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](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-methylenedioxybenzaldahyde + 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-foramide. 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 [University of Bern]. Specifications of manufacture, including solvent and procedures, are translated in the second report of [control# 127822] in Modules 2 and 3 for CTA approved on March 17, 2009, control # 127822.

S.2.3 Control of Materials

See above and contained in report by Brenneisen, p. 1

S.3 Characterization:

Batch number is [information redacted].

S.3.1 Elucidation of Structure and Other Characteristics

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

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

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

Validation: From manufacturer, data available upon request.

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 [information redacted] (see attachment and reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer’s data sheet.
Appearance: White crystalline powder
Identity: IR
UV, in distilled water: \( \lambda_{\text{max}} = 1234 \pm 1 \text{ nm} \)
\( \varepsilon_{\text{mol}} = 3800 \pm 500 \)
Melting Point: 149 \( \pm \) 3 C
Purity HPLC = 98.5%
Free base content = > 82.5%
Water content: 0.3 \( \pm \) 0.3%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol< 5000 ppm, isopropyl ether < 5000 ppm

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

HPLC
HP 1090 DAD; Column = Spherisorb ODS-1, 3 \( \mu \text{m}, 125 \times 4 \text{ mm i.d.}; \) mobile phase: \( \text{H}_2\text{O}: \) Acetonitrile; \( \text{H}_3\text{O}_4 \text{, hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.} \)
Injection volume: 10 \( \mu \text{L} \)
Detection: 198 nm
Identification: DAD spectrum 192-350 nm vs. standard

GC/MS
Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 \( \mu \text{m} \)
Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)
Carrier gas: He1.2 mL/min
Derivatization: MBTFA
Injection: 250 C, splitless 1 \( \mu \text{L} \)
Detection: full scan

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

S.4.3 Validation of Analytical Procedures
Validation upon request from

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 and a report on another source of MDMA also provides relevant information on the 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. Assessed sample purity and found it remained greater than 99% pure no detected. In his report, reported that a sample of MDMA HCl assessed with HPLC also remained pure over a 19-year period. A second evaluation performed upon the same batch by 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.

Identity: IR identical to reference
UV, in distilled water, $\lambda_{(\text{Max})} = 234.0 \text{ nm}$
$\varepsilon_{\text{mol}} = 3939$
$\lambda_{(\text{Max})} = 285.0 \text{ nm}$
$\varepsilon_{\text{mol}} = 3688$
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 < 2000 ppm

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

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

S.4.5 Justification of Specification

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

S.6 Container Closure System

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

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by 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. Assessed sample purity and found it remained greater than 99% pure no decomposition detected. In his report, 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 in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment 4 in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.
S.7.2 Stability protocol and stability commitment

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

S.7.3 Stability Data

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

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

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

P. Drug Product

The drug product will consist of 03 clear gelatin capsules containing racemic 3,4-methyleneoxydimethamphetamine (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.

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.
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.

P.3 Manufacture

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

P.3.1 Manufacture(s)

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

The lactose monohydrate (chemical formula = C\(_{12}\)H\(_{22}\)O\(_{11}\).H\(_{2}\)O) was manufactured by

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled “inner envelopes” within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.
Randomization will be performed via the use of a web-based randomization program. An unblinded randomization monitor will generate the randomization list at the beginning of the study. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions.

**P.3.3 Batch Formula**

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

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

- Full initial dose: 125 mg + 113.5 mg lactose
- Full supplemental dose: 62.5 mg + 174.1 mg lactose
- Active Stage 2 initial dose: 100 mg + 143.0 mg lactose
- Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose
- Comparator initial dose: 50 mg + 184.9 mg lactose
- Comparator supplemental dose: 25 mg + 211.0 mg lactose
- Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose
- Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose

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

**P.4 Control of Excipients**

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

The lactose used will be **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/light absorbance at 210-220 nm NMT: 0.25, absorbance at 270-300 nm: NMT = 0.07, residue on ignition of <= 0.1%. It should be freely but slowly soluble in water and practically insoluble in alcohol. Its specific rotation should be 54.4-55.9 degrees at 20, and in water 4.5 to 5 in water.

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

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

P.7 Container Closure System

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

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

A Attachments:

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


Modules 2 and 3: Common Technical Document Summaries and Quality

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

Amendment 1 Version 2

Sponsor: Multidisciplinary Association for Psychedelic Studies
Principal Investigator: Dr. Ingrid Pacey MB BS, FRCP[C], Research Affiliate, CARBC, University of Victoria
Study Number: M-P4
Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents
2.3 Quality Overall Summary

1 Introduction

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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Study Phase: II
Study Number: MP-4

Principal Investigator: Ingrid Pacey MB-BS FRCP[C], Research Affiliate, CARBC, University of Victoria
Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD

Approved by: IRB Services, BC Ontario Committee, November 24, 2008 July 12, 2013

Abbreviations:

GCMS = Gas chromatography-mass spectrometry
HPLC = High performance liquid chromatography
LiAlH4 = Lithium anhydride
MDA = 3,4-methylenedioxyamphetamine
MDMA = 3,4-methylenedioxymethamphetamine

Study Drug: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)
Form: Capsules
Dosage (strengths): 12.5 mg (full dose-initial dose), 100 mg (active placebo dose Stage 2-initial dose), 62.5 mg (full dose-supplemental dose), 250 mg (comparator-initial dose; also active placebo-initial dose), 62.5 mg (experimental dose Stage 2-supplemental dose), 125 mg (experimental 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 doosedoses 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.]
The investigators will also gather information on physiological effects and side effects after MDMA. Safety Objectives: The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

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

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

Secondary Objectives:

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

In specified subjects:

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

The proposed study employs a randomized, double-blind, active-placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 hours after the first injection, or an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA administered 1.5 to 2.5 hours after the first injection. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three comparison study sessions.

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. During the sessions, participants will receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo all experimental sessions during the study period. The study will be unblinded one month after the second assessment.

Symptoms of PTSD and depression will be assessed through the Beck Depression Inventory (BDI). Neurocognitive function will be assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and the Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and the Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, where they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent assessor will assess PTSD and depression symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy and examining...
neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

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

The open-label study segment for participants assigned to active-placebo will last an additional four used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

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

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

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy experimental session, for a total of about 8 months:

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

**Number of Centres**

The study will take place at one center:

Dr. Ingrid Pacey. Assessments of PTSD symptoms and neurocognitive function will also be performed in the offices of the independent rater, Dr.
The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental full dose condition are identical to those in use in other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the U.S. Previous researchers have also used doses within this range [4-3][1-6]. The supplemental dose is also identical to the one used in the U.S study. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

Dosing Regimen

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

Drug Formulation

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 listed below without meeting any of the exclusion criteria. Participants must reside in Canada.

Drug Formulation

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental full dose condition are identical to those in use in other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the U.S. Previous researchers have also used doses within this range [4-3][1-6]. The supplemental dose is also identical to the one used in the U.S study. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].

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

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental full dose condition are identical to those in use in other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the U.S. Previous researchers have also used doses within this range [4-3][1-6]. The supplemental dose is also identical to the one used in the U.S study. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [1, 2, 7-10].
Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [3, 11, 12]. The initial full dose is expected to produce all the common effects of MDMA, including changes in affect (+, mood), and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25 mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions. The doses to be compared in this study have been chosen on the basis of the Sponsor’s ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [4, 5] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [5]. The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

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

There will be no changes in dose regimen across the three MDMA-assisted first two blinded sessions. If the participant experienced hypertension that required clinical intervention or had a serious adverse event during an experimental session full dose participants will receive the same dose regimen during a third session in an open-label context after unblinding per protocol. Subjects in the comparator dose condition will not complete Stage 1, but will continue to Stage 2. In Stage 2, they will receive the active dose for the first Stage 2 session, and they can receive the active or full dose during the second and third sessions via a clinical titration dosing strategy.

If the participant experiences hypertension that required clinical intervention or had a serious adverse event that is possibly or probably related to study drug, then no further doses of MDMA will be administered.
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 been performed with MDMA-HCl. The drug product is described by the chemical formula C₁₁H₁₉N₂O₂. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by this analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as N-alpha-Dimethyl-1,3-benzodioxole-5-ethanamine, and is described by the chemical formula C₁₁H₁₉N₂O₂. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Dr. Franz Vollenweider from the Psychiatric University Hospital Zurich, Switzerland. On January 30, 2006, a quality control analysis was performed by this analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no. with no decomposition products detectable and a HPLC purity >98%. Quality of the drug supply was confirmed annually between the years of 2006 and 2010. Only one lot of MDMA was manufactured by Lipomed, AG. MDMA from this lot has been given to seven people in Israel and 14 people in Switzerland in PTSD clinical trials conducted under the U.S. IND #63,384. See attached documents.

S.1.2: Structure: The drug product is described by the chemical formula C₁₁H₁₉N₂O₂. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.

![Diagram of MDMA HCl](image)

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-methylenedioxymethyllalkyldinitrite + 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 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 MDM-94-HC/94.1B5.5
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: [manufacturer] 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.

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 [manufacturer] (see attachment and listed above reports included with CTA 127822).

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer’s data sheet.

Appearance: White crystalline powder
Identity: IR
UV, in distilled water: \( \lambda_{\text{Max}} = 1234 \pm 1 \text{ nm} \)
\( \epsilon_{\text{mol}} = 3800 \pm 500 \)
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 [manufacturer].
HPLC
HP 1090 DAD; Column = Spherisorb ODS-1, 3 µm, 125 x 4 mm i.d.; mobile phase; H₂O: Acetonitrile: H₃PO₄, 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min 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 × 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: Hel. 1.2 mL/min
Derivatization: MBTFA
Injection: 250 °C, splitless 1 µL
Detection: full scan

Identity (HPLC-DAD): TR = 75.8 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M⁺, MDMA-TFA) 154 (basepeak) 162, 289 (M⁺) MDMA-TFA
Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from

S.4.4 Batch Analysis:

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

Provided on manufacturer’s data sheet

Appearance: Conforms to appearance
Identity: IR identical to reference
UV, in distilled water, λ_MAX.1 = 234.0 nm
ε_mol.1 = 3939
λ_MAX.2 = 285.0 nm
ε_mol.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 < 2000 ppm
Brenneisen reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

S.7.3 Stability Data

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.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by 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. assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, 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 in January 2009 continued to detect greater than 99% purity, and no decomposition products detected (see Attachment number 4, listed below) in original CTA Module 2 and 3, CTA approved March 17, 2009, control # 127822 and see attached documents.

S.7.2 Stability protocol and stability commitment

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

S.7.3 Stability Data

Brenneisen reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.
The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

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 Manufacturer(s)

The principal investigator will transport the MDMA to Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk will encapsulate experimental and active placebo doses of MDMA at Kerrisdale Pharmacy, Vancouver BC.
The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled “inner envelopes” within the primary container. There will be one primary pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses. The IP for each experimental session will be packaged in one primary container, labeled with a clear indication of the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed at Kerrisdale Pharmacy, 5591 West Blvd, Vancouver, BC, V6M 3W6. Pharmacist Colin Holyk, the licensed dealer, has encapsulated all doses of MDMA at Kerrisdale Pharmacy, Vancouver BC. The pharmacy supplied the capsules and lactose. Compounded MDMA was weighed to the appropriate dose and placed in clear gelatin capsules, one dose per capsule. All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A “packing stat” was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. All 108 capsules are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X3923 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. The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will return to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses. The IP for each experimental session will be packaged in one primary container, labeled with a clear indication of the packaging. The material will be held by the licensed dealer, pharmacist Colin Holyk. The compounding has been performed at 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. 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All capsules will be the clear gelatin capsules to ensure that the investigators and subjects are blinded to dose. In order to differentiate initial and supplemental dose capsules, each capsule will be individually packaged. At the time of compounding, the pharmacist determined the capacity of the gelatin capsules to determine the amount of lactose needed for compounding. A “packing stat” was created by filling 10 capsules with the MDMA and 10 capsules with the lactose to calibrate the amount of compounded MDMA and lactose per capsule. All 108 capsules are equivalent in weight. All capsules contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X3923 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.
P.4 Control of Excipients

Opaque Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA. Experimental Full initial dose: 125 mg + 113.5 mg lactose
Experimental Full supplemental dose: 62.5 mg + 174.1 mg lactose
Active Placebo Stage 2 initial dose: 25 mg + approximately 100 mg + 143.0 mg lactose or appropriate amount so that full weight = 125 mg
Active Placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg
Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose
Comparator initial dose: 50 mg + 184.9 mg lactose
Comparator supplemental dose: 25 mg + 211.0 mg lactose
Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose
Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose
Capsules placed in individual inner envelopes, which are placed in a numbered bottle primary container.

P.3.3 Batch Formula

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

Opaque Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA. Experimental Full initial dose: 125 mg + 113.5 mg lactose
Experimental Full supplemental dose: 62.5 mg + 174.1 mg lactose
Active Placebo Stage 2 initial dose: 25 mg + approximately 100 mg + 143.0 mg lactose or appropriate amount so that full weight = 125 mg
Active Placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg
Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose
Comparator initial dose: 50 mg + 184.9 mg lactose
Comparator supplemental dose: 25 mg + 211.0 mg lactose
Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose
Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose
Capsules placed in individual inner envelopes, which are placed in a numbered bottle primary container.

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

The lactose used will be Lactose Monohydrate

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

**P.4.1. Specifications**

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

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

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

Kerrisdale Pharmacy, Pharmacist Colin Holyk will test these capsules for stability assessment and to make sure they will dissolve appropriately. Samples of the compounded MDMA capsules will be retained for visual and tactile inspection at 6, 12, 18 and 24 months, to see that the capsule/MDMA/lactose delivery system remains stable.

**P.7 Container Closure System**

All doses of MDMA will be in the form of opaque-clear capsules. The MDMA capsules will be stored in amber glass bottles (vials) containing one 3 gram silica gel desiccant in each bottle-clear cellophane packages. Each bottlepackage (primary container) will be assigned a container number intended for use in the randomization process so as to maintain the double blind. All bottlepackages will be appropriately stored in the offices of the principal investigator, 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 investigator-pharmacist. The MDMA will be stored in a locked safe and only the investigator-investigator 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 Low and Fully-Active blinded dose capsules/packages.

**A Attachments:**

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

**References:**


MDMA PTSD Studies / CMC / Update 26022010

1. Name, address of MDMA manufacturer

Lipomed AG, Fabrikmattenweg 4, CH-4144 Arlesheim, Switzerland
www.lipomed.com/

2. Method of manufacturing (based on document Lipomed 94.1B5.5, Original in German)

   Step 1: 3,4-Methylenedioxybenzaldehyde + nitroethane → d,l-MDA-nitrostyrol
   Solvent: acetic acid; reaction: 4 h, refluxing; crystallization: from methanol.

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

   Step 3: d,l-MDA + formic acid → d,l-MDA-formamide
   Solvent: benzene; reaction: water separator, 24 h, refluxing; reprocessing: ethyl acetate; crystallization: from diisopropyl ether.

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

3. Methods of CoA

- Manufacturer:
  
  ➤ HPLC, GC, IR, UV, MP etc.: experimental details on request.

- DCR:

  ➤ HPLC (HP 1090-DAD):
    • Column: Spherisorb ODS-1, 3 μm, 125 x 4 mm i.d.; mobile phase: H₂O:acetonitrile:H₃PO₄ 85%:hexylamine = 928:72:5:0.28 mL; isocratic; flow 0.8 mL/min; 40°C
    • Inj.vol.: 10 μL
    • Detection: 198 nm
    • Identification: DAD spectrum 192-350 nm vs. standard
    • Validation data on request.

  ➤ GC/MS:
    • Column: DB-5ms, 25 m x 0.2 mm i.d., film 0.33 μm
    • Temperature program: 60°C (2 min hold) - 250°C @ 20°C/min, 250°C (5 min hold)
    • Carrier gas: He 1.2 mL/min
    • Derivatization: MBTFA
    • Injection: 250°C, splitless, 1 μL
    • Detection: full scan.

4. CoA of clinical test substance

- Manufacturer:

  ➤ Test substance: d,l-MDMA-HCl (± 3,4-methylenedioxymethamphetamine hydrochloride)
  ➤ Art./batch #: MDM-94-HC/94.1B5.5
  ➤ Specifications/QC data: Lipomed "Analysis Data Sheet"

- DCR:

  ➤ 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)
  ➤ Purity (HPLC): 99.9%, no decomposition products detected.

- Interlabor Belp (based on document 0901-00345, Original in German):

  ➤ Heavy metals, according to Ph.Eur. 6.3, 2.4.8: <100 ppm
  ➤ Ignition residue, according to Ph.Eur. 6.3, 2.4.16: <1%
5. Stability data

- Purity (HPLC) update: measured at DCR on Febr. 25, 2010: 99.9%, no decomposition products detected.

6. Container

- The clinical test substance is stored and shipped in a brown-glass bottle for pharmaceutical purposes with white, tightly closing screw cap.
- Content uniformity:

<table>
<thead>
<tr>
<th>Target [mg]</th>
<th>Measured Mean ± s.d. [N = 3, mg]</th>
<th>Deviation from target [± %]</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5</td>
<td>11.76 ± 0.51</td>
<td>-5.93</td>
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<tr>
<td>25.0</td>
<td>23.65 ± 1.55</td>
<td>-5.40</td>
</tr>
<tr>
<td>62.5</td>
<td>66.55 ± 1.85</td>
<td>+6.47</td>
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<tr>
<td>125.0</td>
<td>125.96 ± 5.66</td>
<td>+0.77</td>
</tr>
</tbody>
</table>

- Identity, purity:

MDMA confirmed by HPLC and GC/MS, >99%, no impurities detected

8. Container

Every single capsule is kept in a 10-mL plastic, white, photoresistant, tightly capped container (Aponorm®) and stored at room temperature


No decrease of MDMA purity and decomposition expected for study duration; however, stability data not yet available

10. Conformity decision, release for clinical trial

Based on CoA's of manufacturer (Lipomed) and of second, independent laboratory (DCR, Univ. of Bern) d,l-MDMA-HCl was approved by Swissmedic on June 2, 2006 (notification no. 2006 DR 2157) as clinical test substance and in form of capsules (4 dosages) as clinical test preparation.

Bern, February 23, 2007

Attachment: CoA Lipomed
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Module 1

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1.2.5 Study Protocol

1.2.6 Informed Consents

1.2.6.1 REB Attestation

1.2.7 Clinical Trial Site Information

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   Form HC 3011
   Investigator’s Brochure
   Protocol Synopsis (PSEAT)
   Study Protocol
   Informed Consent Forms

Module 2/3

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   Attached documents

2.4 Electronic Review Documents

   Quality Overall Summary
   Attached Documents
Feb 5, 2009

Dr. John Patrick Stewart
Acting Director,
Office of Clinical Trials
Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator: 3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9

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

Dear Dr. Stewart,

Enclosed is a resubmission of a Clinical Trial Application (CTA) for a Phase 2 study entitled, “A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada.” We originally submitted this protocol on December 18, 2008. We withdrew the application on January 23, 2009, due to the need to wait for some requested chemistry information which we have obtained and are now submitting. On February 3, 2009, Dr. Beata Wiatrowska, M.D., FRCP(C), called to say that she’d accepted our January 20, 2009, responses to her January 16, 2009 Clarifax about protocol design issues.

The principal investigator for the study is Dr. Ingrid Pacey MB BS FRCP[C], Vancouver, British Columbia. The enclosed forms, investigator’s brochure, protocol, consent materials and chemistry information are presented for review for this CTA. This protocol and associated informed consent have already been reviewed and approved by IRB Services, Aurora, Ontario, Canada.

The sponsor of the study is the Multidisciplinary Association for Psychedelic Studies (MAPS), a US-based non-profit research and educational organization working to develop MDMA into a prescription medicine for use in combination with psychotherapy. The enclosed application is for an investigation that is part of an international series of Phase 2 studies, the protocols of which
have all been submitted to FDA as part of MAPS IND #63-384. MAPS has successfully completed an MDMA/PTSD pilot study in the US in 21 subjects and is sponsoring ongoing MDMA/PTSD studies in Switzerland and Israel, each to enroll 12 subjects and estimated to be completed around the end of 2009. Our Canadian MDMA/PTSD is an attempt to replicate our US results.

MAPS has also helped to initiate a study of MDMA-assisted psychotherapy for people with anxiety related to a cancer diagnosis, taking place at McLean Hospital, Harvard Medical School.

I look forward to hearing from you regarding the results of your review.

Sincerely

Rick Doblin PhD
President, MAPS
# DRUG SUBMISSION APPLICATION

## PART 1 - Manufacturer/Sponsor and Drug Product Information

**HC Use Only:**

<table>
<thead>
<tr>
<th>1. Submission No.</th>
<th>2. Responsible Area</th>
<th>3. File No.</th>
<th>4. Date of Receipt</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Type of Submission: CTA

6. Number of Volumes: 2, 0 (no duplicates)

7. Schedule: Schedule III

8. Brand or Proprietary Name: None; see below

9. Proper, Common or Non-Proprietary Name: N-Methyl-3,4-methylenedioxyamphetamine; (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

### A) Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this will be the DIN/NOC OWNER)

For CTA and CTA-A, refer to attached Guidance

<table>
<thead>
<tr>
<th>10. Company Code</th>
<th>11. Manufacturer/Sponsor Name (Full Name - No Abbreviations)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multidisciplinary Association for Psychedelic Studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Francis St.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contact Person for Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this is the DIN/NOC OWNER contact)

17. Name: Rick Doblin PhD

18. Telephone No.: 617-484-8711

19. Fax No.: 617-484-8427

20. Language Preferred: / English 9 French

21. Title: President, MAPS

22. E-mail: Rick@maps.org

### B) Contact for THIS Drug Submission

23. Company Name: Multidisciplinary Association for Psychedelic Studies

24. Street/Suite/PO Box: 3 Francis St.

25. City/Town: Belmont

26. Prov./State: MA

27. Country: USA

28. Postal/ZIP Code: 02478-2218

<table>
<thead>
<tr>
<th>29. Name</th>
<th>30. Telephone No.</th>
<th>31. Fax No.</th>
<th>32. Language Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rick Doblin PhD</td>
<td>617-484-8711</td>
<td>617-484-8427</td>
<td>/ English 9 French</td>
</tr>
</tbody>
</table>

33. Title: President, MAPS

34. E-mail: Rick@maps.org

### C) Regulatory Mailing Address (Complete where a DIN is to be issued, see attached Guidance)

Same as A Above 9

| 35. Company Name: Multidisciplinary Association for Psychedelic Studies |
|-----------------------------|-----------------------------|
| Same as above               |

36. Street/Suite/PO Box: Same as above

37. City/Town: Same as above

38. Prov./State: Same as above

39. Country: Same as above

40. Postal/ZIP Code: Same as A Above 9

Regulatory Mailing Contact

41. Name: Same as A Above 9

42. Telephone No.:

43. Fax No.:

44. Language Preferred: / English 9 French

45. Title: E-mail

### D) Canadian Importer/Distributor (ONLY where Address in A is not in Canada)

Same as C Above 9

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>Dr. Ingrid Pacey MBBS FRCP[C]</td>
<td>3369 West 4th Ave.</td>
<td>Vancouver</td>
<td>BC</td>
<td>Canada</td>
<td>V6R 1N6</td>
</tr>
</tbody>
</table>

---

1. FOR CLINICAL TRIAL APPLICATIONS (HUMAN DRUGS): WHERE THE SPONSOR IS LOCATED OUTSIDE OF CANADA, APPENDIX 1 MUST BE COMPLETED AND SUBMITTED FOR EACH IMPORTER ACTING AS THE SPONSOR'S AGENT IN CANADA. REFER TO THE ATTACHED GUIDANCE AND THE “GUIDANCE FOR CLINICAL TRIAL SPONSORS” FOR ROLES AND RESPONSIBILITIES.

HC/SC 3011 (02)
### PART 2 - Drug Product Formulation Information

54. Proposed Shelf Life _20_ years _0_ months at _EC_.

55. Medicinal (Active) Ingredient(s)

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Standard</th>
<th>Strength</th>
<th>Units</th>
<th>Per</th>
<th>Calculated as Base?</th>
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<tbody>
<tr>
<td>3,4-methylenedioxyamphetamine (MDMA)</td>
<td>USP</td>
<td>125</td>
<td>mg</td>
<td>Capsule</td>
<td>Yes</td>
</tr>
<tr>
<td>Same as above</td>
<td>USP</td>
<td>62.5</td>
<td>mg</td>
<td>Capsule</td>
<td>Yes</td>
</tr>
<tr>
<td>Same as above</td>
<td>USP</td>
<td>20</td>
<td>mg</td>
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<td>USP</td>
<td>12.5 mg</td>
<td>mg</td>
<td>Capsule</td>
<td>Yes</td>
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56. Non-medicinal ingredient(s) (include colouring agents)

A) Preservative(s)

<table>
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<th>Units</th>
<th>Per</th>
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<tbody>
<tr>
<td>None</td>
<td>NA</td>
<td>N/A</td>
<td>NA</td>
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B) Colouring Agents

<table>
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<tbody>
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<td>None</td>
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C) Other

<table>
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<th>Strength</th>
<th>Units</th>
<th>Per</th>
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<tr>
<td>Lactose (to maintain identical capsule weights)</td>
<td>Approx 100</td>
<td>mg</td>
<td>capsule</td>
<td></td>
</tr>
<tr>
<td>Same as above</td>
<td>Approx 50</td>
<td>mg</td>
<td>capsule</td>
<td></td>
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57. Dosage Form: **Opaque capsule**
58. Container Type: 36 individual bottles containing initial and supplemental dose; no take-home doses
Package Size: Bottle with two capsules

59. Therapeutic/Pharmacological Classification: Monoamine releaser and uptake inhibitor, entactogen

60. Route(s) of Administration: Oral

61. Drug Product: 9 Biological/Radiopharmaceutical 9 Pharmaceutical 9 Natural Health Product 9 Drug & Medical Device

62. Drug Use: 9 Human

63. Proposed Indication/Use: For use as an adjunct to psychotherapy for people with posttraumatic stress disorder, to be administered within the context of an extended psychotherapy session.

64. Proposed Dosage (include maximum daily dose): One initial dose (experimental dose = 125 mg, active placebo = 25 mg) possibly followed by one supplemental dose (experimental dose = 62.5 mg, active placebo = 12.5 mg). Maximum dose per session = 187.5 mg. No take-home or daily doses.

65. Draft of Proposed Canadian Label enclosed?: 9 No Package Insert enclosed?: 9 No

66. Rationale for all SNDS, SANDS (all human drug types), SABNDS (veterinary drugs), or for biological drug DIN submissions

67. Type of Notifiable Change (NC) submission if applicable: human drugs only

| Change in expiry period/storage conditions | Change in packaging material composition |
| Change in formulation                      | Change in packaging specifications for parenteral/inhalation drug |
| Change in manufacturing method             | Change in container size for parenteral drug |
| Change in manufacturing site               | Change in specifications (medicinal or non-medicinal ingredient, pharmaceutical form, analytical method) |
| Change in text of labelling                | Other (specify) |

Complete Sections 68 - 70 for Veterinary Products only

68. Species and Subtypes Recommended for use

69. Used for treatment of food-producing animals?: 9 Yes 9 No

70. Withdrawal Time

<table>
<thead>
<tr>
<th>Species</th>
<th>Days</th>
<th>Hours</th>
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<td></td>
<td></td>
</tr>
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</table>

I, the undersigned, certify that the information and material included in this drug submission application is accurate and complete.

71. Name of Authorized Signing Official
Rick Doblin PhD

73. Date

<table>
<thead>
<tr>
<th>YYYY</th>
<th>MM</th>
<th>DD</th>
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<tbody>
<tr>
<td>2023</td>
<td>12</td>
<td>12</td>
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</table>

74. Title: President, MAPS

75. Telephone No.
617-484-8711

76. Fax No.
617-484-8427

77. Name of Company to which the Authorized Signing Official Belongs: Multidisciplinary Association for Psychedelic Studies (MAPS)

---

1. IF THE SIGNING OFFICIAL IS A THIRD PARTY ACTING ON BEHALF OF THE MANUFACTURER/SPONSOR COMPANY IDENTIFIED IN SECTION 11, A LETTER OF AUTHORIZATION, SIGNED BY THE MANUFACTURER/SPONSOR COMPANY (SECTION 11), MUST BE FILED WITH THE COMPLETED SUBMISSION APPLICATION FORM, E.G., APPENDIX 2.
APPENDIX 1 - for Clinical Trial Applications and Amendments only

TEMPLATE AUTHORISATION FOR A THIRD PARTY TO IMPORT THE NEW DRUG DESCRIBED IN THIS CLINICAL TRIAL APPLICATION OR AMENDMENT

I. [Name] 
[Position]
[Organisation]

authorize

[Name]
[Position]
[Organisation]

to import the new drug for the purposes of the clinical trial described within this application.

Signed:

Print name:

Title:

Clinical Trial Sponsor:

Date:

---

3 SUBMIT WITH APPLICATION ONLY IF THE CLINICAL TRIAL SPONSOR IS LOCATED OUTSIDE OF CANADA AND IS AUTHORIZING ONE OR MORE THIRD PARTIES TO IMPORT THE NEW DRUG FOR THE PURPOSES OF THE CLINICAL TRIAL DESCRIBED WITHIN THIS APPLICATION. A SEPARATE AUTHORISATION IS REQUIRED FOR EACH CLINICAL TRIAL APPLICATION AS ADDITIONAL IMPORTERS ARE IDENTIFIED. ADDITIONAL COPIES OF APPENDIX 1 SHOULD BE PROVIDED TO HEALTH CANADA. IF THE IMPORTER HAS NOT CHANGED WHEN A CLINICAL TRIAL APPLICATION AMENDMENT IS FILED, APPENDIX 1 DOES NOT NEED TO BE RE-SUBMITTED.
<table>
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<tr>
<th>78. Clinical Trial Protocol Number (if assigned) M-P4</th>
<th>79. Clinical Trial Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>80. Anticipated Clinical Trial Composition (check all that apply):</td>
<td>81. Phase of Clinical Trial (check appropriate box):</td>
</tr>
<tr>
<td>9 Pediatric population (0-18 years of age) / Females / Males</td>
<td>9 Phase I - bioequivalence study (7 day administration target) / Phase I - study in healthy humans (7 day administration target) / Phase I - other (30 day default) / Phase II (30 day default) / Phase III (30 day default) / Other - specify.</td>
</tr>
</tbody>
</table>

82. Information regarding Research Ethics Board that has refused to approve the protocol and/or informed consent form enclosed:
- Yes
- No
- Not Applicable
- Not known at this time

83. Clinical Trial Site Information Form enclosed for all sites known at time of application:
- Yes
- No
- Not Applicable

84. Investigator's brochure enclosed:
- Yes
- No

85. Information regarding human- and/or animal-sourced recipients enclosed:
- Yes
- No
- Not Applicable

86. Quality (chemistry & manufacturing) information enclosed:
- Yes
- No
- Not Applicable - product has received Notice of Compliance and the Drug Identification Number (DIN)

In respect of the clinical trial identified in Appendix 3 of this form we certify that:

1. The information and material contained in, or referenced by, this application are complete and accurate and are not false or misleading.
2. If requested by Health Canada, additional information or samples required to assess this application will be provided within two days following receipt of the request from Health Canada.
3. The clinical trial will be conducted and the drug used in accordance with the protocol and the requirements set out in Division 3 of the Food and Drug Regulations. The clinical trial will be conducted in accordance with good clinical practices.
4. The trial will not commence at any site until receipt of a No Objection Letter from the Therapeutic Products Directorate or the Biologies and Genetic Therapies Directorate of Health Canada, or 30 calendar days following receipt of the application by Health Canada, whichever comes first.
5. Records will be maintained for a period of 25 years and will be accessible for on-site inspection by Health Canada Inspectors.

<table>
<thead>
<tr>
<th>87. Senior Medical Officer or Scientific Officer in Canada</th>
<th>88. Tel. No.</th>
<th>89. Signature</th>
<th>90. Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingrid Pacey MBBS FRCP(C)</td>
<td>604-732-9309</td>
<td></td>
<td>YYYY MM DD</td>
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<td></td>
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<td>2008 01 22</td>
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<table>
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<tr>
<th>91. Senior Executive Officer</th>
<th>92. Tel. No.</th>
<th>93. Signature</th>
<th>94. Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rick Dubin PhD</td>
<td>617-494-8711</td>
<td></td>
<td>YYYY MM DD</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2006 05 27</td>
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</table>
QUALIFIED INVESTIGATOR UNDERTAKING

An undertaking must be completed by the qualified investigator responsible for the conduct of the clinical trial at the site specified below. The completed undertaking must be retained by the clinical trial sponsor for a period of 25 years.

Please note that the Qualified Investigator Undertaking should not be submitted to Health Canada unless requested.

### PART 1 - Clinical Trial Protocol Information

Please check one of the following:
- Clinical Trial Application (CTA)
- Clinical Trial Application Amendment (CTA-A)

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

2. Clinical Trial Protocol Number (If Applicable)
   M-P4

### PART 2 - Drug Product / Sponsor Information

#### A) Drug Product Information

3. Brand Name **None: see below**

4. Proper or Common Name: (+/-)-3,4-methylenedioxymethamphetamine (MDMA)

#### B) Sponsor of Clinical Trial

5. Company Name (Full Name - No Abbreviations)
   Multidisciplinary Association for Psychedelic Studies

6. Street / Suite / PO Box
   3 Francis St.

7. City / Town
   Belmont

8. Prov. / State
   MA

9. Country
   USA

10. Postal/ZIP Code
    02478-2218

#### C) Contact for THIS Clinical Trial

11. Contact Name: Rick Doblin Ph.D

12. E-mail: Rick@maps.org

13. Company Name (Full Name - No Abbreviations)
   Multidisciplinary Association for Psychedelic Studies

14. Street / Suite / PO Box
   3 Francis St.

15. City / Town
    Belmont

16. Prov. / State
    MA

17. Country
    USA

18. Telephone No.
    617-484-8711

19. Fax No.
    617-484-8427

20. Postal/ZIP Code
    02478-2218

Qualified Investigator Undertaking (01-03)
### PART 3 - Qualified Investigator Information

#### A) Clinical Trial Site

<table>
<thead>
<tr>
<th>21. Name of Site (Full Name - No Abbreviations)</th>
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</table>

<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>Vancouver</td>
<td>BC</td>
<td></td>
</tr>
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</table>

#### B) Qualified Investigator

<table>
<thead>
<tr>
<th>26. Name: Ingrid Pacey MBBS FRCP(C)</th>
<th>27. Title: Psychiatrist</th>
<th>28. Language Preferred:</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>29. Street / Suite / PO Box</th>
<th>30. City / Town</th>
<th>31. Province</th>
<th>32. Postal Code:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3369 West 4th Ave.</td>
<td>Vancouver</td>
<td>BC</td>
<td>V6H 1N6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>33. E-mail</th>
<th>34. Tel. No.</th>
<th>35. Fax No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>604-732-9369</td>
<td>604-733-6951</td>
</tr>
</tbody>
</table>

---

In respect of the identified clinical trial, I certify, as the qualified investigator for this site that:

1. I am a physician or dentist and a **member** in good standing of a professional medical or dental association as defined in Part C Division 5 of the *Food and Drug Regulations*;

2. I will supervise the medical care and medical decisions respecting this clinical trial at this site;

3. I will conduct this clinical trial in accordance with Good Clinical Practices; and

4. I will immediately on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the Research Ethics Board for this site of the discontinuance, provide them with the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons.

#### Signature of Qualified Investigator

**Signature**

<table>
<thead>
<tr>
<th>37. Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>YYYY M D</td>
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<tr>
<td>08 12 6</td>
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Qualified Investigator Undertaking (01-03)
(+-)-3,4-methylenedioxymethamphetamine
(MDMA, “Ecstasy”)
Investigator’s Brochure
Lisa Jerome Ph.D
December 2007
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Preface

In 2001, Baggott, Jerome and Stuart collaborated on a comprehensive review of the literature concerning 3,4-methylenedioxymethamphetamine, or MDMA (Baggott et al. 2001). After writing this monumental work, three additional reviews were created to assist and support the Multidisciplinary Association for Psychedelic Studies (MAPS), first by Jerome and Baggott in 2003, and then Jerome in 2004 and 2005 (Jerome 2004; 2005; Jerome and Baggott 2003). As the amount and pace of research accelerated, and after gaining more knowledge about investigator’s brochures, the present author (Jerome) concluded that information on MDMA should be presented in a more accessible and compact format. Fortuitously, a number of excellent reviews of nearly all aspects of MDMA have appeared in the past four years, making the task of summarizing and presenting this research easier. As in all previous documents, this brochure is based on literature located through the electronic database PubMed, examining relevant journals and communication with researchers. With the exception of some information on ongoing studies and conference presentations, most of the information has been drawn from reports appearing in print or electronic editions of relevant journals.

This document is intended to encapsulate the current state of our knowledge concerning MDMA, especially as it pertains to humans. Rather than follow the format of its predecessors, this document will follow the outline used for recently created investigator’s brochures for LSD and psilocybin. There will be a greater focus on proposed mechanisms of action, cataloguing acute physiological, behavioral and therapeutic effects in humans, and information on planned or ongoing use in medical settings. Readers interested learning more about MDMA or specific areas are strongly encouraged to read reviews by Cole and Sumnall, Dumont and Verkes, Laws and Kokkalis, Zakzanis and others on the pharmacology, acute and potential long-term effects and risks of MDMA and ecstasy, with ecstasy defined here as material represented as containing MDMA (Baylen and Rosenberg 2006; Cole and Sumnall 2003a; b; Dumont and Verkes 2006; Green et al. 2003; Guillot 2007; Laws and Kokkalis 2007; Sumnall and Cole 2005; Zakzanis et al. 2007).

New Developments

Three major developments have transformed our understanding of previous and current findings in the area of MDMA research since the last update of the literature review. The first development affects interpretation of nonhuman animal studies, and the second development relates to our understanding of the presence and degree of long-term effects of ecstasy use. The third development relates to primate studies examining the impact of ambient temperature on the effects of MDMA on body temperature.

MDMA research and Interspecies Scaling

Up until as recently as 2006, investigations of the pharmacology, functional effects or toxicity of MDMA in nonhuman animals injected large and often repeated doses of MDMA (see Baggott et al. 2001). Some of the earliest research used high doses in order to study mechanisms of neurotoxicity. Most researchers continued to employ these doses, and some later explained these dosing regimens in terms of using interspecies scaling to
The Netherlands XTC Toxicity (NeXT) Studies

A team of researchers in the Netherlands embarked upon an ambitious program of research that included prospective studies of people who planned on using ecstasy in the future (De Win et al. 2005). Participants expressing interest in using ecstasy were assessed prior to use. After some reported their first use of ecstasy or soon afterwards, the team assessed these participants as well as another group that had not yet used ecstasy. The researchers studied brain activity, estimated brain serotonin transporter (SERT) sites, neurochemical markers of brain injury, working memory, and cognitive function including verbal memory. These studies are unique in their examination of people before and after drug self-administration rather than making cross-group comparisons between ecstasy users and non-user controls. Hence findings from these prospective studies far more relevant to examining risks and benefits in human MDMA studies than the majority of previous work. In general, studies from this research program failed to find any long-term effects of low to moderate ecstasy use. They did not find any changes in serotonin uptake sites nor chemical markers of brain injury, and they found only minor region-specific changes in cerebral blood volume (de Win et al. 2007; de Win et al. 2006; Jager et al. 2007b). While an examination of change scores before and after use indicated greater improvement in non-users than in ecstasy users, they failed to find impaired working memory after low ecstasy use (Jager et al. 2007b; Schilt et al. 2007). There are a number of problems with this research, including use of change scores and the inclusion of an individual whose ecstasy use was considerably greater than others in the cognitive

arrive at human-equivalent doses. Interspecies scaling is a pharmacological model intended to account for species-specific differences in metabolism (Mahmood and Balian 1996; Mordenti and Chappell 1989). However, interspecies scaling assumes that the target compound has linear pharmacokinetics, and requires data from at least two species to arrive at human-equivalent doses. Findings first reported in humans and later in monkeys (de la Torre et al. 2000; Mechan et al. 2006) demonstrate that MDMA has nonlinear pharmacokinetics, with larger doses producing greater increases in blood MDMA levels than would be expected from linear pharmacokinetics. Furthermore, contrary to earlier reports that found that route of administration had no impact on plasma MDMA levels (Finnegan et al. 1988; Ricaurte et al. 1988), a recent study of MDMA in monkeys found that sub-cutaneous doses produced higher peak plasma MDMA levels than intra-gastric administrations (Mechan et al. 2006). Some recent reports describe findings suggesting that even the doses of MDMA employed in rodent studies are inappropriately high (Baumann et al. 2006; Wang et al. 2005), though see work by Xie and colleagues (Xie et al. 2006). After examining these recent findings, it appears that much of the previous research in nonhuman animals has used inappropriately high doses of MDMA, and this occurred not only in studies of MDMA neurotoxicity, but also in studies of behavioral or pharmacological effects. Studies conducted subsequent to the discovery began employing mg/kg doses similar or identical to those used by humans (e.g. Taffe et al. 2006; Von Huben et al. 2006). Most drug-discrimination and self-administration studies in rodents (De La Garza et al. 2007) have employed and continue to employ doses identical or similar to those used by humans. However, the discoveries concerning the inadequacy of interspecies scaling mean that findings from the majority of previous studies must be considered with caution.

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function assessment. However, despite these findings, the general picture from the NeXT studies is that low to moderate ecstasy use produces very few long-term effects and is not comparable to effects found after heavy use of ecstasy and other drugs.

No Interaction between MDMA and Ambient Temperature on Human Body Temperature

To date, the only novel and relevant finding from human MDMA studies is a study that sought to detect an interaction between MDMA and ambient temperature on human body temperature after 2 mg/kg MDMA (Freedman et al. 2005). Freedman and colleagues found that human body temperature was unaffected by the combination of MDMA and ambient temperature, and that the desirable effects of MDMA are not increased by warm ambient temperature (Freedman et al. 2005). One of two research teams reached similar conclusions in rhesus monkeys (Crean et al. 2006; Von Huben et al. 2006).

1. Drug Substance and Formulation

(+/-) 3,4-methylenedioxymethamphetamine (MDMA, 3,4-methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyamphetamine, ) has the chemical formula of C$_{11}$H$_{15}$NO$_2$. It is a phenylisopopylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in 1912 as an intermediate chemical involved in the production of the styptic hydrastinine (Freudenmann et al. 2006). No significant investigations examined the pharmacological, physiological or psychological effects of MDMA until the 1950s, when the US Army administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991), and there are records of a police seizure of MDMA in the early 1970s that suggests either intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Some have estimated that up to 4000 people underwent MDMA-assisted psychotherapy in North America prior to its placement in Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001). However, none of the therapists conducted controlled studies or published any formal descriptions or analyses of MDMA-assisted therapy at this time. Therapeutic use continued up until its placement in US Schedule 1 in 1986 (Adamson 1985; Greer and Tolbert 1998; Stolaroff 1997). During the early 1980s, increasing numbers of people began using MDMA outside the therapeutic context (Beck and Rosenbaum 1994). The first wave of non-medical use occurred not only in dance clubs but in small groups of people, in a self-exploratory or spiritual context or while attending concerts. Non-medical use continues today in the same contexts (Carlson et al. 2004; Sumnall et al. 2006).

A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986; Greer and Tolbert 1986), including Greer and Tolbert’s study of MDMA in a
psychotherapeutic context. However, controlled human studies of MDMA did not commence until early to mid-1990s, with the publication of research conducted by Grob and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006; Mithoefer 2006; Oehen 2006).

Many researchers categorize MDMA as belonging to a unique class of drugs, the entactogens (Nichols 1986; Vollenweider et al. 1998a), of which it is considered the first identified member, and perhaps a prototype of the class. Entactogens are reported to produce changes in mood, social interactions or feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens (Cami et al. 2000; Gouzoulis-Mayfrank et al. 1999; Liechti et al. 2001b; Tancer and Johanson 2003), but it also appears to possess qualities it shares in common with a small number of related compounds, as methylenedioxymethylamphetamine (MDE) (Gouzoulis-Mayfrank et al. 1999).

Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy (Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). To date only two controlled studies have sought to measure these effects (Farre et al. 2007; Harris et al. 2002). Although researchers have offered several models and explanations for the source of entactogenic effects, it appears that release of serotonin plays a significant role in producing at least some of these effects. Indirect action on 5HT$_{1A}$ or 5HT$_{2A}$ receptors, and neuroendocrine responses, as increases in the hormones oxytocin, vasopressin and cortisol may also play a role in producing the unique effects of MDMA.

2. Pharmacological and toxicological effects

**Overview**

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear.

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