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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 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 (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
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

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**To / A:** [Dr. Carole Legare],  
Director, Office of Clinical Trials

**From / De:** [Paul Smeaton],  
Manager, Clinical Trials Quality Division,  
Office of Clinical Trials

**Subject / Objet:** Quality Overall Summary – Chemical Entities Clinical Trial Application – Phase II  
QOS - CTA GRP(PQ)-01-1(s1): 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-I1 |
| TPD Target Date | 2013-09-07 |
| Control No. / File No. | 167090 | 9427-M2544 - 21C |
| Contact Information | |

**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\HIJKL\Multidisciplinary associates for psychedelic studies\MDMA\167090 cta-2013r01a.doc

**References:** Parent CTA 127822

**Attachments:**
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 ± 1.5mg 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 ± 1.5mg. 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 pursed any further.
## Quality Overall Summary – Chemical Entities Clinical Trial Application – Phase II

**To / A:** [Dr. Carole Legare],
Manager, Office of Clinical Trials

**From / De:** [Paul Smeaton],
Manager, Clinical Trials Quality Division,
Office of Clinical Trials

**Subject / Objet:** Quality Overall Summary – Chemical Entities Clinical Trial Application – Phase II

### Brand (Proprietary) Name of Drug Product
MDMA

### Proper, Common or Non-proprietary Name of Drug Substance
MDMA; 3,4 methylenedioxymethamphetamine

### Manufacturer / Sponsor
Multidisciplinary Association for Psychedelic Studies

### Therapeutic Classification
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

**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**

**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

**Security – Classification – de sécurité:**
HC Protected

**Date:**
[2013-08-19]
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-methylenedioxymethamphetamine (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 FORWARD ED 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.1 drug 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 Feldman; 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.]
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)

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.

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.

Route of Administration: Oral
Indications: For use in combination with therapy in people with PTSD

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, 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
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 at approximately
S.1.2: Structure: The drug product is described by the chemical formula C₁₁H₁₅N₂. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG. It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as N-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅N₂. 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 No. [Lipomed AG, Switzerland, in 12.98 (batch No. Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Lipomed AG, Switzerland. On January 30, 2006, a quality control analysis was performed by Lipomed AG. 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 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 General Information

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as 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 C₁₁H₁₅N₂. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.

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)-methylenedioxynmethamphetamine HCl, also referred to as N-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₅N₂. 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 No. 12.98 (batch No. Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Lipomed AG, Switzerland. On January 30, 2006, a quality control analysis was performed by Lipomed AG. 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 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.
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 Specifications of manufacture, including solvent and procedures, are translated in the second report of 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 p. 1

S.3 Characterization:

Batch number is
S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [Brand name]. 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: 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 (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 [Brand name] (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: \( \lambda_{\text{Max}} = 1234 \pm 1 \text{ nm} \)
\( \epsilon_{\text{Max}} = 3800 \pm 500 \)
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; \( \text{H}_{2}\text{O}: \text{Acetonitrile; HP, 85%; hexylamine} = 928.72: 5: 0.28 \text{ mL: isocratic flow 0.8 mL/min at 40 C.} \)
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)
S.7.1 Stability Summary and Conclusions

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.6 Container Closure System

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.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

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

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
There is stability data for this batch of MDMA, performed by [manufacturer], 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. [manufacturer] assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, [manufacturer] 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 [manufacturer] 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

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

[manufacturer] 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-methylenedioxyamphetamine (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 ± 1.5mg per capsule for all blinded doses. There are no other ingredients in these capsules. 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

<Brand name>
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
Attachments:

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.

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.

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, 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/lipid 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.
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


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Si vous recevez cette télécopie par erreur, veuillez en aviser immédiatement l'expéditeur.

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 Kumaratthan
Tel/Tél.: (613) 941-6059

B-mail/Courier élec.: rajkumar.kumaratthan@hc-sc.gc.ca
Fax/Télécopieur: (613) 954-8867

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RE: Phase II CTA for Methylenedioxyamphetamine 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-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.

If you do not receive all pages, please call the sender.
Si vous ne recevez pas toutes les pages, veuillez téléphoner à l'expéditeur.

RECEIVED TIME AUG. 20, 4:05PM
We have the following comments with respect to your CTA for methylenedioxyamphetamine 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
Office of Clinical Trials
Dear Dr. Kumarakhasan,

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.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial/Supplement</th>
<th>Blinded?</th>
<th>Required/Optional</th>
<th>Total Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>125mg</td>
<td>Initial</td>
<td>Blinded</td>
<td>Required</td>
<td>23</td>
</tr>
<tr>
<td>50mg</td>
<td>Initial</td>
<td>Blinded</td>
<td>Required</td>
<td>12</td>
</tr>
<tr>
<td>62.5mg</td>
<td>Supplement</td>
<td>Blinded</td>
<td>Optional</td>
<td>23</td>
</tr>
<tr>
<td>25mg</td>
<td>Supplement</td>
<td>Blinded</td>
<td>Optional</td>
<td>12</td>
</tr>
<tr>
<td>100mg</td>
<td>Initial</td>
<td>Open-Label</td>
<td>Required</td>
<td>15</td>
</tr>
<tr>
<td>25mg</td>
<td>Initial</td>
<td>Open-Label</td>
<td>Optional</td>
<td>10</td>
</tr>
<tr>
<td>50mg</td>
<td>Supplement</td>
<td>Open-Label</td>
<td>Optional</td>
<td>15</td>
</tr>
<tr>
<td>12.5mg</td>
<td>Supplement</td>
<td>Open-Label</td>
<td>Optional</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
</tbody>
</table>
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-methylenedioxy-methamphetamine (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 12.5 mg capsule strength and the weight range of 236.5 ± 1.5 mg per blinded capsule is thus attributed to the fact that the 12.5 mg 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 controlled environment that will only be disrupted when of study drug to the treatment room. The drug will be ingested by the subject on the same day as being removed Hence
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]

[Redacted]

MAPS
Multidisciplinary Association for Psychedelic Studies
1215 Mission Street, Santa Cruz, CA 95060 USA
Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370
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
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

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 mg (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. Supplementation 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.]
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.

Table 1. Stage 1 Drug Doses

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Dose</th>
<th>Initial Dose</th>
<th>Optional Supplemental Dose</th>
<th>Min-Max Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>Comparator Dose</td>
<td>50 mg</td>
<td>25 mg</td>
<td>50-75 mg</td>
</tr>
<tr>
<td>1, 2, and 3</td>
<td>Full Dose</td>
<td>125 mg</td>
<td>62.5 mg</td>
<td>125-187.5 mg</td>
</tr>
</tbody>
</table>

Table 2. Stage 2 Drug Doses

<table>
<thead>
<tr>
<th>Experimental Session</th>
<th>Dose</th>
<th>Initial Dose</th>
<th>Optional Supplemental Dose</th>
<th>Min-Max Cumulative Dose</th>
<th>Min-Max Cumulative Dose with Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active Dose</td>
<td>100 mg</td>
<td>50 mg</td>
<td>100-150 mg</td>
<td></td>
</tr>
<tr>
<td>2 and 3</td>
<td>Active Dose</td>
<td>100 mg</td>
<td>50 mg</td>
<td>100-150 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Optional Titration Dose</td>
<td>25 mg</td>
<td>12.5 mg</td>
<td>125-187.5 mg</td>
<td></td>
</tr>
</tbody>
</table>

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.
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.

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 100 mg 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 approximately at 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.
S.1.2: Structure: The drug product is described by the chemical formula C₁₁H₁₅NO₂. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.

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

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-α-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 C₁₁H₁₅NO₂. 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

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within first report provided by manufacturer. Specifications of manufacture, including solvent and procedures, are translated in the second report of 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 p. 1

S.3 Characterization:

Batch number is:

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by manufacturer. 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: 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 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 (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: $\lambda_{\text{max}}$=1 234 ±/− 1 nm
$\varepsilon_{\text{max}}$ = 3800 ±/− 500
Melting Point: 149 ±/− 3 C
Purity HPLC = 98.5%
Free base content = > 92.5%
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

HPLC
HP 1090 DAD; Column = Spherisorb ODS-1, 3 µm,125 x 4 mm i.d.; mobile phase; H$_2$O: Acetonitrile; H$_3$PO$_4$ 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

S.4.4 Batch Analysis:

As listed above, the batch is

Provided on manufacturer’s data sheet

Appearance: Conforms to appearance
There is stability data for this batch of MDMA, performed by 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.

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 Nichols 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.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by 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.

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

Identity: IR identical to reference
UV, in distilled water, \( \lambda_{\text{max}} = 234.0 \) nm
\( \varepsilon_{1} = 3939 \)
\( \lambda_{\text{max}} = 285.0 \) nm
\( \varepsilon_{2} = 3688 \)
Melting point = 148.9 to 149.7°C
Purity HPLC = 99.66%
Freebase content: 83.51%
Water content: 0.55%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 200 ppm

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

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Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 200 ppm
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. Drug Product

The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methylenedioxyamphetamine (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 ± 1.5mg 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.

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%.

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%.

Quality Overall Summary and Data 11 MAPS Study M-P4
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.

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