particularly heavy users (Halpern et al. 2004; Wareing et al. 2004) while others failed to find differences between ecstasy user and non-user executive function (Thomasius et al. 2003), or found executive function impairments only in male ecstasy users (von Geusau et al. 2004). Current studies continue to support both presence and absence of a relationship between ecstasy use and executive function. It is possible that polydrug use may also contribute to ecstasy users' impaired executive function (Hoshi et al. 2007b; Medina and Shear 2006).

Psychological Well-being, Affect, Impulsivity, and Sleep

Previous reports had found an association between ecstasy use and reporting greater increases in symptoms of depression or anxiety (see for example MacInnes et al. 2001; Parrott et al. 2000). A meta-analysis of self-reported depressive symptoms detected an association between ecstasy use and scores on the Beck Depression Inventory, a popular self-report measure of depression symptoms (Sumnall and Cole 2005). Sumnall and Cole noted that the association was strongest in studies with small samples, and noted that drug use variables are often incompletely reported and not verified through any methods save self-report in these studies. Findings concerning the long-term effects of ecstasy use on mood, including findings from longitudinal studies, suggested that an association between increased feelings or symptoms of anxiety and depression and ecstasy use exists, but that these findings were more strongly related to polydrug use rather than to use of any one substance (Milani et al. 2004; Sumnall et al. 2004) (Medina and Shear 2006). Some studies found that continued use of cannabis rather than ecstasy was associated with self-reported psychological problems (Dafters et al. 2004; Daumann et al. 2004a; Daumann et al. 2001). At least one study found an association between possessing a genetic variation on the serotonin transporter gene and increased self-reported depression in heavy ecstasy users (Roiser et al. 2006), and another study reported finding greater self-reported psychological problems in ecstasy users than cannabis users, though the two samples did not differ on memory task performance (Lamers et al. 2006). On the other hand, a study of heavy ecstasy users failed to find any increase in diagnosis of depression (de Win et al. 2004), and two studies examining large samples of ecstasy users either

failed to find increased depressive symptoms or found increased symptoms only in a subset of heavy users (Falck et al. 2006; Guillot and Greenway 2006).

The relationship between ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in ecstasy users while others failing to find any differences (see for example McCann et al. 1994; Morgan 1998). Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions (Morgan et al. 2006; Quednow et al. 2007; Roiser et al. 2007). Two recent studies even used the same measure of behavioral impulsivity in samples of heavy ecstasy users, yet obtained different findings concerning the relationship between ecstasy use and impulsivity (Quednow et al. 2007; Roiser et al. 2007). It is possible and likely that people who self-administer ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility. Taken together, self-reported changes or deterioration in psychological well-being and impulsivity in ecstasy users are likely multiply determined and only partially, if at all, uniquely related to ecstasy use.

Drawing conclusions from retrospective studies continued to raise questions concerning the strength and causal link between findings, especially when studies in representative samples suggested that people who chose to use ecstasy and other drugs were liable to have psychological problems prior to use (Huizink et al. 2006; Lieb et al. 2002), and given the fact that polysubstance use is so prevalent among ecstasy users (Gouzoulis-Mayfrank and Daumann 2006a). It is notable that some of the most recent studies have either found that polydrug use was equally associated with impaired cognitive function as was ecstasy use (Hoshi et al. 2007b), or that use of cannabis or other drugs make additional and even greater contributions to differences between ecstasy users and controls (Jager et al. 2007a; Montgomery and Fisk 2007).

Researchers at Johns Hopkins University have investigated the effects of regular ecstasy use on sleep (Allen et al. 1993; McCann et al. 2007). Their earlier study reported detecting less stage II sleep, while a recent study found some differences between ecstasy users and controls, in this case, including less stage II sleep and less reduction in sleep latency after administering a compound that reduced catecholamine neurotransmitters (McCann et al. 2007). To date, no other researchers have examined sleep in ecstasy users, but both studies consisted largely of samples of heavy ecstasy users, and the recent study detected an association between degree of ecstasy use and effects on sleep.

Prospective Studies

The Netherlands XTC Toxicity team mentioned at the beginning of this document is the first to perform prospective research studies comparing ecstasy users before and after their first few uses, sometimes comparing them with controls who have not yet taken ecstasy (De Win et al. 2005). Average cumulative use in these studies ranged from 1.8 to 6 tablets, and maximum use in two of three studies was 10 tablets. In one study, the researchers imaged the brains of 30 people before and approximately seven weeks after having used ecstasy. They failed to find any chemical markers of neuronal injury in

ecstasy users, and they found very few changes in cerebral blood flow, with the exception of decreased cerebral blood volume in the dorsolateral frontal cortex (De Win 2006). Another study examined working memory in 25 people reporting an average use of 2 tablets with 24 controls, failing to find any significant differences either in brain activity as assessed via functional magnetic imagery (fMRI) or on tests of working memory and selective attention (Jager et al. 2007b). A study examining self-reported depression symptoms, failed to find an association between low ecstasy use and symptoms of depression, though they also failed to find a relationship between symptoms of depression and likelihood of taking ecstasy (de Win et al. 2006). Finally, a study comparing 58 people reporting use of 3.2 tablets with 60 controls before and after use, up to 18 months later, and found an association between ecstasy use and performance on measures of verbal memory, and not attention or working memory (Schilt et al. 2007). While all participants exhibited scores within the normal range both times they were tested, people who did not use ecstasy showed greater improvement in performance than did people who used it. Analyses in the study assessing cognitive function apparently included one individual reporting higher cumulative ecstasy use, 30 tablets. In contrast, data from a prospective controlled study that was presented at a conference failed to find impaired cognitive function in drug-naïve individuals after two doses of 1.5 to 1.7 mg/kg MDMA (Ludewig S et al. 2003). Taken together, a majority of the prospective studies failed to find indications of structural or functional change after low ecstasy use, while one study found impairment in memory after low to moderate use. While these prospective studies do not and cannot demonstrate either a definite lack or presence of long-term effects from a few exposures to MDMA, they did not find the types of changes seen in heavy ecstasy users, and they suggest that risks of long-term effects associated with taking part in human MDMA studies are low.

Conclusions

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of impaired serotonin function or verbal memory after exposure to one to three doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggest that this risk is minimal after a low number of exposures. While there may also be risks related to psychological well-being such as increased symptoms of anxiety or depression, support for these long-term effects are even less strong than for the previously listed changes.

Abuse Potential

The US Drug Enforcement Administration (DEA) placed MDMA in Schedule 1, the most restrictive schedule reserved for compounds with high abuse potential and no medical value, and most other nations followed the lead of the US in making MDMA a tightly controlled substance. Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less

intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens but lesser than for psychostimulants.

Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al. 2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al. 1999).

Reproductive and Developmental Toxicity

Previous research supported a possible link between ecstasy use and birth defects (McElhatton et al. 1999), while an epidemiological study conducted in 2004 in a large cohort of pregnant women in England failed to support this link, at least in respect to a specific cardiac defect (Bateman et al. 2004). However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant (Ho et al. 2001).

Several teams of researchers have performed studies of developmental toxicity in rodents (see for example (Koprich et al. 2003a; Koprich et al. 2003b; Piper and Meyer 2004; Williams et al. 2005). In some studies, the researchers administered large, repeated doses to pregnant rats, and in others, the MDMA was administered to neonatal rats. The researchers did not report gross structural abnormalities in rats exposed to high doses of MDMA in utero. However, studies of MDMA in neonatal rats found changes in numbers of serotonin or dopamine cells and impaired learning or memory, particularly when MDMA was administered from the 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose of MDMA in young rats also produced less of an increase in BT and fewer signs of "serotonin syndrome" when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable to some effects of MDMA.

6. Research trial data

Information is being gathered and prepared. Side effects reported in the first clinical trials are similar to those reported in controlled studies, though anxiety may be more prevalent, due in part to the condition under study and in part to the nature of the setting, as participants are encouraged to confront emotionally upsetting thoughts, memories and feelings. In this setting anxiety is not chiefly viewed as a side effect, but as an element of the underlying disorder and the therapeutic process.

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Study Synopsis

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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 5, 2008

Background and Rationale

Background: 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). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems.

PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population of the US. To date the treatment of PTSD has primarily been psychotherapeutic, 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 eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all “bona fide” psychotherapies, including all those listed above, are similarly effective with PTSD [4].

However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with 3,4-methylenedioxymethamphetamine (MDMA), a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA is a ring-substituted phenethylamine that bears structural and pharmacological similarities to amphetamines and the psychedelic compound mescaline. However, it possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [8-11]. MDMA was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. 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 [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e. g. 16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22]. In

contrast, all available Phase I and Phase 2 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. 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.

Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. 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” [8]. 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 [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25]. 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. Though the psychopharmacology and neuropsychological underpinnings of the therapeutic effects of MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli.

Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the 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 [28]. A one-year+ follow-up study is currently underway.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be 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.

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

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 either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 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 during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session. Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression

symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

The study will take place at one location in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, [REDACTED] Assessments of PTSD symptoms and neurocognitive function will be performed in the offices of the independent rater, Dr. Karen Tallman. [REDACTED]

List of Investigators

Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She 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 will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.

Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. 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. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She

is a clinical psychologist who has 15 years of experience and has conducted psychiatric diagnostic and competency assessments.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD who score 50 or higher on the Clinician-Administered PTSD Scale (CAPS). The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all the inclusion criteria listed below without meeting any exclusion criteria. Participants must reside in Canada.

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 [32, 33].
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] 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 [34], 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 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.

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 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 assignment 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 [REDACTED] 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 [REDACTED] 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 psychotherapy	Intro psychotherapy	Experimental 1	Integrative Therapy 1	Integrative Therapy 2	Integrative Therapy 3	Experimental 2	Integrative Therapy 4	Integrative Therapy 5	Integrative Therapy 6	Experimental 3	Integrative Therapy 7	Integrative Therapy 8	Integrative Therapy 9	6 wk post V11	End Randomized Segment	
Approximate Study Day			6	7	14	21	28	29	35	42	49	56	56	63	70	77	78	85	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 interim SES 1	Between V8 and V11	Post V9	3-5 wks post V6	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	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		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				X						
SUD							X			X	X				X						
Common Side Effects							X	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 #	V20	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 V25	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 [REDACTED] 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 [REDACTED]. 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 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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MDMA Psychotherapy for PTSD

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**A Randomized, Active Placebo-controlled Pilot Study of 3,4-
methylenedioxyamphetamine (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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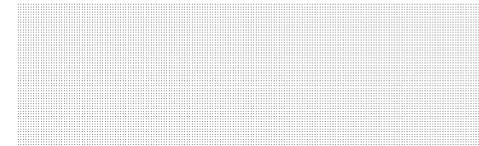


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Study Period

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 (EMA) 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 I 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%. (Perkonig 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
<i>Active Placebo</i>	25 mg	12.5 mg	37.5 mg
<i>Experimental Dose</i>	125 mg	62.5 mg	187.5 mg

Method

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

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

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

Time and Events for Randomized Study segment

Time and Events M-P4	Baseline and Screening			Therapy and Evaluation 1						Therapy and Evaluation 2						Therapy and Evaluation 3				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Visit #																				
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	33	42	49	50	56	63	70	71	78	85	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-experiment session 1	Between V8 and V11	Post-V9	>3x5 wks post V8	24 h post V11	Post V11	Post V13	<3-5 w post V11*	24 h post V15	Post V15	Post V17	8 wk post V15	May be same day as V19
Study Staff	Ingrid/Andrew	Ingrid/Andrew	Ingrid/Andrew, Ingrid/Andrew, Karen	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid+Andrew	Ingrid/Andrew, Karen	Ingrid/Andrew
Telephone Screening	X																			
Provide consent materials		X																		
Study informed consent		X																		
Medical Examination			X																	
EKG			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																				
Consent for Stage 2/open-label																				
RRPQ																				
End Randomized phase																				
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 to 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 assignment to the active placebo condition. This study will employ a blinded adaptive randomization procedure in order to maintain the 66%/33% ratio while maintaining the blind and ensuring that each subsequent condition assignment is not predicated on the previous assignment. A randomization monitor will generate and maintain a list of random numbers between one and 100. A randomization list will be run to assign either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles randomly assigned a number between 1 and 100. The randomization monitor will

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

Psychotherapy

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

Introductory Sessions

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

MDMA-assisted Psychotherapy

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

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

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

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

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

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

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

Table 3. Schedule of procedures and measures for experimental sessions

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

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

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

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

Both therapist-investigators 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 for additional support. Participants will be encouraged to use much of the time during their overnight stay for rest and for a period of reflection and integration in a quiet atmosphere.

Integrative Psychotherapy

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

Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy

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

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

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

Weekly Integrative Sessions

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

Daily Telephone Contact

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

Evaluation Six weeks after the Third experimental session

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

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

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

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

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

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

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

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

Assessment Six weeks after Third Open-Label Session

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

Removal of Subjects from Therapy or Assessment

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

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

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

Premature Discontinuation of the Study

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

Data Analysis

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

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

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

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

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

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

Statistical power

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

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

Monitoring for Toxicity

There is now a considerable body of information indicating that the likelihood of significant toxicity from the doses of MDMA used in a therapeutic setting is very low (Baggott et al. 2001; Dumont and Verkes 2006; Jerome 2004; 2005; 2007). Approximately 390 people have received MDMA during controlled trials without the occurrence of any drug-related serious adverse event, and psychiatrists in the US and

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

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

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

Hypertension and related cardiovascular Effects

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

Angina or Myocardial Infarction:

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

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

Stroke:

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

Psychological Distress:

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

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

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

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

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

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

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

B. Hospitalization for stabilization

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

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

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

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

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

Hyperthermia:

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

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

Dehydration:

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

Hyponatremia:

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

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

Liver toxicity:

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

Neuropsychological toxicity:

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

Abuse and dependence:

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

Medical Emergencies

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

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

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

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

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

Mild: no limitation in normal daily activity.

Moderate: some limitation in normal daily activity.

Severe: unable to perform normal daily activity.

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

1. Not Related

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

2. Possibly Related

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

3. Probably Related

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

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

Serious Adverse Events

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

Results in death

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

Requires or prolongs inpatient hospitalization

Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)

Results in a congenital anomaly/birth defect

Requires intervention to prevent permanent impairment or damage

Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

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

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

Adverse Event Collection

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

Medical Monitor: [REDACTED]

Study Monitor: [REDACTED]

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

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

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

- Common side effects.
- Exacerbation of anxiety.

Collection of Concomitant Medications

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

Laboratory Assessments

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance. After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

Study Monitoring, Auditing and Documentation

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

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

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

Risks and Discomforts

Risks and Discomforts Associated with Drawing Blood

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

Risks and Discomforts Associated with Screening Procedure

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

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

Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy

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

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

Risks and Discomforts of Receiving the Study Drug (MDMA)

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

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

Cardiovascular and Sympathomimetic Effects

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

Perceptual Alteration

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

Psychological Distress

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

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

Immunological Changes

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

Toxicity

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

Potential Neurotoxicity Associated with Ecstasy Use

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

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

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

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

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

Abuse Liability

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

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

Reproductive and Developmental Risks

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

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

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

Alternative Treatments and Procedures

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

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

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

Confidentiality

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

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

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

Costs to Participants

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

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

Risk/Benefits Analysis

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

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

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

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

Chemistry, Manufacturing and Control Information

The drug product is (+/-)-(3,4)-methylenedioxymethamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch [REDACTED]) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by [REDACTED] from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. [REDACTED] DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. [REDACTED] with no decomposition products detectable and a HPLC purity >98%.

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

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

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

Pharmacokinetics and Pharmacodynamics

Primary Pharmacology

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

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

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

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

Though they differ in some respects, early and later pharmacological profiles of MDMA reported an affinity for specific serotonergic, noradrenergic, cholinergic and histaminergic receptors (see Table 3 below). It is possible but not yet demonstrated that 5HT_{2B} and α_2 receptors may contribute to at least some of the subjective effects of MDMA, while little is known as to whether there are any potential contributions from M₃ or H₁ receptors. 5HT_{2B} receptors in the medial amygdala may contribute to the anxiolytic effects of MDMA, as may also be true for the serotonin releaser and 5HT_{2B} agonist fenfluramine. Direct MDMA stimulation of postsynaptic α_2 adrenoceptors may also help individuals remain emotionally calm despite noradrenergic activation, as with related α_2 agonists clonidine and guanfacine, possibly through altering the balance between α_1 to α_2 stimulation (Franowicz and Arnsten 1998).

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

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

Primary Pharmacodynamics

Drug Activity Related to Proposed Action

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

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

Secondary Pharmacology

Safety Pharmacology

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

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

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

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

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

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

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

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

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

Hyperthermia

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

Psychiatric Problems

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

Hepatotoxicity

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

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

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

Hyponatremia

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

Neurotoxicity

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

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

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

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

Developmental Toxicity

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

Common side effects

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

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

Acute Adverse Effects

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

Abuse Liability

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

Pharmacokinetics/Toxicokinetics

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

significance of these differences are unclear, and this is the first detailed study of MDMA pharmacokinetics in men and women.

As can be seen in Table 5, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.

Table 5. MDMA Pharmacokinetics

MDMA Dose	N	C _{max} μg/l	T _{max} H	AUC ₀₋₂₄ μg*h/l	AUC/dose μg*h/(l*mg)	Reference
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8.6	Mas et al. 1999
75	1 2	178 (no SD)	3	Not reported	NA	Lamers et al. 2003
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	24.31 ± 7.7	(de la Torre et al. 2000c)
100	9	180 ± 33	2 ± 0.26	1452 ± 771	14.52 ± 7.7	Farre et al. 2004
100	7	208.7 ± 17.1	16 ± 0.4	Not reported	NA	(Pizarro et al. 2004)
100	7	232.9 ± 45.3	1.5	Not reported	NA	Segura et al. 2005
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	(de la Torre et al. 2000a)

MDMA Dose	N	k _a /h	k _e /h	T _{1/2} H	MDA T _{1/2a} H	Reference
50	2	Na	na	2.7 and 5.1	Na	(de la Torre et al. 2000c)
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.7 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	(de la Torre et al. 2000c)
100	7	na	0.07 ± 0.03	11.8 ± 4.4	na	Pizarro et al. 2004
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	Na	na	6.9 and 7.2	Na	(de la Torre et al. 2000a)

Farre and colleagues reported the pharmacokinetics of a second dose of 100 mg MDMA given 24 hours after an initial 100 mg dose in nine men (Farre et al. 2004). C_{max} was 232. ± 39 μ/L, AUC₍₂₄₋₄₈₎ was 2564 ± 762 μg*h/L, T_{max(24-48)} was 25.5 ± 0.33 h, and AUC/dose was 25.64 ± 7.6 μg*h/l*mg. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), probably as a result of non-linear pharmacokinetics. De la Torre was first to report evidence of non-linear pharmacokinetics, and a recent report supports these findings (de la Torre et al. 2000a; Kolbrich et al. 2008). Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly

higher maximal values than expected after the supplemental dose only or the combined dose, or whether it will instead lengthen T_{max} .

Summary of Pharmacokinetic Parameters :

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called α -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la Torre et al. 2000a; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002)(de la Torre et al. 2000; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004). HMMA appears to be the main metabolite in humans (Pizarro et al. 2004). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

Although a number of researchers hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, an examination of the research does not support this concern. Several *in vitro* studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforge et al. 1999; Wu et al. 1997). Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant.

Relatively recent reports in humans found no evidence that having a CYP2D6 “poor metabolizer” genotype is by itself a major risk factor for acute MDMA toxicity (de la Torre et al. 2004). At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (de la Torre et al. 2005) (Segura et al. 2005) without any adverse events occurring. The individual had 60% greater MDMA AUC after a first and a second dose, but the only other reported difference for this participant was a statistically significant increase in amount of NK cells. A comparison of MDMA metabolism in poor and extensive metabolizers found that reduced CYP2D6 function was associated with higher MDMA AUC after the first of two doses of MDMA, but similar levels of MDMA and metabolites after the second dose (de la Torre et al. 2005). The same lack of effects was originally reported in a participant given the similar compound methylenedioxyethylamphetamine, or MDE (Kreth et al. 2000).

Two teams of researchers have investigated the enzymes involved in the formation of MDA from MDMA in human liver microsomes (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their

experiments. In a publication focusing on MDE metabolism, Kreth and colleagues reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

MDMA is a chiral compound, meaning it comes in two forms or enantiomers. However, all investigations in humans and most in nonhuman animals have almost exclusively administered the racemate (a mixture of both enantiomers). Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-(+)-enantiomer having a shorter elimination half-life and greater excretion than the R-(-)-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Crifasi and Long 1996; Ramcharan et al. 1998). The stereoselective pharmacokinetics of MDMA is reflected in formation of MDA and DHMA enantiomers (Fallon et al. 1999; Pizarro et al. 2004; Pizarro et al. 2003). In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). By contrast, R/S ratios of HMMA are more similar to those for MDA (greater amounts of R-(-)-HMMA than S-(+)-HMMA during the first 24 hours), or there is no findings of a difference between concentrations of the two enantiomers of HMMA (Pizarro et al. 2004; Pizarro et al. 2003).

Absorption, Distribution, Metabolism, Excretion

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a non-enzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991), rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylenation, including CYP1A2 and CYP3A4.

Table 6. Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

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

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Pizarro et al. 2004; Pizarro et al. 2003; Segura et al. 2005; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA reported after administration of 100 mg MDMA to four men are 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

Toxicology

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed (Frith et al. 1987), and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Acute toxicity

Acute toxicity is described above in “Safety Pharmacology”, including both common side effects and effects occurring in ecstasy users. The estimated LD₅₀ for MDMA in humans is between 10 and 20 mg/kg (Frith et al. 1987; Hardman et al. 1973). To date, most controlled studies rarely administered doses above 2 mg/kg. The proposed doses of 150 followed by 75 mg (cumulative dose of 225 mg) or approximately 2.1 mg/kg followed by approximately 1 mg/kg (cumulative dose of 3.21 mg/kg) is below the estimated LD₅₀ in humans.

Reproductive Toxicity

Investigations of the reproductive and developmental toxicity of MDMA are described in “Safety Pharmacology” above. These studies include inconclusive findings in humans and findings in rodents suggestive of a critical period during which exposure to MDMA

may impair learning or memory. Pregnant women will not be enrolled in this training program.

Previous Human Experience

Several accounts describe the use of MDMA as an adjunct to psychotherapy prior to its placement in schedule 1 (Adamson 1985; Stolaroff 2004), and between 1988 and 1993 in Switzerland (Gasser 1994; Widmer 1998). This therapy did not occur in the context of a controlled clinical trial. MDMA may have been given to thousands of individuals during these time periods without any fatalities or serious adverse events (Gasser 1994; Holland 2001; Rosenbaum and Doblin 1991). Psychotherapists used MDMA-assisted psychotherapy in the treatment of moderate psychological difficulties (“neuroses”), relationship difficulties, posttraumatic stress disorder, and anxiety in response to diagnosis with a potentially fatal illness. Therapists described relying on a mixture of therapeutic techniques that included confronting and working with the experience as it occurred and speaking openly with others during the experience.

In the 1980s, two researchers independently published an uncontrolled clinical trial and an uncontrolled investigation into MDMA-assisted psychotherapy (Downing 1986; Greer and Tolbert 1986). The psychotherapy that Greer and Tolbert conducted took place in a setting similar to that used for psychedelic-assisted psychotherapy, including focusing on inner experience. Greer and Tolbert used doses between 75 and 150 mg MDMA, sometimes with supplemental doses administered later (Greer and Tolbert 1986). Participants in the uncontrolled study of MDMA-assisted psychotherapy reported changes in attitudes and benefits afterwards.

The first controlled investigation of MDMA took place almost a decade after the uncontrolled studies (Grob et al. 1996), followed two years later by another controlled trial (Vollenweider et al. 1998). Starting in the mid to late 1990s, at least seven research teams in Europe and the US began conducting and publishing clinical MDMA research using healthy volunteers, and two recent reviews summarized findings from many of these studies (Baylen and Rosenberg 2006; Dumont and Verkes 2006). Since then, a second team of researchers in the Netherlands and a team based in Maryland published their first findings from human MDMA studies (Dumont et al. 2008; Kolbrich et al. 2008). Findings from controlled human studies of MDMA are also discussed in detail in the investigator’s brochure (Baggott et al. 2001; Jerome 2004; 2005; 2007; Jerome and Baggott 2003), and they are addressed earlier in this section. The first studies assessed physiological, subjective, psychological and neuroendocrine effects, and reported that MDMA possessed a unique pharmacological profile. Some of these first studies examined brain activity (Frei et al. 2001; Gamma et al. 2000) cardiac function (Lester et al. 2000), and effects of MDMA on attention and information processing (Cami et al. 2000b; Gamma et al. 2000).

To date, MDMA has been administered to approximately 390 research participants, without any occurrences of drug-related serious adverse events. Human MDMA studies have continued to investigate the subjective and physiological effects of MDMA, and its metabolism and detectability in several body fluids. In published reports, investigators

administered doses ranging from approximately 35 mg (0.5 mg/kg) to 145 to 150 mg (2 mg/kg) (Freedman et al. 2005; Harris et al. 2002; Lester et al. 2000) (Kolbrich et al. 2008), and in an unpublished report, researchers administered 0.25 and 2.5 mg/kg MDMA as well (Grob 2001). The average dose examined in human MDMA studies is between 1 and 2 mg/kg. Studies of the physiological effects of MDMA include investigations of immunological effects (as Pacifici et al. 2004; Pacifici et al. 1999b; Pacifici et al. 2002; Pacifici et al. 2001b), neuroendocrine effects (Forsling et al. 2001; Grob et al. 1996; Harris et al. 2002; Liechti and Vollenweider 2001), cardiovascular and cardiac effects (Lester et al. 2000; Mas et al. 1999) and body temperature (Freedman et al. 2005), and employed brain imaging and quantitative electroencephalography (Frei et al. 2001; Gamma et al. 2000). Researchers have studied self-reported subjective and reinforcing effects (Cami et al. 2000b; Dumont et al. 2008; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003) and observed effects (Harris et al. 2002), and they have studied such specific effects as enhancement of pre-pulse inhibition (Vollenweider et al. 1999), performance on attentional and information processing tasks such as the continuous performance, Stroop and digit symbol tasks (Cami et al. 2000b; Dumont et al. 2008; Gamma et al. 2000), cognitive skills related to driving motor vehicles (Kuypers and Ramaekers 2005; 2007; Kuypers et al. 2006; Ramaekers and Kuypers 2006; Ramaekers et al. 2006), including specific effects of nocturnal dosing (Kuypers et al. 2007), and similarity to a stimulant versus a serotonergic drug (Johanson et al. 2006). As described above, researchers have also examined the role of serotonin release, 5HT_{2A} and D₂ receptors in producing MDMA effects and MDMA pharmacokinetics (de la Torre et al. 2004; Farre et al. 2007; Liechti and Vollenweider 2001; Tancer and Johanson 2007).

A team of researchers in the US are about to complete their research study of MDMA-assisted psychotherapy in people with PTSD, while researchers in Switzerland are engaged in an ongoing study of MDMA-assisted psychotherapy (Mithoefer 2007a; b; 2008; Oehen 2006) and researchers in Israel are conducting a study of MDMA-assisted psychotherapy in people with PTSD (Mojeiko 2006). After undergoing introductory and preparatory psychotherapy, study participants in these studies receive two to three day-long sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Participants receive integrative psychotherapy on the day after each session and often on a weekly basis in between and after each MDMA-assisted session. These studies employ an initial dose of 125 mg MDMA followed 2 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. One of the two ongoing studies has enrolled all study participants, and preliminary results appear promising (Mithoefer 2007b). The other study has enrolled half of the 12 subjects planned for this study. Another study will soon be recruiting people with advanced-stage cancer to examine MDMA-assisted psychotherapy as a means of reducing anxiety arising from the cancer diagnosis (Halpern 2006). To date, the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored three of four studies, with the fourth sponsored by the principal investigator and private benefactors.

Previous experience with MDMA indicates that it can be safely administered to humans within a research or therapeutic setting, and preliminary examination of data from a study of MDMA-assisted psychotherapy in people with PTSD suggests that MDMA improves

PTSD symptoms when used as a psychotherapeutic adjunct. The independent rater conducted a preliminary analysis of CAPS scores at baseline and two months later detected a significant condition effect ($p < 0.05$). Average baseline scores for people in both conditions were comparable (79.6 for MDMA condition and 78.4 for placebo), but two months after the second experimental session, the average CAPS score for people in the MDMA condition was 27.6, while the average CAPS for people in placebo was 59.1. Eight of 13 participants no longer met criteria for PTSD two months after the second experimental session while only two of eight placebo participants no longer met criteria for PTSD diagnosis. Furthermore, a comparison of baseline assessment of neurocognitive function and assessment two months after the second experimental session did not find any significant differences in either MDMA or placebo participants (Wagner 2008, personal communication). The data examined in this analysis has not yet been subjected to quality assurance and data from one participant remains to be added, but there were few outliers in the data and it is unlikely that additional data will change results.

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Additional Information

Facilities

Introductory, MDMA-assisted and integrative psychotherapy

rooms, including a private bathroom and kitchen and include a refrigerator and microwave. The main room is comfortably furnished and private. There is artwork on the walls, and stained glass in some windows. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. The offices are lower than ground level. They can be heated, and fans are used for cooling. The offices have an enclosed courtyard. The office will contain equipment for assessing blood pressure, pulse, and body temperature and an automatic external defibrillator.

One therapist can reach the offices within five to ten minutes of contact if necessary.

Abuse Liability

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.

Appendix A: Visit by Visit Description

Participants who consent to take part in the study will undergo the following sequence of events:

- *Randomized sessions*
- **Screening/Evaluation (Visit 3):** A two to three hour long medical and psychiatric evaluation. A physician working with the investigators will perform medical history and physical examination and ECG. The independent assessor will diagnose psychiatric disorders with the SCID, and will perform a face to face interview and administer the ASIQ to assess suicide risk. The physician or principal investigator will draw blood for laboratory tests. The independent rater will administer the CAPS and the participant will complete the BDI. The independent rater will administer the RBANS and PASAT. If a participant meets study eligibility criteria after evaluation, he or she will be scheduled for an introductory psychotherapy session. The independent assessor will re-evaluate any participant who undergoes the screening and baseline evaluation prior to discontinuing psychiatric medication. During re-evaluation, the independent assessor will administer the CAPS and the participant will complete the PDS and BDI during a visit occurring after an interval of at least five times drug half-life.
- **Introductory Psychotherapy visits (Visits 4-6):** Three 60 to 90 minute introductory psychotherapy sessions with both psychotherapist investigators. These sessions will help the therapists and participant to learn about each other and discuss the participant's goals, hopes and fears in relation to upcoming MDMA-assisted psychotherapy, and the events and procedures that will occur during MDMA-assisted psychotherapy. Introductory sessions will be recorded to audio and video, and participants will have an opportunity to review the recordings. On the third introductory session, participants will receive instructions and restrictions relating to food and drug consumption for the night before and morning of the MDMA-assisted session. Participants must be randomized to one of the two conditions (active placebo or experimental dose) prior to the first MDMA-assisted psychotherapy session.
- **MDMA-assisted Psychotherapy Session 1 (Visit 7):** First eight-hour long randomized (active placebo versus experimental dose) MDMA-assisted psychotherapy session. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapists deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of the session recording upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant during the experimental session or at some time after it has ended. The significant other can remain overnight with the participant but does not have to do so. All participants will remain at the offices of Dr. Pacey overnight. A same-sex attendant versed in caring for people

- undergoing difficult psychological experiences will remain with the participant during the overnight stay.
- **Integrative Psychotherapy On the Day After Experimental Session (Visit 8):** A ninety-minute long psychotherapy session with both psychotherapist-investigators always occurring on the morning of the day after MDMA-assisted psychotherapy. The participant will discuss his or her thoughts, feelings, memories or experiences that occurred during the experimental session and the participant and investigators will seek to integrate this material into everyday life. The session will be recorded to audio and video and participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.
 - **Integrative Psychotherapy Sessions Between Experimental MDMA-assisted Session 1 and 2 (Visit 9-10, 10.x):** Two or more sixty to ninety minute psychotherapy sessions with both psychotherapist-investigators during which they and the participant continue to integrate material from MDMA-assisted psychotherapy sessions. The investigators and participant may schedule additional integrative sessions upon participant request and therapist-investigator mutual agreement. These sessions will be recorded to audio and video and participants may view session recordings upon request.
 - **MDMA-Assisted Psychotherapy Session 2 (Visit 11):** The second eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during the experimental session or after the experimental session is over. All participants will remain Significant others may remain overnight with participants but do not have to do so.
 - **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 2 (Visit 12):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the second experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.

- **Integrative Psychotherapy After MDMA-Assisted Session 2 (Visits 13-14, 14.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the second MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
- **MDMA-Assisted Psychotherapy Session 3 (Visit 15):** The third eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during or after the experimental session. All participants will remain [REDACTED]. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 3 (Visit 16):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the third experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.
- **Integrative Psychotherapy After MDMA-Assisted Session 3 (Visits 17-18, 18.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the third MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.
- **Evaluation Six weeks After Third MDMA-assisted Session (Visit 19):** A ninety to 120 minute long (1.5-2 hour long) evaluation. The independent assessor will administer the CAPS, RBANS and PASAT, and the participant will complete the BDI and PDS.
- **Study Blind Broken for Individual Subject (Visit 19):** A 30 to 60 minute long meeting with the therapist-investigators. The participant and both therapists will learn participant condition assignment. The independent rater will remain blind to participant condition

assignment. If the individual received active placebo MDMA, then he or she will receive consent materials for the open-label study segment, Stage 2. Any participant who received active placebo and does not consent to take part in Stage 2 will complete the RRPQ.

- *Open-label Sessions for Active Placebo Participants (Stage 2)*
- **Consent for stage 2 (Visit 20):** A 30 to 60 minute meeting with the investigator therapists for participants who learn they received active placebo. They will receive consent materials concerning the open-label study segment. They must give written informed consent to take part in this study segment. Visit 20 may occur on the same day as Visit 19.
- **Stage 2 Baseline Evaluation (Visit 21):** Baseline evaluation for stage 2 (active placebo participants only). CAPS, PDS and BDI scores from the evaluation six weeks after the third experimental session (Visit 19) will serve as baseline scores except in the case where thirty days have passed between those evaluations and the time when the participant entered Stage 2, in which case the independent assessor will perform and additional evaluation, administering the CAPS and BDI prior to entry into Stage 2.
- **Review and Introductory Psychotherapy (Visit 22):** A sixty to ninety minute psychotherapy session with both therapist-investigators and the participant enrolled in Stage 2. The participant and therapist-investigators will re-acquaint themselves with each other, and the participant will review information about MDMA-assisted therapy and all three will discuss, review and possibly revise goals for MDMA-assisted psychotherapy. The session will be recorded to audio and video. Participants may listen to or view recordings upon request.
- **Open-label MDMA session 1 (Visit 23):** The first eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in Stage 2 only.** This option is not applicable to participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and 125 mg MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of their open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of 62.5 mg MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during the experimental session or after the session is over. All participants will remain with participants but do not have to do so. Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 1 (Visit 24):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the first open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to integrative psychotherapy sessions after experimental MDMA-assisted therapy sessions. This session will be recorded to audio and video. Participants can listen to or view recordings upon request.
- **Integrative Psychotherapy Between Open-Label Session 1 and 2 (Visits 25-26, 26.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the first and second Stage 2 open-label

- MDMA-assisted session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can review session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.
- **Open-label MDMA session 2 (Visit 28):** The second eight-hour long open-label session with a full dose of MDMA (125 mg), **applicable for participants in stage 2 only.** Participants not enrolled in Stage 2 may decline to take part in this session. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants may receive copies of their open-label sessions upon request. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during or after the experimental session to remain with the participant. All participants will remain overnight with participants but do not have to do so.
 - **Integrative Psychotherapy One Day after Open-Label MDMA Session 2 (Visit 29):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the second open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. The session will be recorded to audio and video, and participants can listen to or view session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.
 - **Integrative Psychotherapy Between Open-Label MDMA 2 and 3 (Visits 30-31, 31.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the second and third Stage 2 open-label MDMA-assisted session. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request. These will be the final integrative sessions for participants not enrolled in stage 2. The therapists and investigator will continue working on integrating MDMA session material into everyday life.
 - **Open-label MDMA session 3 (Visit 32):** The third eight-hour long open-label session with a full dose of MDMA (125 mg) for participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the 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 body

temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive sometime during the experimental session or after it has ended or near the end of the session to remain with the participant. All participants will

. Significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 3 (Visit 33):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the third open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. This session will be recorded to audio and video. Participants can listen to or view their recordings upon request. Participants will complete the ASIQ after completing psychotherapy.
- **Integrative Psychotherapy After Open-Label Session 3 (Visits 34-35, 35.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval after the third open-label session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request.
- **Evaluation Six weeks after Third Open-Label Session for Participants Enrolled in Stage 2 (Visit 36):** A ninety to 120-minute visit with the independent assessor and the therapist-investigators for participants enrolled in Stage 2 occurring six weeks after the third open-label session. The independent assessor will administer the CAPS and the participant will complete the BDI and PDS.
- **Study Termination for Stage 2 Participants (Visit 37):** After completing CAPS, PDS and BDI, the participant will meet for approximately a half hour (0.5 hours) with the therapist-investigators. The participant will complete the RRPQ.

Appendix B: Case Report Forms

These are sample case report form drafts for the study “A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Posttraumatic Stress Disorder (PTSD)-Canada.”

The series of case report forms represents the series of events from screening up through the first experimental session of MDMA-assisted psychotherapy. The series does not include CRFs for subsequent experimental sessions or open-label sessions as the information contained is identical or nearly identical in content and format.

CONTAINS

SCREENING AND BASELINE EVALUATION
INTRODUCTORY PSYCHOTHERAPY
FIRST EXPERIMENTAL SESSION
INTEGRATIVE PSYCHOTHERAPY
FINAL EVALUATION
MEDICATION AND ADVERSE EVENTS

Study Entry Criteria

Subject screened under protocol version: Original Amendment # _____

Did subject meet all study entry criteria specified in the protocol Yes No

If No, please mark nature of deviation in the chart below and on the following pages

Inclusion not Met / Exclusions Met	Criterion number (as listed in protocol)	Protocol deviation entry granted?	If yes, date granted (dd-mmm-yy)
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___
<input type="checkbox"/> Inclusion not met <input type="checkbox"/> Exclusion met	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No	___ - ___ - ___

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Baseline Clinical Labs Visit #1

Date of Result _____ - _____ - _____

If any clinically significant lab results, please record in Adverse Event CRF dd mmm yy

Comprehensive Metabolic Profile	Result	Unit	Clinically Significant?
AG ratio			<input type="checkbox"/> Yes <input type="checkbox"/> No
Albumin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Alkaline Phosphatase			<input type="checkbox"/> Yes <input type="checkbox"/> No
AST (SGOT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
ALT (SGPT)			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
BUN			<input type="checkbox"/> Yes <input type="checkbox"/> No
Bun/Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Calcium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Chloride			<input type="checkbox"/> Yes <input type="checkbox"/> No
Creatinine			<input type="checkbox"/> Yes <input type="checkbox"/> No
Globulin			<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose			<input type="checkbox"/> Yes <input type="checkbox"/> No
Potassium			<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein Total			<input type="checkbox"/> Yes <input type="checkbox"/> No
Sodium			<input type="checkbox"/> Yes <input type="checkbox"/> No

Urinalysis	Result	Clinically significant?
Specific gravity		<input type="checkbox"/> Yes <input type="checkbox"/> No
PH		<input type="checkbox"/> Yes <input type="checkbox"/> No
Protein		<input type="checkbox"/> Yes <input type="checkbox"/> No
Glucose		<input type="checkbox"/> Yes <input type="checkbox"/> No
Ketones		<input type="checkbox"/> Yes <input type="checkbox"/> No
Occult blood		<input type="checkbox"/> Yes <input type="checkbox"/> No
Leukocyte Esterase		<input type="checkbox"/> Yes <input type="checkbox"/> No
Nitrite		<input type="checkbox"/> Yes <input type="checkbox"/> No
Bilirubin		<input type="checkbox"/> Yes <input type="checkbox"/> No
Urobilinogen		<input type="checkbox"/> Yes <input type="checkbox"/> No

Thyroid Panel with TSH	Result	CS= Clinically significant
Thyroxine		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid hormone binding ratio		<input type="checkbox"/> Yes <input type="checkbox"/> No
Thyroid Stimulating Hormone		<input type="checkbox"/> Yes <input type="checkbox"/> No
Free Thyroxine Index		<input type="checkbox"/> Yes <input type="checkbox"/> No

Past Psychiatric Medical History

Record any Psychiatric Diagnosis made prior to visit 1. If Diagnosis date is not known write UNK, try to provide at least a year.

Diagnosis	Diagnosis Start date mm-dd-yyyy	Ongoing?	Stop Date mm-dd-yyyy
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> Yes <input type="checkbox"/> No	

Type and Duration of Previous Therapy

Record any non drug therapy prior to visit 1 using the codes provided to the side of this chart. If date is not known write UNK, try to provide at least a year. Record any drug therapy on the Psychotropic Medication page.

Type	Other Therapy Type	# Sessions	Per	Start Date mm-dd-yyyy	Ongoing ?	Stop Date mm-dd-yyyy
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	
		_____	<input type="checkbox"/> Week <input type="checkbox"/> Month <input type="checkbox"/> Total		<input type="checkbox"/> Yes <input type="checkbox"/> No	

Type of Psychotherapy Code

- 1 = CBT (Cognitive Behavioral Therapy)
- 2 = Behavioral
- 3 = Prolonged Exposure

- 4 = EMDR
- 5 = IPT (Interpersonal Therapy)
- 6 = Psychodynamic

- 7 = Holotropic Breathwork
- 8 = Group Psychotherapy
- 9 = Other

History of Suicide Attempts or Thoughts

Suicidal Tendencies: Check the box that in your opinion most represents the frequency which the subject has thoughts of death or suicide, as determined via psychiatric interview.

- None at all
- Slight: occasional thoughts of death without suicidal thoughts
- Mild: frequent thoughts of being better off dead/occasional thoughts of suicide (without a plan)
- Moderate: often thinks of suicide or has thought of specific method
- Severe: frequent suicidal thoughts, mentally rehearsed plan, has made a suicide gesture
- Extreme: made recent preparations for serious suicide attempt
- Very

Adult Suicidal Ideation Scale at Screening

Score at Screening: _____

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Past Use of Ecstasy

Has the subject ever used "Ecstasy"? YES NO

If Yes, # of Occasions _____

If Yes, when

- Within the last six months
- Seven to 11 months ago
- 12 to 24 months ago
- 25 to 36 months ago
- 37 to 48 months ago
- 49 to 60 months ago
- 61 months to 120 months
- Over 120 months ago.

Past Substance Use

Previous Alcohol Abuse/dependence yes no # of prior treatments_____

In the last six months yes no

Previous Drug Abuse/dependence ***yes*** ***no*** # of prior treatments_____

In the last six months ***yes*** ***no***

Psychiatric History: SCID-Baseline diagnoses Visit #1

Date of Evaluation ____ - ____ - ____
 dd mmm yy

DSM Diagnosis	Yes	No
PTSD		
Unipolar Depression		
Panic Disorder		
Generalized Anxiety Disorder		
Bipolar Affective Disorder-1		
Bipolar Affective Disorder-II		
Dissociative Identity Disorder		
Psychosis		
Eating Disorder		
if Yes Active Purging?		
Borderline Personality Disorder		
Substance Abuse or dependence (60 days)		
Other DSM IV diagnosis-1		
Other DSM IV diagnosis-2		

General Well Being -Non-Experimental Sessions- Baseline

	Visit Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit #4			
Visit #5			
Visit #6			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of
 significant deterioration.
B= Probably faces risk of
 significant deterioration.
C= Faces risk of significant
 deterioration.

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Experimental Session # 1 Visit #7

Review of Inclusion and Exclusion Criteria

Has the subject refrained from consuming prohibited food or beverages? Yes No

Have all meds finished tapering? Yes No NA

Urine Pregnancy Test

Positive

Negative

Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen

Positive

Negative

Does subject continue to meet **All Inclusion** and **No Exclusion Criteria**? Yes No

If No Specify _____

Dosing

Date _____ - _____ - _____
 dd mmm yyyy

Record time initial dose MDMA administered _____

Record Bottle number of active placebo/ experimental MDMA _____

Second Dose of active placebo/experimental dose MDMA Administered?

Yes No

If yes, Record time second dose was administered _____

Record Bottle number of MDMA _____

Vital Signs -Experimental Session #1 Visit #7

Mark point where supplemental dose given. Make no mark if supplemental dose not given.

Monitoring: Blood Pressure and Pulse

Postdrug (h.min)	Time	SBP	DBP	Pulse
15 min predrug				
5 min predrug				
30 min postdrug				
1 hour post-drug				
1 h 30 min postdrug				
2 h postdrug				
2 h 30 min postdrug				
3 h postdurg				
3 h 30 min postdrug				
4 h postdrug				
4 h 30 min postdrug				
5 h postdrug				
5 h 30 min postdrug				
6 h postdrug				
6 h 30 min postdrug				
7 h postdrug				
7 h 30 min postdrug				
8 h postdrug				

Temperature

Postdrug (h.min)	Time	BT
		<input type="checkbox"/> F <input type="checkbox"/> C
15 min predrug		
1 hour post-drug		
2 hours post-drug		
3 hrs post-drug		
4 hrs post-drug		
5 hrs post-drug		
6 hrs post-drug		

Record any additional time points here:

SUDS -Experimental Session #1 Visit #7

Postdrug (h.min)	Time	SUDS						
15 min predrug		1	2	3	4	5	6	7
5 min predrug		1	2	3	4	5	6	7
1 h postdrug		1	2	3	4	5	6	7
2 h postdrug		1	2	3	4	5	6	7
3 h postdrug		1	2	3	4	5	6	7
4 h 30 min postdrug		1	2	3	4	5	6	7
6 h postdrug		1	2	3	4	5	6	7
7 h postdrug		1	2	3	4	5	6	7
8 h postdrug		1	2	3	4	5	6	7

Record any additional time points here:

		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7
		1	2	3	4	5	6	7

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Integrative Psychotherapy After Experimental Session #1 (Visit 8)

Subject Belief of Condition Assignment Visit #8

Indicate what condition the subject believes they were assigned

- Low dose MDMA
- Experimental Dose MDMA

Indicate the subject's certainty about this belief of condition assignment

- Not at all certain
- Somewhat certain
- Certain
- Very certain

Adult Suicidal Ideation Scale After Experimental Session 1

Please administer the ASIQ after completion of integrative psychotherapy during Visit 8. Record the total score below.

Score: _____

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Spontaneously Reported Side Effects Post Experimental Session #1 Visit #7-9

Please record the maximum intensity of any spontaneously reported effects for 7 days after drug administration.
 Report Duration for the first 24 hours.

Visit/Day	Visit 7 Day 0	Visit 7 Day 0	Visit 8 Day 1	Phone Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Duration in hours	Intensity								
Report Max Intensity for the 24 hour period 0= None Reported 1= Mild 2= Moderate 3= Severe	Report Duration to the nearest ½ hour for the first 24 hours only									
Check None if no symptoms are reported for the 24 hour period	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None
Anxiety										
Difficulty Concentrating										
Dizziness										
Drowsiness										
Dry mouth										
Fatigue										
Headache										
Heavy legs										
Impaired gait/balance										
Increased irritability										
Increased private worries										
Insomnia										
Jaw clenching, tight jaw										
Lack of appetite										
Low mood										
Nausea										
Need more sleep										
Nystagmus										
Parasthesias										
Perspiration										
Restlessness										
Sensitivity to cold										
Thirst										
Weakness										

General Well Being Visit #8-10

Complete at Visit 8; Since the Experimental Session at Visit 7 the subject has:

worsened remained pretty much the same improved

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit # 8			
Phone Day 1			
Phone Day 2			
Phone Day 3			
Phone Day 4			
Phone Day 5			
Phone Day 6			
Phone Day 7			
Visit #9			
Visit #10			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of significant deterioration.
B= Probably faces risk of significant deterioration.
C= Faces risk of significant deterioration.

Additional Non-Drug Psychotherapy

Check this box if the participant did not schedule any additional non-drug psychotherapy sessions in the period between Visit 8 and Visit 10. If this box is checked, then draw a diagonal line through the page. If any additional non-drug psychotherapy visits were scheduled, complete general well-being ratings for all additional visits and draw diagonal lines through any empty rows. Label each additional non-drug psychotherapy session with a fraction after 10, using consecutive numbers for each session (as 10.1, 10.2, etc).

Number of additional Visits = _____

General Well Being

	Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit 10.__			

1= Very stable and calm
 2= Stable and calm
 3= Slightly stable and calm
 4= Slightly distressed
 5= Distressed
 6= Very distressed

A= Does not face risk of significant deterioration.
 B= Probably faces risk of significant deterioration.
 C= Faces risk of significant deterioration.

Final Evaluation (Visit 19)

CAPS Scoring – PTSD Diagnosis Visit #19

Date of Evaluation _____ - _____ - _____
 dd mmm yy

Criterion A met (traumatic event)	Specify	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO	Frequency	Intensity
B (re-experiencing) sx (≥ 1)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
C (Avoidance) (≥ 3)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
D (Hyperarousal) (≥ 2)?	Score	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
E (duration ≥ 1 month)?	Duration in Months	Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
F(Distress/impairment)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
CURRENT PTSD (Criteria A-F)		Criterion met? <input type="checkbox"/> YES <input type="checkbox"/> NO		
PTSD Global	Score			

Associated Features

#25	#26	#27	#28	#29	#30

General Well Being Visit # _____ (16, 26, 35)

	Visit Date	Subject Demeanor and State of Mind enter code	Subject currently enter code
Visit # 19			

- 1= Very stable and calm
- 2= Stable and calm
- 3= Slightly stable and calm
- 4= Slightly distressed
- 5= Distressed
- 6= Very distressed

- A=** Does not face risk of significant deterioration.
- B=** Probably faces risk of significant deterioration.
- C=** Faces risk of significant deterioration.

Please check only one Visit 20 (End Randomized) Visit 37 (End Stage 2))

Reactions to Research Participation Questionnaire (RRPQ)

Please write in the numbers corresponding to the three top-ranked reasons for participating (the numbers to the left of each reason on the form. Write the number “1”, “2” or “3”) for each reason.

_____ 1. I was curious	_____ 4. I don't know	_____ 7. For the money
_____ 2. To help others	_____ 5. Thought it might improve my access to health care	_____ 8. I didn't want to say no
_____ 3. To help myself	_____ 6. Felt I had to	_____ 9. Other: _____ _____

Please write in the scale scores the RRPQ below.

- 1. Participation 1 _____
- 2. Personal Benefits 2 _____
- 3. Emotional Reaction 3 _____
- 4. Perceived Drawbacks 4 _____
- 5. Global Evaluation 5 _____

Check here if participant did not continue on to Visit 19

Date of Termination - -
 dd mmm yy

Last Visit # Completed _____

Did the subject complete the protocol Yes No

If the answer to the item above is “**No**” indicate the reason for early termination

- | | |
|--------------------------|-------------------------------------|
| <input type="checkbox"/> | Protocol violation |
| <input type="checkbox"/> | Adverse event |
| <input type="checkbox"/> | Death (Please Fill out Death Report |
| <input type="checkbox"/> | Investigator withdrew subject |
| <input type="checkbox"/> | Subject wished to withdraw |
| <input type="checkbox"/> | Lost to follow-up |
| <input type="checkbox"/> | Other _____ |

Subject Number _____

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Concomitant Medication CRF

Page X1 Series ____ √ if Last Page

Non Psychotropic Concomitant Medications

At Visit 3 record all non psychotropic medications currently being taken and check the prestudy box (include start date if known) Provide diag# (from Med Hx page). Record all new prescription and non-prescription non psychotropic medications taken after visit 3 through termination visit. Provide AE# (from AE page) or other Reason for Treatment. Check the continuing box if continuing at study termination. **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Med HX Diag #	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> continuing			

Subject Number _____

CRF DRAFT

Visits 3 through Termination

PI: Pacey, I.

Psychotropic Medication CRF

Page X2 Series _____ √ if last page

Psychotropic Medication and Tapering

- Record psychotropic medications previously used **and** psychotropic medications subject is on at visit1. Check the Prestudy box (include start date if known) and provide Disorder Code. Check Tapered box for medications tapered from V2 or V3. Provide route, dose and stop date for all medications.
- Record **all new psychotropic medications** taken after visit 1 through termination visit. Provide route, dose and start date. Provide AE# (from AE page) and check Rescue box if used as a rescue medication or complete Other Reason for Treatment. Check the Continuing box if continuing at study termination. **CHECK IF NONE**

Medication	Route	Dose	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)	Reason for Treatment Complete at least one column		
					Prestudy Disorder Code#	AE#	Other
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	
			<input type="checkbox"/> Prestudy	<input type="checkbox"/> Tapered <input type="checkbox"/> Con't		<input type="checkbox"/> Rescue	

***Code for prestudy disorders**

- 1 = Depression
- 3 = Panic Disorder
- 5 = Pain management (PRN)
- 7 = Obsessive-Compulsive Disorder (OCD)

- 2 = Anxiety
- 4 = Pain management (routine)
- 6 = Illness-related anxiety
- 8 = PTSD

Adverse Events

CHECK IF NONE

AE #	Adverse event Diagnosis	Serious? a	Onset date (dd/mmm/yy)	Resolution date (dd/mmm/yy)	Severity b	Frequency c	Action taken for Study d	Action taken- treatment e

a Serious?

- 1 = Serious*
- 2 = Not serious

* Serious = Fatal, life-threatening, requires prolonged hospitalization, results in persistent or significant disability, or requires medical or surgical intervention to prevent one of the outcomes defined as "serious" listed above.

b Severity

- 1 = Mild
- 2 = Moderate
- 3 = Severe

c Frequency

- 1 = Single/Intermittent
- 2 = Continuous

d Action Taken: Study

- 1 = None
- 2 = Interrupted session
- 3 = Delayed experimental session
- 4 = Discontinued experimental session
- 5 = Removed from study

e Action Taken: Treatment

- 1 = None
- 2 = Procedure or therapy
- 3 = Blood or Blood products
- 4 = Withdrawn from study due to AE
- 5 = Prescription Med
- 6 = Non Prescription Med
- 7 = Hospitalization
- 8 = IV Fluids
- 9 = Other specify

f Outcome

- 1 = Full recovery/return
- 2 = Persists, diminish
- 3 = Persists, worsen
- 4 = Persists, the same
- 5 = Alive with sequelae
- 6 = Death

VIDEOTAPING OF HUMAN SUBJECTS

SUBJECT INFORMATION AND CONSENT FORM (Stage 1) FOR VIDEOTAPING

Study Title: 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

PROTOCOL NO.: M-P4

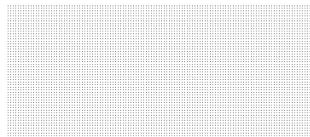
Study Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
3 Francis St., Belmont, MA 02478
Phone: 617 484-8711 Fax: 617 484-8427

Investigator: Dr. Ingrid Pacey M.B. B.S. FRCP

Address (es):
3369 West 4th Ave.
Vancouver BC V6R 1N6

Daytime telephone number(s): 604-732-9309

24-hour contact number(s):



Cellular number(s):

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This consent form applies to your decisions about what the study doctors should do with videotapes of sessions in the research study for which you already signed an informed consent form, the study, "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."

If you have completed the study, you are now going to be asked what you would like the study doctors to do with the recordings of your study sessions.

PURPOSE AND BACKGROUND

The purpose of this study consent is to ask you about your decisions about the videotapes of non-drug and MDMA-assisted psychotherapy during this study. Sessions will be recorded to video so that the study doctors will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. They plan to write up a series of standard instructions and methods for doing the therapy

VIDEOTAPING OF HUMAN SUBJECTS

called a manual for this therapy. The manual will help other scientists and therapists perform MDMA-assisted psychotherapy. The study doctors may also use the video recordings to train therapists for future research studies. If they use video recordings as part of this training program, you can either give permission for these recordings to be shown to people in the program with or without any identifying information removed. The study doctors will record each introductory, MDMA-assisted and non-drug psychotherapy session to video. They will begin recording MDMA-assisted psychotherapy starting shortly before you take MDMA and continuing for the whole six to eight hours of the experimental session with the exception of some periods of silence. You can stop the recording at any point in time, and you may request that portions of the video recordings be erased after they are recorded. Neither your full name nor your address will be included on the tape. You can ask to have other identifying information, such as your face, be removed from any video recordings used in programs for training therapists to learn to do MDMA-assisted psychotherapy. The study doctors and other scientists involved in this study and the sponsor of this study may review these videotapes to refine and improve this experimental treatment. All participants will receive a recording of each experimental session. The study doctors will provide a copy or permit you to view recordings of non-drug assisted psychotherapy sessions if you want to view them.

At the end of the study, when you have completed all of the questionnaires and measures, you can now make one of three decisions about video recordings and a decision about audio recordings of your study sessions. These include erasing all or some of the recordings of your study sessions and not saving a copy, having all facial images removed from copies of recordings shown to therapists in a training program to learn to do MDMA-assisted therapy, or allowing the study doctors to show people learning how to do MDMA-assisted psychotherapy video recordings of your psychotherapy sessions that still have your face or facial images in the recordings.

ALTERNATIVES

If you consented to be in this study, you can either agree to have your therapy session videorecordings shown to therapists in a program for training in MDMA-assisted psychotherapy without removing any additional identifying information, you can have them shown to people learning to do MDMA-assisted psychotherapy only if identifying information, such as your face, are removed from the recordings, or you can have the recordings erased.

CONFIDENTIALITY

All information collected will be treated and handled as confidentially as possible.

The study doctors will listen to or watch the video and audio recordings and no identifying information will be written or otherwise attached to the recordings. If you allow it, other scientists or therapists could watch the recordings to learn how to do MDMA-assisted psychotherapy.

VIDEOTAPING OF HUMAN SUBJECTS

Absolute confidentiality cannot be guaranteed.

This does not limit the duty of the researchers, study doctors and others to protect your privacy.

When not in use, information will be stored in a locked office. Any copies of the video recordings used for training purposes will also be kept in a locked office.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your decision to take part in this component of the research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to take part.

You can stop the recordings at any time during the session or request to have part or all of them erased afterwards.

In addition, you may withdraw your consent to use the audio or video tapes at any time. There will be no penalty if you decide to withdraw from the research study. You must notify your study doctor that you wish to withdraw your consent. This notice will let the study doctors know that you do not wish to have experimental sessions videotaped or audiotaped. If you decide to stop the audio and/or videotaping component, you may still participate in the research study testing MDMA-assisted psychotherapy for PTSD.

QUESTIONS

If you have any questions about this study, its procedures, risks, benefits or your alternatives or rights or if at any time you feel you have experienced a research-related injury, contact:

Dr. Ingrid Pacey MBBS
3369 West 4th Ave.
Vancouver BC V6R 1N6
Office: 604-732-9309
Cell: [REDACTED]

If you have other questions about other effects of MDMA, you can contact Rick Doblin, Ph.D., President of MAPS, the organization sponsoring this study.

The address is:

Rick Doblin, Ph.D.
3 Francis St.
Belmont, MA 02478
USA
Tel: 617 484-8711

VIDEOTAPING OF HUMAN SUBJECTS

SUBJECT'S STATEMENT OF CONSENT

“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 –

Your participation in this study and decision about your video recordings is voluntary. Your decision will not affect your current or future regular medical care or any benefits to which you are entitled at this site, or your participation in “Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada.”

You have read the information in this consent form and it has been discussed with you. All of your questions so far about the study and your participation in it have been answered. You freely decided what will be done with your video recordings.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. **You have been told that you will be given a copy of the consent form signed by you and the study doctor.**

Your signature below indicates your consent to have your experimental sessions videotaped.

- If you check the box to the left, you are indicating that you would like the study doctors to erase the video recordings of all or some of your sessions so that no copy will be saved.
- If you check the box to the left, you are indicating that you wish to have images of your face removed from any video recordings that may be shown to therapists as part of a program training therapists to do MDMA-assisted psychotherapy.
- If you check the box to the left, you are indicating that you do not wish to have images of your face removed from any video recordings that may be shown to therapists as part of a program training therapists to do MDMA-assisted psychotherapy.

	SUBJECT	
Printed name		
Signature		
Date		

VIDEOTAPING OF HUMAN SUBJECTS

PERSON ADMINISTERING CONSENT	
Printed name	
Signature	
Date	

INVESTIGATOR	
Printed name	
Signature	
Date	

SUBJECT INFORMATION AND CONSENT FORM (Stage 1)

Study Title: 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

PROTOCOL NO.: M-P4

Study Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
3 Francis St., Belmont, MA 02478
Phone: 617 484-8711 Fax: 617 484-8427

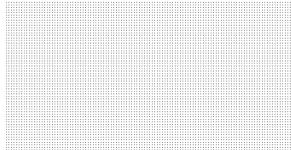
Investigator: Dr. Ingrid Pacey M.B. B.S. FRCP

Address (es): 3369 West 4th Ave.
Vancouver BC V6R 1N6

Daytime telephone number(s): 604-732-9309

24-hour contact number(s):

Cellular number(s):



PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This consent form describes a research study and your role as a participant. Please read this form carefully. Do not hesitate to ask anything about the information provided; it is expected that you will have questions about it. After reading the consent form, the study doctors will give you a short quiz to spot any parts of the study that need to be explained even further or in a better way than in the consent form, but your being in the study will not be related to your answers on the quiz.

You are being asked to participate in this research study because you have been diagnosed with posttraumatic stress disorder (PTSD) and because your symptoms have failed to go away after psychotherapy or medications for PTSD.

Please ask the study doctors to explain any words or information in this consent that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE AND BACKGROUND

This small, early study is designed to provide information on whether MDMA-assisted psychotherapy is safe and helpful for subjects with posttraumatic stress disorder (PTSD). The study doctors plan to use the results of this study to design further studies.

MDMA is experimental, which means it has not been approved by Health Canada for medical use, except within research studies like this one. MDMA is illegal to use outside of research and is sometimes known as "Ecstasy" (which is supposed to contain MDMA but can often contain other drugs instead of or in addition to MDMA).

Before it became illegal, some psychotherapists combined MDMA with psychotherapy ("talk therapy") to help people with psychological problems, sometimes including PTSD. Though we do not know why it helps people with PTSD, we know that MDMA increases positive mood and also changes the way we see and think about the world around us, making it easier to think about and recall upsetting experiences, and people say they feel caring and forgiving toward themselves and others after MDMA. Most types of therapy that treat PTSD involve facing the trauma and PTSD symptoms and going over trauma-related emotions. Doing this reduces fear, defensiveness, avoiding things, places or feelings that trigger unwanted feelings or thoughts, and feeling emotionally numb or distant from relationships. If MDMA can temporarily decrease fear and avoidance and increase trust and connection between the person with PTSD and their therapist, then MDMA will make the therapy stronger and more likely to work. It is possible that these effects, when combined with psychotherapy, help people confront and go through the thoughts, memories and emotions related to PTSD.

This study will compare 125 and 62.5 mg MDMA, the study high dose, with the study low dose of 25 and 12.5 mg MDMA. The study low dose is an "active placebo" meaning it will produce some but not most of the effects of the study high dose of MDMA.

Length

This study can take up to four months and 19 visits if you get the study high dose from the beginning. The study can last an additional two and a half months and twelve more visits if you get the study low dose and decide to go on to have MDMA-assisted therapy in a second part of the study, "Stage 2."

Subject Responsibilities

If you and Dr. Pacey agree that you can and want to be in the study, you will have to come to all study visits. You will have to avoid taking any psychiatric medications from the beginning of the study up until your last study visit unless the study doctors make a specific exception, such as giving you medication for sleep or anxiety if needed temporarily between experimental sessions. If you are taking psychiatric medication, you will need to give Dr. Pacey permission to talk with your doctor about how best to stop taking your medication.

If you are currently seeing a psychotherapist, you may not begin any new psychotherapy or change the frequency or length of visits with your psychotherapist until after the final evaluation session.

For your safety, it is very important to tell the study doctor about all medications you are taking, including herbal or “natural” remedies, and to check with the study doctor before you begin taking a new medication while in this study.

PROCEDURES/WHAT WILL HAPPEN TO YOU

SCREENING/EVALUATION AND BEGINNING OF STUDY

Before you can be in the research study, the study doctors must first make sure that you qualify for the study and that you are generally physically healthy. The screening process will take about 3 to 4 hours.

The tests will include the following:

- A questionnaire about your PTSD symptoms and how you deal with them in your everyday life. Your score on this questionnaire will be used to decide if you can be in the study. The study doctor asking you these questions will be a different person from the study doctors.
- A questionnaire that you complete yourself on your PTSD symptoms
- A questionnaire about feelings of depression or other symptoms or feelings you might experience.
- Questions about your medical history, including questions about your emotional and psychiatric history. This may include any previous medical or psychiatric problems or treatment and may include questions about difficult experiences you may have had during childhood or at other times of your life.
- A questionnaire about thoughts and feelings you might have about hurting or killing yourself.
- Two different tests of attention, memory and different types of problem solving. These are not tests of intelligence.
- A physical examination that will include measures of your blood pressure, pulse, temperature, and body weight.
- An ECG (electrocardiogram) will also be taken, which is a recording of the electrical activity of your heart.
- A sample of your blood (about 2 tablespoons) and a urine sample for routine laboratory testing, including tests of metabolism and liver function.
- A urine test for drugs of abuse. Your urine drug screen must be negative to take part in the study.
- A urine pregnancy test if you are a woman and are able to get pregnant. Your urine pregnancy test must be negative for you to take part in the study.

BEGINNING OF STUDY

If you have decided that you want to be in the study and if the study doctors find that you are eligible, you will schedule your first introductory psychotherapy session with the two therapist-investigators. If you were taking psychiatric medicines when the study doctors first checked to see if you could be in the study, you will have your PTSD and depression symptoms measured again after you have stopped taking your medication.

SCHEDULE OF EVENTS I

Time is counted from the first study visit after you are selected to be in the study. These are the events up until you learn if you got study low dose or study high dose MDMA

	Screen /Start Study	Intro & Preparation			MDMA & non-Drug Therapy 1				MDMA & Non-drug Therapy 2				MDMA & Non-Drug Therapy 3				End Random	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		16
Screening	x																	
Measure symptoms	x																	x
Psychotherapy		x	x	x		x	X	x		x	x	x		x	x	x		
Attention and Memory Tests	x																	x
Psychotherapy With MDMA					X				X				X					
Medical Exam	x																	
Learn dose you got																		x

INTRODUCTORY PSYCHOTHERAPY SESSIONS:

You will meet with the study doctors on three separate occasions before the first experimental session. These visits will last from 60 to 90 minutes. During each introductory session, you will discuss the traumatic incidents that led to your PTSD, the ways PTSD symptoms are affecting your life and what you would like to achieve during these sessions. You will also learn more about what to expect during experimental sessions. The introductory session will be recorded to audio and video, so that the study doctors will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. You can ask the study doctors to let you hear or see these recordings if you wish.

SELECTION OF DRUG – MDMA OR PLACEBO?

Each subject in this study will be randomly assigned (by chance, as if by flipping a coin) to get either 25 and 12.5 or 125 and 62.5 mg MDMA. This study will have 12 subjects. Eight (67%), will receive the study high dose of 125 and 62.5 mg and four (33%) will receive the study low dose of 25 and 12.5 mg MDMA. You will take the same dose on each of the three experimental sessions.

Neither you, the person measuring your PTSD symptoms, or the study doctors will know who is getting the study high dose of MDMA and who is getting the study low dose (“double-blinded”) until after the study is completed. However, this information is available if needed in an emergency.

EXPERIMENTAL SESSIONS:

There will be three experimental sessions (with either the study low dose or high dose MDMA), each happening three to five weeks apart. The first experimental session (study low dose or high dose MDMA) will occur after you have had three introductory sessions.

Each experimental session will last approximately eight hours, though both study doctors will remain with you for a longer period of time if necessary.

You must not eat or drink any alcohol after midnight on the night before each session, though you can drink non-alcoholic liquids during this time, such as water or juice.

First, you and the study doctors will discuss your goals for the experimental session, and the study doctors will answer any questions you still have about this session.

Before an experimental session:

- Your urine will be tested for drugs of abuse.
- If you are a woman who can become pregnant, a urine pregnancy test

Throughout an experimental session

- Your blood pressure and pulse will be measured every 30 minutes.
- Your temperature will be measured every hour.
- You will also complete a very brief, simple test of how comfortable or distressed you feel by marking a number on a sheet of paper that coincides with the way you feel at that moment. You will complete it every 60 to 90 minutes throughout each experimental session.
- The study doctors will check in on you every hour or so to see how you are doing

The experimental session will be audiotaped and videotaped, so that the study doctors will have accurate records of the session and so that they can gather more information about drug-assisted psychotherapy sessions. The study doctors can give you copies of these recordings for you to keep and watch if you want them.

After urine test results come back, you will receive a capsule containing 25 or 125 mg MDMA. After taking the capsule, you will sit or lie down in a comfortable position. You can ask for an eye shade if you wish. You will listen to music through headphones during much of each experimental session. Periodically you will be asked to remove the headphones to talk to the study doctors, and you may also remove them yourself if you want to talk to the study doctors or for periods of silence. Lying or sitting in a comfortable position and listening to music are meant to bring out thoughts and feelings, including thoughts and feelings about the trauma. Both study doctors will remain with you, and they will help you if you need them to do so. They will speak with you and ask you to talk to them at least once an hour, but you can talk to them whenever you wish. There may be times when the study doctors will suggest that you stop talking for a while in order to pay attention to your thoughts and feelings. There will be water, juices or Gatorade available to drink whenever you wish within the limits of what is safe for your body,

and you will be encouraged to drink an adequate amount of fluid. Later on, food will also be provided.

Approximately one and a half to two and a half hours later, you and the study doctors will talk about taking a second dose of MDMA. The second dose will be half the amount of the first dose. If you and the study doctors agree, then you will take the second dose. If you or the study doctors notice problems after the first dose of MDMA, then you will not get the second dose of MDMA.

The study doctors will continue to measure blood pressure, pulse and temperature, and they will watch for any side effects (unwanted effects or health problems), which will be treated if they occur. If this happens, the study doctors will let you know what they are doing.

If you are still confused or very upset eight or more hours after the start of the experimental session, the study doctors will stay with you until you have recovered more fully. If the study doctors think you are at risk for hurting yourself or someone else, they will either remain with you all night or have you stay in a nearby hospital until they are certain you are not at risk. If the study doctors decide that the effects of the drug have worn off and you are in an appropriate frame of mind, they will leave the office with the attendant in charge.

You will be spending the night in a comfortably furnished room [REDACTED] If you request and Dr. Pacey agrees, you may also have someone of your choosing stay with you at the office during or after an experimental session. An attendant who will be the same sex as you will stay in another room at the same location from the time after you are done with the experimental sessions until the non-drug session on the next day. The attendant will offer dinner and breakfast, assist you with any physical needs if requested, and contact Dr. Pacey to speak with her or to have her return to the office at your request or if the attendant considers it necessary.

On the next day, you will have a non-drug therapy session with the study doctors. You will need to arrange ahead of time to have someone take you home from this non-drug session, because we don't know how MDMA will affect you and some people report feeling tired or less alert. If you cannot find anyone to take you home, the study doctors will either call a taxi or make arrangements with a volunteer they know who is familiar with the study.

After you return home, the study doctors will telephone you every day for a week to inquire about how you are feeling and determine whether you should see Dr. Pacey before your next scheduled non-drug psychotherapy session. These telephone calls will take approximately 5 to 15 minutes, though they can last as long you need them to be. You may schedule additional meetings with the study doctors besides those that are scheduled as part of the study.

You can contact the study doctors at any time. The study doctors will give you a card with telephone numbers for reaching Dr. Pacey, the organization sponsoring the study, or the Institutional Review Board – IRB Services (an independent committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants). Dr. Pacey will be on call (reachable by telephone or pager) 24 hours a day throughout the research study, except

on occasions when she is out of town. At those times another psychiatrist familiar with the study will be on call and can be reached through Dr. Pacey's phone number.

If there are delays in following the usual study schedule, you will let the study doctors telephone you at least once a week to talk about how you're doing. These telephone calls will take approximately 15 minutes, and you agree to telephone the study doctors if any of these things happen; you have an increase in symptoms for which you were previously took medication, you need to contact your outside therapist other than for the usual appointments, and/or you start or stop taking prescribed medication.

If you have very high blood pressure, get sick, or have a significant lasting negative reaction (unwanted effect or health problem) after the first experimental session, you or the study doctors may decide that you should not participate in the second experimental session. You may make this decision to stop being in the study for any reason. If the study doctors decide to take you out of the study, they will let you know that they are doing this and their reason for doing this. If you are taken out of the study or decide you do not want to be in the study, the study doctors will ask you to complete some final questionnaires about your PTSD symptoms and tests of memory and problem solving. If you decide you do not want to continue in the study during an experimental session, you will still have to stay in the office until the study doctors think that you are well enough to go and that all the effects of the drug have worn off.

The second experimental session will occur three (3) to five (5) weeks after the first, and the third experimental session will occur three to five weeks after the second session. The second and third sessions will also be carried out in an identical manner to the first session.

At this time MDMA is not available for use outside of research studies. The study doctor will discuss treatment options with you at your last study visit.

PSYCHOTHERAPY AFTER EXPERIMENTAL SESSIONS :

You will have regular psychotherapy to help you express, understand and integrate (bring together and connect to your life) any thoughts or feelings you may be having about your symptoms and their causes and about your experiences during experimental sessions. You will have psychotherapy with the study doctors the morning of the day after each experimental session and then once every week for about two weeks after each experimental session. These sessions will last 60 to 90 minutes. You and the study doctors will also discuss ways to use what you learned to help work on treating your PTSD, face and solve difficulties you may have faced during the experimental sessions and gain maximum benefit and understanding from experimental sessions. Each regular psychotherapy session will be recorded to audio and video, just like the introductory and experimental sessions, and you can hear or see these recordings.

Before starting psychotherapy on the day after each experimental session, you will be asked to guess whether you received the study low dose or study high dose of MDMA. You will not be told if your guess is correct. After you finish psychotherapy on the day after an experimental session, you will fill out a questionnaire about thoughts and feelings you might have about

hurting yourself. This is so the study doctors can have another way of making sure you are no in danger of hurting yourself.

MEASURING PTSD, DEPRESSION AND OTHER TESTS AFTER EXPERIMENTAL SESSIONS

Approximately two and a half months after the start of the study (six weeks after the third experimental session), a study doctor will ask you about your PTSD symptoms and feelings and symptoms of depression again. This visit should last about two to two and a half hours. These tests are so that the study doctors can tell if your symptoms have changed or stayed the same over time. You will also complete the tests of attention, memory and problem-solving you completed at the start of the study. As before, the tests will be given by another researcher who is not one of the study doctors.

After you complete these tests, you will meet with the other study doctors and all of you will learn whether you got the study low dose or the study high dose of MDMA. The study doctor that measured your PTSD symptoms will not find out.

If you learn that you had the study low dose of MDMA, then you will finish the randomized part of the study. You will then be enrolled in the next part of the study, described below.

If you learn that you had the study high dose MDMA, then one of two things may happen. You may finish the study, completing the same research subject experience questionnaire described above.

OPEN-LABEL MDMA SESSIONS FOR PEOPLE WHO RECEIVED STUDY LOW DOSE MDMA (STAGE 2)

If you are one of the four subjects who got the study low dose of MDMA, you can take part in three open-label MDMA-assisted sessions scheduled 3 to 5 weeks apart as part of Stage 2. In this study segment, you will receive the study high dose of MDMA (125 mg possibly followed by 62.5 mg) during each session. Signing this consent form means you agree to take part on the second part of the study. However, you will be asked to give your written consent again before you start Stage 2. **The eight people who receive a study high dose of MDMA during the first stage of the study cannot take part in Stage 2.**

If you take part in stage 2, you will have 15 more visits with the study doctors. These sessions will be like experimental sessions you had during the first part of the study, except that you will know you are getting a full dose of MDMA. You will also only have one review and introductory session rather than three sessions. Otherwise, you will have three experimental sessions scheduled three weeks apart followed by an overnight stay and integrative therapy afterwards. You will have tests of your PTSD and depression symptoms six weeks after the third open-label session. At the end of this study, you will complete a questionnaire about your experience as a research subject before you leave the study.

POSSIBLE RISKS OR DISCOMFORTS

MDMA has not been widely tested in human subjects.

Side effects during the MDMA experience that are less severe but more frequently reported, are:

- lack of appetite (70%)
- teeth grinding or tight jaw muscles 63%,
- dry mouth (57%)
- difficulty balancing or walking (44%)
- decreased concentration (42%),
- neck or back pains (50%)

Forty to 70% of subjects in previous studies and in a placebo-controlled study of MDMA-assisted psychotherapy in people with PTSD reported these side effects. Less commonly, 15% to 40% of research subjects reported feeling hot or cold, feeling that their heart was racing, sweating, dizziness, drowsiness, upset stomach, diarrhea, anxiety, tenseness, weakness, shaking, headache, or feeling faint (from most to least commonly reported). When any of these side effects occur, they usually last less than four hours, though some subjects report that some of these side effects can last for more than twenty-four hours, and rarely longer, but no more than four days.

Risks from MDMA

Changes in vision, hearing or other senses: In previous studies in which MDMA was given to volunteers, including a total of about 365 subjects without emotional disorders and 21 with PTSD, most subjects reported experiencing minor changes in vision and hearing, such as sounds seeming closer or farther away than usual, or objects seeming brighter than usual, with these changes lasting 2 to 3 hours. People also reported unusual feelings in their bodies, such as tingling or numbness (12%-33%). These studies did not report exactly how many people experienced perceptual changes.

Blood pressure and heart rate. These effects of MDMA usually last 4 to 6 hours. At the dose in this experiment, the increases in blood pressure and heart rate are likely to be moderate. Average increase in systolic blood pressure is 35 mmHg (measurement unit for blood pressure) and average diastolic blood pressure increase is 20 mmHg. Heart rate may increase by 20 beats per minute (BPM).

Blood pressure rose well above normal levels in a few subjects (a little less than 5%) after MDMA was given in previous studies, but these subjects did not report any discomfort and did not require any treatment. Although these increases in blood pressure are similar to what happens after heavy exercise, they could cause serious problems in individuals with pre-existing heart or blood vessel defects. These serious problems could include heart attack or stroke. We will screen all potential subjects for preexisting heart problems before they are allowed to be in this study. This doesn't guarantee that no heart problems will occur, but it does greatly reduce the risk of this happening.

Anxious or jittery feeling: Some subjects in previous studies (16%) reported feeling over-stimulated or anxious. It usually lasted less than 30 minutes. Due to your PTSD, you may be more likely to have severe anxiety or panic attacks. Letting yourself accept and feel those emotions deeply can be part of the psychotherapy. If you are not able to deal with these experiences in a way that helps you, the study doctors will work with you to deal with these feelings. It is possible that if such periods of heightened emotion do not clear up or grow weaker during the session, you could be at increased risk for suicide or other self-harm afterwards. You will be encouraged to ask the attendant to call the study doctors immediately if you have any thoughts about hurting or killing yourself so they can help you resolve them safely. If necessary, they may prescribe anti-anxiety medication or medication for sleep.

If you are in immediate danger of hurting or killing yourself or hurting someone else, then the study doctors may require you to stay in a nearby hospital.

Serious problems and death: There have been some serious problems, and even deaths, associated with the use of Ecstasy outside of controlled clinical or laboratory settings. Serious problems have included high fever, drinking too much liquid, convulsions, and liver damage. Some recreational users of Ecstasy have become severely anxious, depressed or paranoid (thinking that other people are against them). Since you will be receiving moderate amounts of uncontaminated MDMA in a controlled setting with trained therapists who will be closely monitoring your physical and psychological reactions, these problems are not expected to occur during or after the experimental session, but this does not guarantee that they could not occur. If they do occur, the study doctors are prepared to respond to these problems.

Insomnia & drowsiness: In previous studies, less than 40% (17%-23%) of subjects have reported insomnia (difficulty sleeping), and feeling tired, irritable, or drowsy for as long as 3 days after MDMA.

Mood: Some after-effects of MDMA may be noticeable up to 2 or 3 days later. While some subjects feel that their mood is better, 14% feel it is worse.

Immune System: You will probably have a less active immune system for 2 or 3 days after MDMA. This may make you more likely to become sick with a cold or other infection during this time. The study describing this finding did not say how many people in the study showed these changes.

Addiction: There is a small chance that you will become dependent on (addicted to) MDMA. One study found that up to 6% of people using Ecstasy for recreational purposes were dependent on it. However, a study of people who had received MDMA for the first time in a legal laboratory setting found that they did not want to try MDMA again outside of the laboratory.

People who have recently (in the last 60 days) had problems with drug abuse should not take part in this study.

There may be unknown side effects or risks from the use of MDMA.

Possible Brain Damage

Experiments in rats and monkeys show that high and repeated doses of MDMA can change brain cells that release a chemical called serotonin; in mice only, the affected cells release dopamine. The changes include loss of the part of the cell (called "axons") that connects different brain areas. Rodents given repeated, high doses of MDMA are less sensitive to a later dose of MDMA, are more likely to become overheated when placed in a warm room, and some studies find they perform worse in difficult tests of memory. Recent studies in monkeys and rodents suggest that the doses in studies finding damaged axons are too high to reflect typical human doses of ecstasy or MDMA used in studies.

Many studies found that people who had used Ecstasy many times in recreational contexts were not able to recall words, pictures or patterns as well as people who did not use Ecstasy and performed less well on tests of planning and impulse control. These differences are not great, but they have lasted for at least a year after people had stopped taking Ecstasy. Not all studies have found Ecstasy users to have difficulty recalling words or pictures or to have impulse control problems. When compared with people who do not use Ecstasy, studies found Ecstasy users were more likely to report feeling generally anxious or depressed. Many of these studies found that using alcohol or other drugs was also associated with feeling anxious or depressed. At least two studies found that people who are anxious, depressed or have psychological problems before taking any drugs are more likely to take ecstasy than people without these problems.

Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA, and did not see any changes in the brain, though it is possible that there were changes that were too small to notice. Other studies looked at people before and after they decided to take a few tablets of ecstasy in a recreational setting, and only saw one small change, and did not see signs of brain injury. Findings from these studies suggest that the amount of MDMA you will receive in this study will not produce any lasting changes in your brain, though this is not guaranteed.

Studies of people receiving one or two doses of MDMA in a medical laboratory setting have not found any lasting changes in memory or planning. Studies comparing people before and after they decided to take a few ecstasy tablets in a recreational setting with people who did not take them found less improvement in memory in the people who took ecstasy, and no other changes in thinking or planning. It is believed that the amount of MDMA you will receive will not produce any lasting changes in recall or planning ahead, though this cannot be guaranteed. You will not get a second dose of MDMA if they believe you are showing signs of memory problems.

Other Risks:

You should not drive or use machinery immediately after each experimental session (up to 24 hours afterwards). This is because the study medication may cause drowsiness, lack of coordination or slower reaction time.

If you are tested for drugs of abuse within three days of each experimental session, you may test positive. The study doctors will provide you with an information card in case you are tested for drugs of abuse, and if you are tested for drugs of abuse while you are in this study, you can have the person(s) testing you call Dr. Pacey to verify that you are in this study.

The interviews you will have during the course of the study involve no specific risks or discomforts beyond those of a standard clinical interview situation. You may feel upset at the review of your emotional experiences, or you may feel boredom or fatigue. The medical evaluations involve some blood tests. The risks of blood drawing include temporary discomfort from the needle stick, bruising and, rarely, infection at the site of the needle stick. Fainting could also occur.

It is possible that after you stop taking psychiatric medication (as for depression or anxiety) as part of the study, you may start to have symptoms again. If this happens, you should talk with your outside therapist and Dr. Pacey. If you have to start taking medication again, then the study doctors will have to take you out of the study.

If you suffer a serious or lasting injury as a result of participation in this study, it may affect your ability to obtain private health insurance, your employability, and/or quality of life.

Reproductive Risks:

Effects of MDMA on the growth and development of an unborn baby are not known. Birth defects could include physical deformities, mental retardation and premature birth; therefore you will not be allowed to enter the study if you are pregnant.

Women who are able to become pregnant must use one of the allowed birth control methods, such as birth-control pills or shots, IUDs, and diaphragms used along with spermicide and with partner use of condoms while they are in the study and for at least one month afterward. The study doctors will explain these methods to you and will help you decide which might be best for you, and they can suggest to you where you can get more information and advice.

You will be tested at the start of the study and again before each MDMA or placebo session to see if you are pregnant. If, at any time during the study, you suspect that you may be pregnant or are concerned that you may become pregnant, you must advise Dr. Pacey immediately. If you should become pregnant during the study, the study doctors will help you get proper advice and help you and your unborn baby get proper care while you are pregnant.

NEW FINDINGS

If any new information becomes available about MDMA while you are participating in this study, the study doctors will tell you about it as soon as possible.

POSSIBLE BENEFITS

There is no guarantee that you will benefit from taking part in this research study.

COSTS

The sponsor of this study, Multidisciplinary Association for Psychedelic Studies (MAPS), will cover the costs that are directly related to this study. This includes the costs for all psychotherapy sessions, for the psychological and laboratory testing, for medical examinations, and for the experimental drug. You, your private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study.

You or your insurance will remain responsible for on-going treatment unrelated to the study.

REIMBURSEMENT FOR PARTICIPATION

The Sponsor, MAPS, will reimburse you up to \$1500.00 for your travel expenses, including expenses from driving, parking or flying to the site. The sponsor will pay for an economy class ticket [REDACTED]. The sponsor will also pay for meals and lodgings.

The sponsor is paying your study doctor for the time, effort and expenses to conduct this study.

ALTERNATIVES

One alternative to being in this study is to decline to participate. You may decide to try other treatments for PTSD. There are other medications, such as Paxil (paroxetine) or Zoloft (sertraline) and anti-anxiety medications such as Xanax (alprazolam) and other forms of psychotherapy that you could try. If you are currently receiving psychotherapy and/or medication, you could continue with those for a longer period of time.

CONFIDENTIALITY

All information collected will be treated and handled as confidentially as possible, except where disclosure is required by law. **Absolute confidentiality cannot be guaranteed. This does not limit the duty of the study doctors and others to protect your privacy.**

As part of this research, the study doctor will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. When not in use, information will be stored in a locked office and will be kept for 25 years after study completion, as required by Canadian clinical trial regulations. Audio and video recordings will be stored for up to 20 years after their creation.

Some people need access to the information to monitor the study. Any paperwork copied will have any information that could be used to identify you removed first. Session recordings will not have your name printed on them, only a number.

Medical records, including audio and video recordings, which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes. First any information that could directly identify you will be removed except when impossible to do so (as through unique voice or image identity), or if you give permission not to have your face obscured on video recordings. Medical records may be looked at, at the study site, by

- the sponsor, MAPS

- Health Canada and similar agencies in other countries, as the U.S. Food and Drug Administration (FDA)
- governmental agencies in other countries; and
- IRB Services

This inspection is to check the accuracy of study records.

Information from this study will be submitted to the sponsor, and to Health Canada and to governmental agencies in other countries (e.g. FDA). Information sent from the study site will not contain your name.

Results from this study may be presented in meetings or in publications. Your identity will not be disclosed in those presentations, which will mostly give average scores or averaged data.

All records in British Columbia are subject to subpoena by a court of law.

Audio and video recordings: Only the study doctors will listen to or watch these recordings, and no identifying information will be written or otherwise attached to the tape recordings. You can request to have your face electronically (by placing an opaque circle over your face) obscured from video recordings by checking the “Yes” box below. You may be asked to give an additional consent at the end of the study in order for your audio or video recordings to be viewed by others, such as therapists learning how to perform MDMA-assisted psychotherapy, but you do not have to agree to this in order to participate in the study. You will receive a copy of the audio recording of your experimental sessions. You may listen to the tape if you wish, but you do not have to listen to it. You will not automatically receive a copy of the video recording of your experimental session, but if you wish, you may also receive a copy of the video recording.

I wish to have my face obscured from video recordings:

YES NO

You have the right to check your study records and request changes if the information is not correct.

By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

TREATMENT AND COMPENSATION FOR INJURY

In the event of a study-related injury, the Sponsor (MAPS) will cover any costs that arise from treating the injury that is not covered by the provincial health plan or your private medical insurance (if any). Neither the Sponsor nor the study doctor has a program in place to provide other compensation in the event of an injury.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your decision to take part in this research study is completely voluntary. There will not be any penalty or loss of benefits to you if you decide not to take part.

In addition, you may withdraw from the study at any time. There will be no penalty if you decide to withdraw from the research study. Before withdrawing from this study, notify your study doctor that you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic for tests.

WITHDRAWAL

The study doctors, the sponsor company, Health Canada and the US Food and Drug Administration (FDA) has the right to stop the study at any time, with or without your consent, for any of the following reasons: if you have an adverse effect (unwanted effect or health problem) from the study drugs or if for any other reason the study doctor judges that it is not in your interest to continue in the study, if you need a treatment not allowed in this study, such as restarting medication for depression or anxiety, if you do not keep appointments and follow study rules, if you do not take the study drug as instructed, if you become pregnant, or if the study is canceled by the FDA, Health Canada or the sponsor company

QUESTIONS

If you have any questions about this study, its procedures, risks, benefits or your alternatives or rights or if at any time you feel you have experienced a research-related injury, contact:

Dr. Ingrid Pacey MBBS
3369 West 4th Ave.
Vancouver BC V6R 1N6
Office: 604-732-9309
Cell: [REDACTED]

If you have other questions about other effects of MDMA, you can contact Rick Doblin, Ph.D., President of MAPS, the organization sponsoring this study.

The address is:

Rick Doblin, Ph.D.
3 Francis St.
Belmont, MA 02478
USA
Tel: 617 484-8711

In case of an emergency, please contact Dr. Ingrid Pacey at tel. 604-732-9309/604-767-8570 OR go to the nearest hospital emergency department.

If you have concerns that you don't feel comfortable asking the study doctor or sponsor, you may contact the Research Ethics Board (IRB Services) that reviewed this study at: The Director, Human Research Protection Program, IRB Services, 372 Hollandview Trail, Suite 300, Aurora, ON, L4G 0A5. You may also call IRB Services' bilingual Representative at 1-866-449-8591, or contact IRB Services by email at subjectinquiries@irbservices.com.

IRB Services is an independent committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

SUBJECT'S STATEMENT OF CONSENT

"A TEST OF MDMA-ASSISTED PSYCHOTHERAPY IN SUBJECTS WITH CHRONIC POSTTRAUMATIC STRESS DISORDER (PTSD)"

Your participation in this study is voluntary. You may refuse to take part in or you may stop taking part in this study at any time. You should call the study doctors if you decide to do this. Your decision will not affect your current or future regular medical care or any benefits to which you are entitled at this site. The study doctors and/or the sponsor may stop your participation in this study at any time without your consent if they decide it is in your best interest or if you do not follow the study doctors' instructions.

You will need to have someone drive you home on the day after the experimental session. If you cannot find anyone to take you home, the study doctors will find someone to drive you.

You have read the information in this consent form and it has been discussed with you. All of your questions so far about the study and your participation in it have been answered. You freely consent to participate in this research study.

You will not donate blood while you are in the study and for at least 30 days after.

By signing this consent form, you have not waived any of the legal rights which you otherwise would have as a subject in a research study. **You will be given a copy of the consent form signed by you and the investigator.**

The study doctor has my permission to tell my regular doctor about my being in this study:

YES NO

	SUBJECT	
Printed name		
Signature		
Date		

PERSON ADMINISTERING CONSENT	
Printed name	
Signature	
Date	

STATEMENT OF INVESTIGATOR:

(Investigator preferably to sign the consent form on the same date as the subject, but prior to first patient visit)

I acknowledge my responsibility for the care and well being of the above subject, to respect the rights and wishes of the subject, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

INVESTIGATOR	
Printed name	
Signature	
Date	

IRB APPROVAL/REB ATTESTATION FORM



STUDY UNCONDITIONAL APPROVAL DATE: NOVEMBER 21, 2008

THE APPROVAL IS VALID FOR ONE YEAR AND EXPIRES ON NOVEMBER 20, 2009

ORIGINAL APPLICANT: Mr. Rick Doblin, Multidisciplinary Association for Psychedelic Studies (MAPS)

INITIAL REVIEW:

The following protocol, plus MDMA Investigator's Brochure Dated December 2007, CAPS-DX Scale dated December 1995, Subject Units of Distress, Script for Phone Screening, PDS Questionnaire, Reactions to Research Participation Questionnaire – Short Form, Beck Depression Inventory, Informed Consent Quiz, Informed Consent Form Quiz Answer Key, Dear Dr. Letter and Informed Consent Document undated, were reviewed by the British Columbia Institutional Review Board (BC IRB) of Institutional Review Board Services on September 10, 2008, and were:

- APPROVED as submitted
- CONDITIONALLY APPROVED, reasons previously communicated
- APPROVAL WITHHELD, reasons previously communicated
- REJECTED / REFUSED TO APPROVE / DISAPPROVED, reasons previously communicated

Final Protocol Number and Date: M-P4 dated 09/03/08

Final Protocol Title: 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

Sponsored by: NAME: Multidisciplinary Association for Psychedelic Studies (MAPS)
 ADDRESS: 3 Francis Street
 Belmont, MA 02478 USA

FINAL REVIEW AND APPROVAL DETAILS:

Additional information and/or revised documents have been submitted for review and approval. They have been reviewed for compliance with the changes and/or clarification required at the IRB meeting noted above.

The protocol and informed consent documents as described below now conform to the IRB's requirements, and are hereby **UNCONDITIONALLY APPROVED**.

Final Protocol Number and Date: M-P4 dated 11/17/08

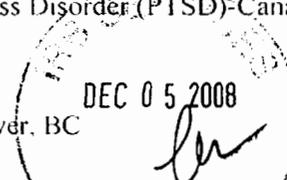
Final Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Informed Consent Date: November 19, 2008 (Main) and October 24, 2008 (Video)

INVESTIGATOR APPROVAL:

Qualified Investigator Name/Site Address: Dr. Ingrid Pacey, 3369 West 4th Ave., Vancouver, BC

Other Investigator(s) at the site: Drs.: A. Feldmar and K. Tallman



COMPLIANCE STATEMENT / ATTESTATION: The membership of this IRB complies with the requirements defined in Health Canada regulations, 21 CFR parts 56 and 312.3 and 45 CFR 46. The IRB carries out its functions in accordance with good clinical practices (e.g., ICH GCP Guidelines) and Health Canada regulations and in compliance with FDA 21 CFR parts 50 and 56, for US federally funded research DHHS 45 CFR part 46, for Canadian federally funded research - and the Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans.



Stephen Hopton Cann, Ph.D.,
Scientist Representative, (BC) Institutional Review Board



CLINICAL TRIAL SITE INFORMATION FORM

A separate form for each clinical trial site must be completed by the sponsor and filed with Health Canada.
All fields must be completed prior to submitting this form to Health Canada.

PART 1 - Clinical Trial Protocol Information				
Please check one of the following: Clinical Trial Application (CTA) / Clinical Trial Application Amendment (CTA-A) 9				
1. Clinical Trial Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada				
2. Clinical Trial Protocol Number (if applicable) M-P4	3. Clinical Trial Control Number (if assigned)	4. CR File Number (if assigned)		
PART 2 – Drug Product / Sponsor Information				
A) Drug Product Information				
5. Brand Name: None				
6. Proper or Common Name: (+/-)-3,4-methylenedioxyamphetamine (MDMA)				
B) Sponsor of Clinical Trial				
7. Name of Sponsor (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies (MAPS)				
8. Street / Suite / PO Box 3 Francis St.	9. City / Town Belmont	10. Prov. / State MA	11. Country USA	12. Postal/ZIP Code 02478-2218
Contact Person for Sponsor				
13. Name Rick Doblin PhD	14. Telephone No. 617-484-8711	15. Fax No. 617-484-8427	16. Language Preferred / English 9 French	
17. Title President, MAPS	18. E-mail Rick@maps.org			
C) Contact for THIS Clinical Trial				
19. Contact Name Rick Doblin PhD.		20. E-mail Rick@maps.org		
21. Company Name (Full Name - No Abbreviations) Multidisciplinary Association for Psychedelic Studies				
22. Street / Suite / PO Box 3 Francis St.	23. City / Town Belmont	24. Prov. / State MA	25. Country USA	26. Postal/ZIP Code 02478-2218
27. Telephone No. 617-484-8711	28. Fax No. 617-484-8427	29. Language Preferred / English 9 French		





PART 3 - Clinical Trial Site Information			
A) Clinical Trial Site			
30. Name of Site (Full Name - No Abbreviations)			
31. Street / Suite / PO Box	32. City / Town Vancouver	33. Province BC	34. Postal Code
35. Commencement Date of Clinical Trial or Clinical Trial Amendment ¹ December 21, 2008			
B) Qualified Investigator A Qualified Investigator Undertaking must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified above. The completed undertaking must be retained by the clinical trial sponsor for a period of 25 years.			
36. Name Ingrid Pacey MBBS FRCP[C]	37. Title Psychiatrist	38. Language Preferred / English 9 French	
39. Street / Suite / PO Box 3369 West 4th Ave.	40. City / Town Vancouver	41. Province BC	42. Postal Code V6R 1N6
43. E-mail	44. Tel. No. 604-732-9309	45. Fax No. 604-733-6951	
C) Research Ethics Board Approval A Research Ethics Board Attestation must be completed by the Research Ethics Board that reviewed and approved the protocol and informed consent form for this clinical trial at the site specified above. The completed attestation must be retained by the clinical trial sponsor for a period of 25 years.			
46. Name of Research Ethics Board IRB Services		47. Date of Approval 11/21/2008	
48. Street / Suite / PO Box 372 Hollandview Trail, Suite 300	49. City / Town Aurora	50. Province ON	51. Postal Code L4G 0A5
52. Name of Contact Person	53. Telephone No. 905-727-7989 Ext.	54. Fax No. 905-727-7990	55. Language Preferred / English 9 French
56. Title Protocol Review (Phase II-IV Team)		57. E-mail @irbservices.com	

¹Date of commencement of the trial: For the purposes of the Clinical Trial Site Information form - this is defined as the date when the clinical trial site is ready to enrol patients in the clinical trial. (Before a start date can be determined, both Health Canada and Research Ethics Boards approval must be obtained).

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies

Principal Investigator: Dr. Ingrid Pacey MB.BS. FRCP[C]

Study Number: M-P4

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

Study Title: 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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

Approved by: IRB Services, BC Committee, November 21, 2008

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

Form: Capsules

Dosage (strengths): 12.5 mg (active placebo supplemental dose), 25 mg (active placebo-initial dose), 62.5 (experimental dose-supplemental dose), 125 mg (experimental dose-initial dose). Supplemental dose administered by mutual agreement of investigator and participant 1.5 to 2.5 hours after an initial dose

Route of Administration: Oral

Indications: For use in combination with therapy in people with PTSD

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

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 compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) 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 compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

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 either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 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 during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression 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. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). 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 and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling

participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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 six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

The study will take place at one center in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, will take place

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD and with a CAPS score of 50 or higher. The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all of the inclusion criteria listed below without meeting any of the exclusion criteria. Participants must reside in Canada.

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 [1-3]. 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 [4, 5] 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 [5].

As described above, capsules containing the initial dose of MDMA 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.

S Drug Substance

S.1 General Information

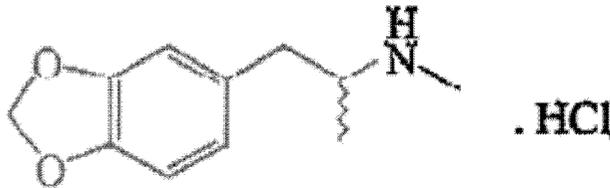
The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N₁-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅NO₂. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by Prof. Dr. R. Brenneisen, DCR, University of Bern, Switzerland. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94.1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-

methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was 148.9-149.7 C.

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 Manufacturer: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is <http://www.lipomed.com>

S.2.1 Method of Manufacture (see also p. 1 of report).

Step 1: 3,4-methylenedioxybenzaldehyde + nitroethane -> MDA-nitrostyrol. Solvent = acetic acid; Reaction 4 hours, refluxing. Crystallization from methanol.
Step 2: MDA-nitrostyrol + $LiAlH_4$ -> d,l-MDA. Solvent = tetrahydrofuran (dried); Reaction = 2 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether; distillation of free base under vacuum

Step 3 d,l-MDMA + formic acid -> d,l-MDA-formamide. Solvent = Benzene; Reaction = water separator, 24 hours, refluxing; reprocessing, ethyl acetate; crystallization from diisopropyl ether.

Step 4: d,l-MDA-methylcarbamate + LiAlH₄ -> MDMA-HCl. Solvent = tetrahydrofuran (dried); reaction = 3 hours, refluxing; reprocessing, isopropanol, methyl-tert-butyl ether, distillation of free base under vacuum, crystallization from ethanol/hydrochloric acid and diisopropyl ether; recrystallization from isopropanol/diisopropyl ether.

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by [REDACTED]. Specifications of manufacture, including solvent and procedures, are translated in the second report of [REDACTED].

S.2.3 Control of Materials

See above and contained in report by [REDACTED].

S.3 Characterization:

Batch number is [REDACTED].

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]. One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: Brenneisen performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2).

Validation: From manufacturer, data available upon request ([REDACTED]).

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by [REDACTED] and listed above.

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

UV, in distilled water: $\lambda_{(\text{Max})}$ = 1 234 +/- 1 nm

ϵ_{mol} = 3800 +/- 500

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by Brenneisen:

HPLC

HP 1090 DAD; Column = Spherisorb ODS-1, 3 μm , 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile; HP₃O₄ 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 μm

Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

Injection: 250 C, splitless 1 μL

Detection: full scan

Identity (HPLC-DAD): TR = 7 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA)

Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from 

S.4.4 Batch Analysis:

As listed above, the batch is MDM-94-HC/94.1B5.5.

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

UV, in distilled water, $\lambda_{(MAX).1} = 234.0$ nm

$E_{mol.1} = 3939$

$\lambda_{(Max).2} = 285.0$ nm

$E_{mol.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%

Freebase content: 83.51%

Water content: 055%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 100 ppm

Isopropyl ether < 2000 ppm

Further analyses, performed by Interlab Belp on January 20, 2009:

Test of residue on ignition: **Ignition residue (Ph.Eur. 6.3, 2.4.16): <1%**

Tests for presence of heavy metals: **Heavy metals (Ph.Eur. 6.3, 2.4.8): <100 ppm**

More details are presented in the attached report (in German).

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug will be stored and shipped in a brown glass bottle. The container is closed with a white, tightly closing screw-on cap.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by [REDACTED], and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. [REDACTED] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In

his report, [REDACTED] reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period. A second evaluation performed upon the same batch by [REDACTED] in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment number 4, listed below).

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

[REDACTED] reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

[REDACTED] also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

P. Drug Product

The drug product will consist of 00 opaque gelatin capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: Experimental dose initial dose 125 mg MDMA per capsule; experimental dose supplemental dose 62.5 mg MDMA per capsule; active placebo initial dose 25 mg MDMA plus lactose to reach equivalent weight of 125 mg capsule per capsule; active placebo supplemental dose 12.5 mg MDMA plus lactose to reach weight of 62.5 mg per capsule. There are no other ingredients in these capsules. The capsules will be prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but will be compounded by Kerrisdale Pharmacy, a Vancouver-area pharmacist. The capsules and lactose are certified BSE/TSE free.

The sponsor has based dosage on previous research studies (2, 4) and on narrative reports of MDMA-assisted therapist (as Adamson and Metzner 1980; Stolaroff 2004). A dose of 125 mg has been used in a previous sponsor-supported research study conducted in the US (3). The sponsor chose the active placebo dose on the basis of a previous research study (4), with 25 mg expected to produce very few effects. The sponsor selected an inactive material to help maintain the blind by ensuring that all doses are of equal weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

The principal investigator will transport the MDMA to Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk will encapsulate experimental and active placebo doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy will supply the capsules and lactose. MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all 108 capsules have equivalent weights. All capsules will contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X39) and a varying amount of lactose to maintain equal weights.

The lactose will be lactose monohydrate (chemical formula = $C_{12}H_{22}O_{11} \cdot H_2O$) manufactured by [REDACTED]

The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses.

The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, the randomization monitor selects a number from amongst a set of cards based on the list, and that number is the bottle number used for that participant.

P.3.3 Batch Formula

The batch analyses for [REDACTED] lactose monohydrate are provided in the reports supplied by the manufacturer. [REDACTED] passed all batch analyses, as detailed on the reports supplied by the manufacturer, including visual inspection of powder and solution, acidity/alkalinity, presence of heavy metals, microbial count, protein/light analysis (absorbance at 210-220 nm, 0.04, absorbance at 22, 0.01), residue on ignition (0.03%), rotation of 54.7 degrees at 20 and 5% in water.

Opaque 00 gelatin capsules will be filled with the appropriate dose of MDMA.

Experimental initial dose: 125 mg

Experimental supplemental dose: 62.5 mg

Active Placebo initial dose: 25 mg + approximately 100 mg lactose or appropriate amount so that full weight = 125 mg

Active placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg

Capsules placed in numbered bottles

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all “active placebo” doses of the product. Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA capsules are of equal weight.

The lactose used will be Lactose Monohydrate [REDACTED]

See attachment for more information. The quality standard for this lactose, as listed on the manufacturer website, is NF.

P.4.1. Specifications

As described on p. 2 of the product safety sheet for lactose monohydrate, [REDACTED], issued by the manufacturer, [REDACTED] lactose monohydrate is an odorless white crystalline powder with the molecular weight of 360.31 g/mole. Its melting point is 214 C, and its specific gravity is 1.525 (water = 1). It is stable and partially soluble in cold or hot water. As further stated in reports supplied by the manufacturer to the pharmacist, specifications also include appearance in solution (clear, nearly colorless), identification of NMT 5.0 mcg/g, no detectable heavy metals, microbial levels (total aerobic 100 cfu/g, mold and yeast 50 cfu/g, negative for e. coli per 10 g), protein/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of < = 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

All doses of MDMA will be in the form of opaque capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

The sponsor will monitor the encapsulated product for stability. The sponsor will maintain four 125 mg capsules of MDMA for the purpose of stability analysis. These capsules will be compounded by Colin Holyk of Kerrisdale Medical Centre as described above and stored with the rest of the capsules in a separate closed bottle [REDACTED] will bring them to the pharmacist every six months for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

P.7 Container Closure System

All doses of MDMA will be in the form of opaque capsules. The MDMA capsules will be stored in amber glass bottles (vials) containing one 3 gram silica gel desiccant in each bottle. Each bottle will be assigned a number intended for use in the randomization process so as to maintain the double blind. All bottles will be appropriately stored in the offices of the principal investigator.

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

A Attachments:

1. Lipomed manufacturer's specification and batch analysis
 2. Quality Analysis of R Brenneisen; pp. 1-2 concern this batch of MDMA and p. 3 concerns capsules produced for a sponsor-supported study in Switzerland
 3. Additional details of manufacture provided by Lipomed and translated by Rudolf Brenneisen and additional tests performed by Interlab Belp
 4. Original reports from Interlab Belp and Lipomed (German)
 5. Stability report of David Nichols referring to different source and batch of MDMA but supporting long-term stability
 6. Certificate of suitability for capsules
 7. Letter associated with certificate of suitability for capsules to be used in this study
 8. Product description for lactose ordered in this study
 9. Certificate of suitability of lactose ordered for study
 10. Batch analyses for the lactose used in this study
 11. Certification that the lactose is BSE/TSE free
-
1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation]*. J Clin Psychopharmacol, 2000. **20**: 455-66.
 2. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting*. J Psychoactive Drugs, 1986. **18**: 319-27.
 3. Mithoefer, M., *MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): Eleventh update on study progress*. MAPS Bulletin, 2008. **17**: 11-12.
 4. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA*. 2001.
 5. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans*. Psychopharmacology (Berl), 2002. **162**: 396-405.