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

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

P.3.3 Batch Formula

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

Clear 03 gelatin capsules will be filled with the appropriate dose of MDMA.
Full initial dose: 125 mg + 113.5 mg lactose
Full supplemental dose: 62.5 mg + 174.1 mg lactose
Active Stage 2 initial dose: 100 mg + 143.0 mg lactose
Active Stage 2 supplemental dose: 50 mg + 184.9 mg lactose
Comparator initial dose: 50 mg + 184.9 mg lactose
Comparator supplemental dose: 25 mg + 211.0 mg lactose
Optional titration to add to active initial dose: 25 mg + 211.0 mg lactose
Optional titration to add to active supplemental dose: 12.5 mg + 359.2 mg lactose

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

P.4 Control of Excipients

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

The lactose used will be

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

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

P.7 Container Closure System

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

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

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

A Attachments:

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

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

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

Modules 2 and 3: Common Technical Document Summaries and Quality

Study Title:
A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada
Amendment 1 Version 2
Sponsor: Multidisciplinary Association for Psychedelic Studies
Principal Investigator: Dr. Ingrid Pacey MBBS FRCP[C], Research Affiliate, CARBC, University of Victoria
Study Number: M-P4
Control # 167090 Parent CTA Control # 127822

Quality Overall Summary and Referenced Documents

Health Canada / Santé Canada

Office of Clinical Trials

Screening Template for CTA-A

CR File #: **9427-M2544-21C**	DSTS Control #: **167090**
Date received in OCT : 2013.08.02 Review 1 Start Date: **2013.08.08**	Due Date: **2013.09.07**
Study Phase: Phase II (30 day)	Data Description: CL/2VO/ICD
Study Population: Males and Females	Clinical Division: Vol 1
Document I.D. #: 847977	Quality Division: Vol 2

RECEIVED AUG 12 2013

Attached Documents: ☐ SOAD Form ☐ CTSI Form ☐ Other:

Product Name : **MDMA**

Protocol # or Identifier: **MP-4**

Amendment type: **Amendment # 1 to Protocol # MP-4 (Version 2) and Quality Amendment**

Therapeutic/Pharmacological Classification: Monoamine releaser and uptake inhibitor / for the treatment of Post-Traumatic Stress Disorder **[Clinical Group II: CNS]**

Sponsor Name : **MULITDISIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES** | Country: USA

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

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

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

N. Widmer

Natasha Widmer - Screening Officer

B. Wiatrowska

Assessment Officer

2013.08.06 / 2013.08.09

Screening start date / Completion date

12/08/2013, 15 hours

Assigned date / Review Hours

Health Canada / Santé Canada

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

Your file *Votre référence*

Our file *Notre référence*

12 August 2013

9427-M2544-21C

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

ACKNOWLEDGMENT
CLINICAL TRIAL AMENDMENT

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

Dear [redacted]

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

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

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

Yours sincerely,

Natasha Widmer
Submission Screening Officer
Office of Clinical Trials

NW/en

Canada

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

Show Details

Received:
2013.08.08
- NAW

History: This message has been replied to.

Dear Natasha
With Regards to clinical trial amendment application:

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

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

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

1) Quality Amendment

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

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

Best Regards

of Clinical Research
MAPS
1215 Mission St.
Santa Cruz CA 95060

Mobile
@maps.org
.maps@gmail.com
www.maps.org

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

Good afternoon Amy Emerson,

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

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

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

1) You have recorded in the submitted Drug Submission Application (HC-SC 3011) form, three new strengths (100 mg, 50 mg, and 25 mg), which were not recorded on the initial form submitted with CTA control # 127822. Additionally, the 20 mg strength is no longer recorded.
If the Drug Products being used in this trial have changed, a Quality Amendment will be required for these new dosage forms. Therefore:

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

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

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

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

Kind regards,

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

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

Health Canada Santé Canada

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

Your file *Votre référence*

Our file *Notre référence*

9427-M2544-21C

17 March 2009

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

No Objection Letter RE: Protocol # MP-4

Dear Dr. Doblin:

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

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

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

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

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

Yours sincerely,

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

EK/en

Canada

Health Canada Santé Canada

Canada

Hea[illegible]roducts and Food Branch
Direc[illegible]on générale des produits de santé et des aliments

REQUEST FOR ADDITIONAL INFORMATION

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

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

Organization/Organisme: MAPS

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

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

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

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

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

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

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

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

Comment:
Re: Informed consent:

1. I e correct in the addiction section the time-frame for people who recently had problems with drug abuse, from 30 days to 6 months.

2. Re: possible brain damage section: Please explain in simple terms what was the "small change" that was seen in the brain scans of people who took ecstacy in recreational setting

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

Yours sincerely,

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

Health Canada / Santé Canada

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

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

Type of Submission / Phase of Trial	CTA	
Target Date	18/03/09	
Control Number / File Number	127822	9427-M2544-21C

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

MANAGER		
Decision / Date	Agree with above recommendation.	
Manager's Name	Dr. E. Komsta	Mar 17/09
Manager's Signature		

Canada

1. INTRODUCTION

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

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

Email Address	

2. INVESTIGATOR'S BROCHURE

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

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

Study Synopsis
A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects
with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada
Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Study Number: MP-4
Principal Investigator: Ingrid Pacey MB BS FRCP[C]
Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD
Expected Study Dates Jan 2009-April 2010
Approved by: IRB Services, BC Committee, November 5, 2008

Background and Rationale

Background: This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems.

PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population
of the US. To date the treatment of PTSD has primarily been psychotherapeutic, the effect size for psychotherapy being higher than for psychopharmacologic treatment. Cognitive behavioral therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD [4]. However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

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

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

rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of
extensive non-medical use [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.
There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e. g.16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22]. In

contrast, all available Phase I and Phase 2 data indicate that it is unlikely that the MDMA
exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Recent retrospective and prospective
studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no
attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity.
Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in
the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity"
[8]. Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some
clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity
for a corrective emotional experience [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25].
The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others. Though the

psychopharmacology and neuropsychological underpinnings of the therapeutic effects of
MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli.
Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the primary outcome measure, with PTSD symptoms measured by a blinded, independent assessor at baseline, a week after each experimental (MDMA or placebo) session, and two months after the final experimental session. To date, all participants in this study have tolerated MDMA, and preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo. A recent analysis conducted by the independent rater detected a significant decline in CAPS score in the MDMA condition when compared with placebo [28]. A one-year+ follow-up study is currently underway.
Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be an innovative treatment
for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.

Trial Objectives

Primary Efficacy and Safety Objectives: The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) session.
The investigators will also gather information on physiological effects and side effects after MDMA.
Secondary Objectives: The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

The proposed pilot study will employ a randomized, double-blind, active placebocontrolled
design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of
125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA

1.5 to 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or
active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.
Symptoms of PTSD and depression will be assessed by an independent assessor who will
be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third
double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via
Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.
Participants in the active placebo condition will have the opportunity to enroll in an openlabel
study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression

symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.
The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the
study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.
The randomized, double-blind, active-placebo controlled study segment will last approximately four months from screening and baseline evaluation up until the evaluation six weeks after the third experimental session.
The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy session, for a
total of about 8 months.

Number of Centres

List of Investigators

Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She is a practicing psychiatrist in Vancouver, BC. She has worked as a psychiatrist for 36 years. She has a private practice in Vancouver, BC. She has performed Holotropic Breathwork,
a therapeutic breathing practice capable of producing alterations in consciousness, in people with PTSD. She will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.
Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. Andrew Feldmár, M.A., has practiced psychotherapy as a psychologist for almost 40 years in Vancouver, Canada. He has given workshops, lectures and seminars on psychotherapy and topics of psychotherapeutic interest. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She

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

Sample Size

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

Patient Population (Target population)

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

Inclusion Criteria

Participants who meet the following criteria will be considered for inclusion in this study:
1. Participants must meet DSM IV criteria for current PTSD. They must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must either:
a. have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI) and one unsuccessful treatment with any form of psychotherapy for which there exist a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety

management, and insight-oriented psychotherapy, and eye movement desensitization (EMDR) [5, 29-31]. Treatment with an SSRI must have lasted for at least three months, or the participant must have refused to take SSRIs. Psychotherapy must have lasted for six months and included at least twelve sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.

b. Be a veteran who meets all criteria listed above in 2a and with PTSD symptoms that have persisted for no longer than ten years.

3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because there is marked frequency of co-existence of other psychiatric disorders among people with PTSD [32, 33].

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

5. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If they are being treated with psychoactive drugs at the time they are recruited into the study, the prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, and will be required to give Dr. Pacey permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). No new medications may be started until after the evaluation session, which will occur six weeks after the third experimental session. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.

6. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. They must sign a release if they want to permit the investigators to communicate directly with their therapist. They may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session six weeks after the third experimental session.

7. Participants must agree that, for one week preceding each MDMA/placebo session:

a. They will refrain from taking any herbal supplement (except with prior approval of the research team).

b. They will not take any nonprescription medications (with the exception of nonsteroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).

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

medications approved by the research team).
8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.
9. Participants must be willing to remain overnight at after each experimental session until the non-drug session occurring the next morning. An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. Pacey at the request of the participant or if there are signs that the participant is under physical or psychological distress. At the participant's request and with Dr. Pacey's approval, a significant other can

remain with the participant for support between the end of the experimental session and the non-drug session the next morning.
10. Participants will be asked to locate an individual willing to drive them home the morning after the experimental sessions, after the non-drug therapy session. If a participant is unable to locate someone to transport them home, the investigators will assist the participant in obtaining transport from the clinic to the participant's home or any other location where he or she is staying temporarily.
11. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
12. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
13. Participants must be literate. They must be proficient in reading documents written in English.

Exclusion Criteria

Prospective participants will be excluded from the study if they have the following conditions or characteristics:
1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. People with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).

5. People with hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions [34], peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. People weighing less than 48 kg
7. People with prior use of "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
8. People who would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, with suicide risk ascertained via face to face interview and and through the use of the Adult Suicidal Ideation Questionnaire (ASIQ).
9. People requiring ongoing concomitant therapy with a psychotropic drug.
10. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 6 months.
11. Any person who is not able to give adequate informed consent.

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Drug Formulation

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

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in other MAPS-supported studies of MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy
performed prior to the scheduling of MDMA in the US [14, 27, 35]. The supplemental dose is also identical to the one used in the US study. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental
dose will prolong subjective effects without producing physiological effects any greater than peak effects occurring after the initial dose.
Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [36, 37] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [37].
As described above, capsules containing the initial dose of MDMA will be administered at approximately 10:00 AM. Supplemental doses will be administered upon mutual agreement by the investigators and participant one and a half to two and a half hours after the initial dose. There will be no take-home doses. The investigators may decide not to administer the supplemental dose of MDMA if they

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

Washout Period

Participants taking psychiatric medications will undergo a medication-appropriate washout period beginning upon study entry and lasting for at least five times the medication half-life before an experimental session. Participants who undergo medication
washout will have PTSD and depression symptoms assessed again after completing the
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washout. This is to ensure that an appropriate comparison will be made between baseline
symptoms of PTSD and symptoms six weeks after the third experimental session, when individuals will be medication-free. The first experimental session cannot occur until after a participant has completed medication washout.

Pre-study Screening and Baseline Evaluation

Participants will undergo medical and psychiatric screening after giving written informed consent take part in the study. Screening will include medical history and physical examination, psychiatric interview, including administration of the SCID, for diagnosis of included and excluded psychiatric disorders, assessment of suicide risk via face to face
interview and assessment with the ASIQ, urinary drug and pregnancy screening, and baseline CAPS administration by the independent rater. Medical screening will also include a blood draw for performance of standard laboratory measures of liver function, thyroid function and metabolism, and an electrocardiogram to assess heart function. The
independent rater will administer the CAPS after undergoing medical and psychiatric examinations. If participants continue to meet all study criteria without meeting any exclusionary criteria, they will be enrolled in the study.
Upon enrollment, participants will undergo baseline evaluation. CAPS, PDS and BDI scores from screening evaluation will serve as baseline measures of symptoms of PTSD
and depression in all cases except those of participants who underwent screening while still taking psychiatric medication, as described above.
Upon enrollment into the study, each participant will be randomly assigned to one of two conditions, active placebo or experimental dose. Each participant has a 66.6% chance of
assignment to the experimental dose condition and a 33.3% of assignation to the active placebo condition. This study will employ a blinded adaptive randomization procedure in order to maintain the 66%/33% ratio while maintaining the blind and ensuring that each

subsequent condition assignment is not predicated on the previous assignment. A randomization monitor will generate and maintain a list of random numbers between one
and 100, and this individual will have charge of maintaining randomization procedures. A
randomization list will be run to assign random numbers from one to 100 and either experimental dose or active placebo dose MDMA (125 and 62.5 or 25 and 12.5 mg) MDMA to 12 prescription bottles. The investigators will contact the randomization monitor after enrolling a participant, and the randomization monitor will select a number from amongst the set of 12 numbers, represented as cards or other indicators, thus providing the investigators with the bottle number to be used for the participant. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken
for an individual participant.

Treatment Visits

After baseline assessment, the study will consist of twelve 60 to 90 minute "conventional" or non-drug augmented psychotherapy sessions and three experimental

sessions of MDMA-assisted psychotherapy, and two assessments of symptoms of PTSD
and depression. The investigators will break the blind individually for each participant after the assessments six weeks after the third experimental session.

Participants who learn they are assigned to active placebo can enroll in the open-label study segment. The sequence of events and procedures in Stage 2 is nearly identical to that of Stage 1 except that participants undergo one and not three introductory psychotherapy sessions and all three MDMA-assisted psychotherapy sessions are openlabel.

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

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

Experimental Sessions: All participants will receive three double-blind experimental sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Each experimental session will last approximately eight hours. Experimental sessions will be conducted by the male and female co-therapist team. Procedures for MDMA-assisted psychotherapy will remain the same across all sessions, and all procedures except drug dose will be the same for participants assigned to the full dose and active placebo

condition.

Participants will arrive [redacted] approximately one hour before drug administration for collection of a urine specimen for drug and pregnancy screening. If drug screening results are negative and pregnancy test is negative or not applicable and

the participant reports that he/she followed appropriate rules and restrictions, then the session will proceed. Before administering MDMA, the therapists and participant will discuss and review the participant's goals, intentions and concerns and some of the commonly experienced effects of MDMA. Participants will complete the Subjective Units of Distress (SUD), a single-item measure of degree of psychological distress, just prior to initial dose administration. At approximately 10:00 AM, participants will receive the initial dose of MDMA along with a glass of water. The initial dose will either be 25 or 125 mg MDMA in accordance with condition assignment, and the dose will be administered in a double-blind manner. The supplemental dose will always be one half (1/2) the initial dose and will be administered between 1.5 and 2.5 hours after the initial dose.

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Time and Events for Randomized Study segment

Table 1: Schedule of Events for Randomized study Segment

Time and Events M-P4 Baseline and Screening Therapy and Evaluation 2 Therapy and Evaluation 3
Visit # V1 V2 V3 V4 V5 V6 V7 V8 V9 V10 V11 V12 V13 V14 V15 V16 V17 V18 V19 V20
Type of Visit Prestudy Consent
Screening/Baseli
ne
Intro
Psychotherapy
Intro psychotherapy2
Intro
psychotherapy3
Experimental 1
Integrative
Therapy1
Integrative Therapy2 Integrative Therapy3 Experimental 2
Integrative
therapy4
Integrative Therapy5
Integrative
Therapy6
Experimental 3
Integrative
Therapy 5
Integrative Therapy6
Integrative
Therapy7
6 wk post V11
End Randomized
Segment
Approximate Study Day
0 7 14 21 28 29 35 42 49 50 56 63 70 71 78 85 112 113
Visit Timing and Windows Post telephone
(Post-consent,
may be same day
(-4/+3 d) Post V4 Post V5 post V6
24 h post-experim.
session 1
Between V6 and V11 Post-V9 >3<5 wks post V6 24 h post V11 Post V11 Post V13 >3<5 w post V11" 24 h post V15 Post V15 Post V17 6 wk post V15
May be same day as
V19
Study Staff Ingrid/Andrew Ingrid/Andrew
Physician,
Ingrid/Andrew, IA
Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid/Andrew, IA Ingrid/Andrew
Telephone Screening X
Provide consent materials X
Study informed consent X
Medical Examination X
ECG X
Liver FCT X
Drug Screen X X X X
Pregnancy Screen X X X X
Psychiatric examination X
SCID X
Baseline evaluation X
CAPS X X
PDS X X
BDI X X
RBANS X X
PASAT X X
Study Enrollment X
Record to audio & video X X X X X X X X X X X X X X X
Psychotherapy-No Drug X X X X X X X X X X X X
General Well-Being X X X X X X X X X
Administer MDMA X X X
Psychotherapy + MDMA X X X
Administer higher dose MDMA
Blood Pressure X X X X
Pulse X X X X
Body Temperature X X X
SUD X X X
Common Side Effects X X X X
Overnight stay X X X X
Serious Adverse Events X X X x X X X X X X X X X X
Adverse Events Requiring Dr

Visit X X x X X X X X X X X
Unblinding X
Consent for Stage 2/open-label X
RRPQ X
End Randomized phase X
IA=Independent Assessor
*=Optional & for nonresponders only
Therapy and Evaluation 1

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Time and Events for Open-Label Study Segment after Randomized Study for Active Placebo Participants

Visit # 20 V21 V22 V23 V24 V25 V26 V28 V29 V30 V31 V32 V33 V34 V35 V36 V37
Type of Visit Consent "Baseline"
Review/Intro
Therapy
Open-Label 1
Integrative
Therapy8
Integrative
Therapy9
Integrative
Therapy10
Open-Label 2
Integrative
therapy11
Integrative
Therapy12
Integrative
Therapy13
Open Label 3
Integrative
Therapy14
Integrative
Therapy15
Integrative
Therapy16
6 wk post Open-
Label 3
End Stage 2
Approximate Study Day 112 113 120 127 128 135 142 149 150 157 164 171 172 179 186 213
Visit Timing and Windows On/Post V15 On/Post V19 Post V16 Post V17
24 h post Open
Label 1
Between V24
and V28
Post V25
"=>3<5 wks post
V23"
24 h post Open
Label 2
Between V29 and
V32
Post V30
"=>3<5 wks post
V28"
24 hours post
Open Label 3
Between V33
and V36
Post V34 6 wk post V32
Study Staff Ingrid/Andrew
Karen,
Andrew/Ingrid
Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Andrew Ingrid+Amdrew
Ingrid+Andrew
Ingrid/Andrew,
Karen
Ingrid/Andrew
Telephone Screening
Provide consent materials X
Study informed consent X
Medical Examination
Liver FCT
Drug Screen X X X X
Pregnancy Screen X X X X
Psychiatric examination X
SCID
Baseline evaluation X
CAPS X X
PDS X X
BDI X X
RBANS X
PASAT X
Study segment enrollment X
Psychotherapy-No Drug X X X X X X X X X X

General Well-Being X X X X X X X X X X x
Administer MDMA X X X
Psychotherapy + MDMA X X X
Administer higher dose MDMA X*
Blood Pressure X X X
Pulse X X X
Body Temperature X* X* X*
SUD X X X
Common Side Effects X X X X X X
ASIQ X X X
Overnight stay X X X
Serious Adverse Events X X X X X X X X X X X X X X
Adverse Events Requiring Dr Visit X X X X X X X X X X X X X X
RRPQ X
End Stage 2
***=if appropriate**

After the session begins, participants will lie or recline in a comfortable position with eyes closed or wearing eyeshades if preferred. They will listen to a program of music designed to support their experience by initially aiding relaxation and later evoking and supporting deep emotions and the emergence of unconscious material [38-40]. Throughout the duration of this session, the therapists will support and encourage the participant in emotional processing and resolution of emerging memories, thoughts or feelings. The therapist-investigators will also encourage periods of time in which the participant remains silent, focusing attention inward, in order to allow for the further unfolding of their inner experience. Water and electrolyte-containing beverages will be available for participant consumption, and food will be offered later on in the session. Blood pressure and pulse will be measured at the outset of each experimental session and
once every thirty minutes (0.5 hour) for the duration of the experimental session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure participant body temperature via tympanic thermometer every 60 to 90 minutes. SUDs will be every 60 to 90 minutes until the session is over. The exact timing will be at the discretion of the
therapists so that testing will not interfere unnecessarily with the therapeutic process, and
if necessary, the investigators can make a greater number of measurements. Approximately 1.5 to 2.5 hours after the initial dose, the therapist-investigators will offer the participant the supplemental dose of MDMA. They will only do so if, in their judgment, the participant does not show any signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event.
With the permission of the therapists, a significant other, such as a spouse, relative or close friend, may join the participant during the experimental session or at some point after it has ended. The therapist-investigators and participant will discuss the issue of having a significant other present prior to permitting a significant other to accompany the
participant.
If all medical parameters are acceptable and the subject is alert, ambulatory and emotionally stable, the session will end. The investigators will depart the site when they

have concluded that the participant is emotionally and medically stable. Both therapistinvestigators reside near and can quickly return to the site if necessary. Throughout the study, at least one of the therapist-investigators will remain available to participants via 24-hour cellular phone.

Participants will remain overnight in an appropriately furnished room With prior approval, a significant other may accompany the participant during the overnight stay. A same-sex attendant will remain with the participant during the overnight stay, even if a significant other is present. The attendant will monitor participant health and will help participants relax during the overnight stay. The attendant will be anyone with training or background in health care, particularly psychiatric health care with previous training in managing psychological distress, including distress

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

Starting on the day of the non-drug psychotherapy session following each experimental session, one of the investigators will contact the participant via telephone on a daily basis for one week.

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

An integrative psychotherapy session will take place on the morning of the day after each experimental psychotherapy session. The participant and investigator will discuss and review events, thoughts, feelings and memories that occurred during the experimental session. If necessary, the therapist-investigators will help the participant to reduce any residual psychological distress he or she is experiencing. Participant and investigator beliefs about participant condition assignment will be assessed on the morning of the day after each experimental session. After this psychotherapy session, a person previously selected by the subject will provide a ride home. The investigators will help secure a ride home for participants who are unable to locate a ride.

The participant will meet with the therapist for at least two more integrative psychotherapy sessions to be scheduled between experimental sessions or after the third and final experimental session. The participant and investigators will continue to work on supporting the participant as she or he considers his or her experiences during experimental sessions. The investigators may arrange to work on reducing the distress at

a specially scheduled non-drug therapy session, through continuing contact, or at the next
regularly scheduled non-drug therapy session. The participant may also initiate contact with the investigators at any time throughout the study. There will be no more visits for approximately one month between integrative psychotherapy after the third experimental
session and assessment six weeks after the third experimental session.
Evaluation Six Weeks After the Third Experimental Session: The final evaluation in the double-blind portion of the study will occur six weeks after the third experimental session. Participants will meet the independent rater for a 90 to 120 minute evaluation wherein the independent rater will administer the CAPS and participants will complete the BDI and PDS. The independent rater will also administer the RBANS and PASAT.
Unblinding and Opportunity for Participants in Active Placebo Condition Enroll in Open-Label Study Segment ("Stage 2"): After undergoing assessment of symptoms of PTSD and depression with the independent rater, the blind will be broken for the therapist-investigators and the participant, with the independent rater remaining blind to condition assignment. During this 30 to 60 minute meeting, the investigators will provide consent materials for the open-label study segment to participants assigned to the active

placebo condition. These participants who elect to enroll in stage 2 will undergo a course
of therapy and evaluation nearly identical to the randomized study, but with experimental
dose MDMA given in an open-label context. They must give written, informed consent before enrolling in the open-label study segment.
Assessment of PTSD symptoms and depression six weeks after the third experimental session will serve as baseline assessments for comparison with assessments made after
final open-label sessions except in the case of people who begin open-label sessions more
than thirty days afterwards. In that case, the independent rater will re-administer the CAPS, PDS and BDI, and these scores will serve instead as baseline for comparison to assessment after final open-label session.
Participants who are not continuing on to the open-label study segment will complete the
Reactions to Research Participation Questionnaire (RRPQ), a measure of experience as a
research participant.
Open-Label Study Segment for Active Placebo Participants ("Stage 2"): Participants assigned to active placebo during the randomized study segment will undergo three openlabel
MDMA-assisted therapy sessions that follow a course and schedule similar to the randomized study except that participants undergo one instead of three introductory sessions. After giving written informed consent, participants enrolled in Stage 2 will meet

with both therapist-investigators for a single review and re-introductory psychotherapy session, followed by an open-label MDMA-assisted therapy session. Participants will have the same sequence of integrative therapy and open-label sessions scheduled three to
five weeks apart.
All participants in Stage 2 will be assessed by the independent rater six weeks after the third, final open-label session. The independent rater will assess all participants on the CAPS and participants will complete the PDS and BDI, and RRPQ.
Audio and Video Recording: All sessions from introductory psychotherapy through weekly integrative psychotherapy and including experimental and open-label MDMAassisted
sessions, will be recorded to audio and video in their entirety. These recordings will be used for further analysis of patient behaviour, defense mechanisms, and therapist
interventions and for development of a manual of standard procedures for performing MDMA-assisted psychotherapy in people with PTSD.

Premature Withdrawal/Discontinuation Criteria

The participant, or where applicable, the participant's legally acceptable representative(s)
can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. Cause for withdrawal from the study include, but is not limited to, positive urinary pregnancy screen, positive urinary drug screen, drug-related adverse event requiring hospitalization
or immediate clinical intervention (as high, sustained elevation in blood pressure,

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

Rescue Medication and Risk Management

Approximately 390 people have received MDMA during controlled trials without the occurrence of any drug-related serious adverse event, and psychiatrists in the US and Europe reported administering MDMA to at least a thousand patients before the drug was
made illegal without any occurrence of drug-related serious adverse events [9, 11, 14, 41]. MDMA side effects include loss of appetite, dry mouth, impaired concentration, impaired gait or balance and tight jaw muscles, and fatigue lasting for up to two days afterwards [37, 42-46]. Increased anxiety, mild perceptual alterations (as colors seeming
brighter) and increased anxiety are reported in clinical trials [35, 37, 46-48].
Approximately 5% of study participants exhibit clinically significant elevation in blood

pressure, none requiring clinical intervention [46, 49].
Currently there is no known antidote to MDMA. There are pharmacological or psychotherapeutic treatments for specific effects of MDMA. Anti-hypertensives can be used to reduce elevated blood pressure. Supportive care can be used in response to anxiety or panic reactions. Benzodiazepines could also be used in response to panic reactions or psychotic responses. Human drug co-administration studies suggest that conventional (first generation) anti-psychotics will not reduce, and may even increase, anxiety after MDMA [44]. It is possible but currently uncertain, that serotonergic antipsychotics, such as olanzapine, could be used to treat psychotic response to MDMA.
The investigators will not administer a subsequent dose of MDMA if an individual exhibits a severe panic response or signs of liver disease, and they may decide not to administer a subsequent dose of MDMA after elevation in blood pressure that required clinical intervention.
Serious adverse effects of ecstasy (material represented as MDMA) are rare even outside
controlled settings [50]. In uncontrolled settings, hyperthermia is the most common of these events [42, 51]. In addition to hyperthermic syndromes, other rare adverse events include dysphoric, panic or psychotic response, hepatotoxicity and hyponatremia.
Hypertension and Cardiovascular Effects: Participants with hypertension, cardiovascular,
coronary, pulmonary or cerebrovascular disease will be excluded from study participation. The investigators will address the cardiovascular effects of MDMA through periodically monitoring blood pressure and pulse at regular 30-minute intervals. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the
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investigator to be safe. The investigators may send the participant to an emergency department if they judge it necessary to do so.
Psychological Distress: Preparation for each experimental or open-label session and supportive care during each session will be used to address and potentially reduce psychological distress. Participants with psychiatric conditions that place them at increased risk of psychosis, such as past or current psychotic disorders or dissociative identity disorder, will be excluded from study participation. Preparation will include discussing what might occur during an MDMA-assisted therapy session and teaching techniques such as diaphragmatic breathing. The investigators will explain to participants
that anxiety will not be treated pharmacologically during the sessions because anxiety presents an opportunity to therapeutically address the symptoms and underlying causes of
PTSD. Every effort will be made to help participants move through difficult emotions and arrive at a more comfortable and relaxed state by the conclusion of the session. In the event that a participant is experiencing severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an experimental session, the

principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem. The investigators may remain with the participant until they believe that he or she is stable, and they have the option to hospitalize any participant who may be in danger of harming him or herself or others.

Hyperthermia: The investigators will address risk of hyperthermia by assessing body temperature every 60 to 90 minutes with a tympanic thermometer. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, the investigators will consult by telephone with a physician at the nearest emergency room to discuss whether the subject should be transported for further evaluation. If the temperature continues to rise, or if an elevated temperature is associated
with delirium or muscle rigidity paramedics will be summoned to stabilize and transport the subject to a nearby emergency department.

Hypnatremia: Electrolyte solutions such as Gatorade will be available throughout each experimental or open-label session. Participants will not be allowed to drink more than 3 L. of fluids over the course of the experimental session, and fluid intake will be spread out appropriately during the session. The investigators will ensure adequate fluid intake by encouraging the subject to drink electrolyte solution or water at least hourly if subjects
are not doing so spontaneously. If there are any signs or symptoms of hyponatremia such
as confusion, vomiting, myoclonus or ataxia, beyond mild, transient symptoms that may be associated with MDMA effect the subject will be transported to the nearest emergency
department.

Liver Toxicity: People with liver disease will be excluded from study participation. Participants will be monitored for signs of liver toxicity. If a participant exhibits signs of liver toxicity after an experimental session, then he or she will not receive a subsequent experimental session.

Neuropsychological toxicity: Psychological and neurological status will be clinically monitored by the therapists during MDMA sessions and during therapy sessions at frequent intervals thereafter. If, on clinical examination after each experimental session, a
participant is found to have cognitive deficits that persist for more than two weeks, this participant will not be given a subsequent experimental session. Cognitive function will be assessed at baseline and again six weeks after the third experimental session.

Abuse and dependence: The investigators will exclude all participants meeting the criteria
for substance abuse or dependence within six months prior to screening and all participants who report using ecstasy on five or more occasions or at any time in the past
six months. Urine drug testing will occur before each experimental or open-label MDMA session. The researchers will be alert to the question of MDMA abuse during the

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

Concomitant Medication

Participants are not allowed to take any psychiatric medications throughout the course of
the study, with the exception of gabapentin for pain management. This includes antidepressants, anti-anxiety medication and antipsychotics.
For one week preceding each experimental or open-label MDMA-assisted psychotherapy
session and by extension including the entire day of the experimental or open-label session, participants may not take any herbal supplement, nonprescription or prescription
medication except any supplement or medication that the investigator has reviewed and given prior approval for use. However, participants may take these medications at all other times during the study.
Medications allowed throughout the study include birth control pills, non-steroidal antiinflammatory
medication (as aspirin, ibuprofen), acetaminophen and thyroid hormones.
Specific anxiolytics, as benzodiazepines, may be administered to treat insomnia or anxiety more than 24 hours after an experimental or open-label session.

Efficacy Variables & Analysis

Global CAPS scores assessed six weeks after the third experimental (blinded) session will serve as the primary endpoint for assessing treatment efficacy. An independent rater
who will not be present during any experimental or non-drug assisted sessions will administer the CAPS at baseline and again six weeks after the third experimental session.
The CAPS provides a means to evaluate the frequency and intensity dimensions of each

symptom, impact of symptoms on the patient's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [52, 53].
The primary endpoint of six weeks after the third experimental session was chosen to take place after all three experimental sessions of active placebo or experimental dose MDMA and after the participant had completed the course of psychotherapy for the study. The endpoint was also selected to make it comparable with the primary endpoint employed in earlier and ongoing sponsor-supported studies of two months after two experimental sessions. The endpoint is intended to examine the stability of response and

to avoid any immediate effects of the experimental sessions.
Secondary endpoints for assessing efficacy will also occur six weeks after the third experimental (blinded active placebo or experimental dose MDMA) sessions, and will include scores on the PTSD Diagnostic Scale (PDS) and assessing symptoms of depression with the Beck Depression Inventory (BDI). The PDS was designed to assess PTSD following DSM criteria [54, 55]. This 49-item self-report scale assesses degree of distress, and presence of intrusive thoughts, avoidance of situations that trigger intrusive
thoughts, and hypervigilance. The PDS assesses duration of symptoms and degree of impairment. The Beck Depression Inventory (BDI) is a 21-item a self-report measure of depressive symptoms [56, 57] that will serve as a measure of depression. It takes five to ten minutes to complete.
PTSD and depression symptoms will be assessed in people enrolled in the open-label Stage 2 study segment six weeks after the third open-label session in order to compare PTSD symptoms at the start of the study, after receiving active-placebo dose MDMA and
after experimental-dose MDMA.
The final endpoint for assessing neurocognitive function after active-placebo or experimental dose MDMA-assisted psychotherapy will also occur six weeks after the third experimental session, with scores at this time compared with baseline performance.
The RBANS, a battery of neurocognitive tests [58] and the PASAT, a measure of information processing speed and efficiency [59] will all be administered at these two time points. The RBANS is used to support the broad-based assessment of multiple cognitive domains with index scores for immediate memory, visuospatial/constructional, language, attention, and delayed memory. The PASAT is a sensitive measure of information-processing speed and efficiency, concentration skills, and immediate memory which has an extensive literature associated with the effects of brain dysfunction.
Laboratory Assessments: Before the study, the investigator will supply the sponsor with a
list of the normal ranges for clinical laboratory assessments. Urinary screens for drugs of
abuse and pregnancy will be performed just prior to each experimental or open-label session; all other laboratory tests will be performed as part of screening for study

enrollment. Tests will include assessment of thyroid and liver function. All abnormal laboratory values require a comment from the investigator on the laboratory report, regardless of the clinical significance. After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by
the investigator.
Side Effects and Adverse Events: The investigators will record spontaneously reported side effects during and for one week after each experimental or open-label session.

Adverse events that will be collected for the duration of the study include any events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions and any adverse event leading to withdrawal from the study.
All serious adverse events will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study IP or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to either the medical monitor or the sponsor study monitor.
Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.
The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

Statistical Analysis

The investigators will examine the effects of active placebo versus experimental dose MDMA-assisted psychotherapy on symptoms of PTSD as assessed via CAPS global scores by conducting between subjects / within-subjects analyses of variance (ANOVAs)
with condition (active placebo versus experimental dose) as a between-subjects variable
and time of administration (baseline versus six weeks after third experimental session) as
a repeated measure. The investigators will perform post-hoc tests on any interaction and
probability of rejecting the null hypothesis will be set at 0.05. If there is a significant interaction between condition and time of administration, the investigators will perform separate between-subjects / within-subjects ANOVAs on CAPS sub-scale scores to examine whether any facet of PTSD symptoms is particularly affected by MDMAassisted
psychotherapy. The investigators will perform the same analyses upon PDS scores.
The investigators will perform a correlational analysis examining possible relationships between symptoms of PTSD and depression by correlating CAPS global scores and BDI

scores at each time of administration, with the probability of rejecting the null hypothesis set at 0.05, and by correlating PDS and BDI scores at each time of administration.
The investigators will examine the effects of psychotherapy combined active placebo versus experimental dose MDMA on symptoms of depression, measured by BDI scores,
by performing a between-subjects / within subjects ANOVA with condition (active placebo versus experimental dose) as a between-subjects factor and time of administration (baseline versus six weeks after the third experimental session) as a repeated measure.
The investigators will further examine the effects of MDMA-assisted psychotherapy on

symptoms of PTSD and depression by comparing symptoms after experimental and open-label sessions. The investigators will perform repeated-measures ANOVAs comparing CAPS, PDS and BDI scores at randomized study baseline and six weeks after
the third open label session, with time of administration as a within-subjects factor and with p. set at 0.05. They will perform one analysis comparing CAPS, PDS and BDI scores after experimental and open-label sessions for participants in the experimental condition and another analysis for participants enrolled in "Stage 2."
The investigators will examine the effects of MDMA on neurocognitive function by performing a between-subjects / within-subjects ANOVA with condition as a betweensubjects
factor (active placebo versus experimental dose MDMA) and with time of administration (baseline, six weeks after the third double-blind session) as a withinsubjects
factor and with p. set at 0.05. Participant scores on the RBANS and PASAT will be compared at both times.
Safety of MDMA-administered psychotherapy will be assessed by performing descriptive
statistics of vital signs and subjective distress during each experimental or open-label session. The investigators will informally or formally compare peak blood pressure, heart
rate and body temperature for participants after sessions using 125 and 150 mg MDMA, depending upon the number of times, if any, ,the investigators administer 150 mg during the study.

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4. INFORMED CONSENT FORM

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

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

5. OVERALL ASSESSMENT

Current Problems/Concerns:

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

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

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

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

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

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

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

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

3. **a) What is the abuse/addiction potential of MDMA?**
b) What would be the estimated risk of abuse of MDMA for a participant in this trial after the completion of all MDMA-assisted psychotherapy sessions?
c) How does the abuse potential of MDMA compare to abuse potential of psychostimulants used as medications (e.g. methylphenidate, dexedrine etc..)?

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

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

<u>Abuse Liability (from pp. 45-46)</u>

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

Abuse Liability (from p. 87)

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

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

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

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

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

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

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

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

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

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

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

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

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

7. **Re: Informed Consent**:

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

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

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

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

b) We will clarify the IC however you require, after you have reviewed our request to retain the current exclusion of subjects with active substance abuse in the prior 6 months.

c) From previous studies of 365 people and using identical or similar doses of MDMA, average increase in SBP was 30-35 mmHg and average increase in DBP was 15-20 mmHg. Average elevation in heart rate was 18-20 beats per minute (BPM).

The cited attachments are available as a hard copy.
The questions and sponsor's responses were discussed with Dr. E. Komsta.

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

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

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

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

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

We added the following statement:

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

Reviewer's Discussion/Summary:

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

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

Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female cotherapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the

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

Symptoms of PTSD and depression will be assessed by an independent assessor who willbe blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.
Participants in the active placebo condition will have the opportunity to enroll in an openlabel study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression symptoms six weeks after the third open-label session.
Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

In the event that a participant is experiencing severe emotional distress, such as panic attacks, severe generalized anxiety or insomnia, following an experimental session, the principal investigator may prescribe a benzodiazepine or other anxiolytic drug, as zolpidem. The investigators may remain with the participant until they believe that he or she is stable, and they have the option to hospitalize any participant who may be in danger of harming him or herself or others.
The investigators will not administer a subsequent dose of MDMA if an individual exhibits a severe panic response or signs of liver disease, and they may decide not to administer a subsequent dose of MDMA after elevation in blood pressure that required clinical intervention.
The investigators will address the cardiovascular effects of MDMA through periodically monitoring blood pressure and pulse at regular 30-minute intervals. If at any time the blood pressure exceeds 160 systolic or 110 diastolic, or the pulse exceeds 110, measurements will be taken every 5 minutes until the values fall below these levels or until they have been decreasing for 15 minutes or have stabilized at a level judged by the investigator to be safe. The investigators may send the participant to an emergency department if they judge it necessary to do so.
If there are any signs or symptoms of hyponatremia such as confusion, vomiting, myoclonus or ataxia, beyond mild, transient symptoms that may be associated with MDMA effect the subject will be transported to the nearest emergency department.
The investigators will address risk of hyperthermia by assessing body temperature every 60 to 90 minutes with a tympanic thermometer. If temperature rises more than 1° C, attempts will be made to lower it by removing blankets and layers of clothing, decreasing ambient temperature and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above baseline despite these efforts, the investigators will consult by telephone with a physician at the nearest

emergency room to discuss whether the subject should be transported for further evaluation. If the temperature continues to rise, or if an elevated temperature is associated with delirium or muscle rigidity paramedics will be summoned to stabilize and transport the subject to a nearby emergency department.

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

NON-CLINICAL AND CLINICAL SAFETY & EFFICACY ASSESSMENT

Overview

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

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

Pharmacological and toxicological effects

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see
also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use
high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear.
MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture.
Thenature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978),
and an a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).
Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al.
2003). Typically, human trials have used doses between 1 and 2 mg/kg.

Pharmacokinetics and biological disposition

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