

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

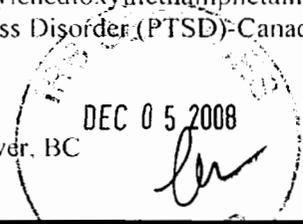
Final Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

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

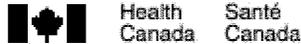
Other Investigator(s) at the site: Drs.: A. Feldmar and K. Tallman



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

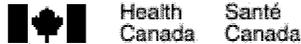


CLINICAL TRIAL SITE INFORMATION FORM

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

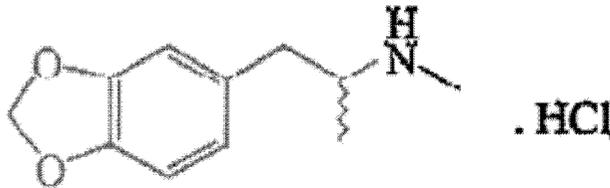
The drug product is (+/-)-(3,4)-methylenedioxyamphetamine HCl, also referred to as N₁-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅NO₂. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in 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]
[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.
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 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.