

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

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

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

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

Safety and effectiveness in humans obtained from prior clinical studies

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

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

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

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

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

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

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

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

Possible Risks and Side Effects

Fatalities

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

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

Common Adverse Effects and Side Effects

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

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

Investigator's Brochure: MDMA MAPS: 12/2007

21

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

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

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

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

sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with subacute

effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006).

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

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

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

Abuse Potential

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

Investigator's Brochure: MDMA MAPS: 12/2007

29

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

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

but lesser than for psychostimulants.

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

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

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

Reproductive and Developmental Toxicity

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

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

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

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

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

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

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

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

to some effects of MDMA.

Research trial data

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

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

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

the underlying disorder and the therapeutic process.

March 6, 2009

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

Dear Dr. Wiatrakowska,

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

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

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

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

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

We added the following statement:

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

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

Sincerely,

Rick Doblin Ph.D.
Rick@maps.org

March 6, 2009

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From Beata Wiatrakowska M.D. FRCP(C)
Tel: 613- 941-2132 Fax: 613-952-9656
Study Control# 127822
File # 9247-M2554-21C

Dear Dr. Wiatrakowska,

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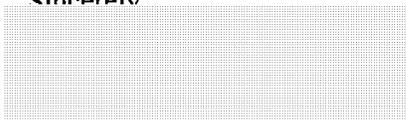
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Please find along with this fax the pages of relevant text from the informed consent form and the changes made. I will also send a copy of this letter and the entire informed consent form containing these revisions via email.

Sincerely,



Rick Doblin Ph.D.
Rick@maps.org

Risks from MDMA

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

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

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

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

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

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

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

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

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

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

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

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

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

Possible Brain Damage

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

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

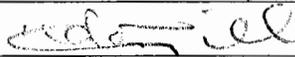
Only one study has looked at brain scans of people before they got MDMA and then again after they have received one or two moderate doses of MDMA, and did not see any changes in the brain, though it is possible that there were changes that were too small to notice. Other studies looked at people before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

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

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

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

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

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

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

Evaluator's Introduction/Discussion:

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

Dose Formulation : Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg.

Dosing: An Experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later.

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION SPONSOR

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

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

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

Response: See attachment

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

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

Response: See attachment

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

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

Response: See attachment

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

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

March 3, 2009

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

Dear Rajkumar Kumarabasan, Ph.D.,

Please find the answers to your queries below.

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

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

Above is the chart that you requested.

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

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

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

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

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

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


Rick Doherty, Ph.D.
MAPS President

Rick Doherty, Ph.D.
MAPS President



Canac

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

Therapeutic Products Directorate

Direction des produits thérapeutiques

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

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

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

TO/À

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

Organization/Organisme : Multidisciplinary Association for Psychedelic Studies

Tel./Tél. (617) 484-8711

Fax/Télécopieur : (617) 484-8427

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

FROM/DE

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

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

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

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

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

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

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

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

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

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

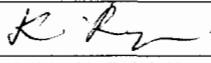


Rajkumar Kumarathasan, PhD.
Chemistry Advisor
Clinical Trials Quality Division
Office of Clinical Trials

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

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

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

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

Attachments	EDQM certificates, Lactose, DS information
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Evaluator's Introduction/Discussion:

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

Dose Formulation : Racemic MDMA will be placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg.

Dosing: An Experimental dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 2.5 h later.

Placebo: Active Placebo (low dose MDMA + Lactose); active placebo doses are 12.5 mg and 25mg. Active placebo doses of MDMA will also contain the inactive substance, lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

Drug Substance:

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

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

Drug Product:

The drug product is compounded at Kerrisdale pharmacy, Vancouver BC. Racemic MDMA is placed into gelatin capsules containing MDMA in doses of 12.5, 25, 62.5 and 125 mg. The experimental doses of MDMA are 125 and 62.5 mg and the active placebo doses are 25 and 12.5 mg. The active placebo capsules contain lactose to ensure that experimental dose and active placebo dose capsules weigh the same amount.

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

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

PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION

SPONSOR

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

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

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

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

Modules 2 and 3: Common Technical Document Summaries and Quality

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

Sponsor: Multidisciplinary Association for Psychedelic Studies

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

Study Number: M-P4

Quality Overall Summary and Referenced Documents

2.3 Quality Overall Summary

1 Introduction

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

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)

Study Phase: II

Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]

Co-Investigators: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010

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

Abbreviations:

GCMS = Gas chromatography-mass spectrometry

HPLC = High performance liquid chromatography

LiAlH₄ = Lithium anhydride

MDA = 3,4-methylenedioxyamphetamine

MDMA = 3,4-methylenedioxymethamphetamine

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

Form: Capsules

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

Route of Administration: Oral

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

1(a) Excerpt from Protocol Synopsis (PSEAT)

Trial Objectives

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

The investigators will also gather information on physiological effects and side effects after MDMA.

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

Study Design and Duration

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.

Symptoms of PTSD and depression will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

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

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

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

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

The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

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

Sample Size

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

Patient Population (Target population)

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

Drug Formulation

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

Dosing Regimen

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the experimental condition are identical to those in use in other MAPS-supported studies of

MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the US [1-3]. The supplemental dose is also identical to the one used in the US study. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective effects without producing physiological effects any greater than peak effects occurring after the initial dose.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [4, 5] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [5].

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

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

S Drug Substance

S.1 General Information

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

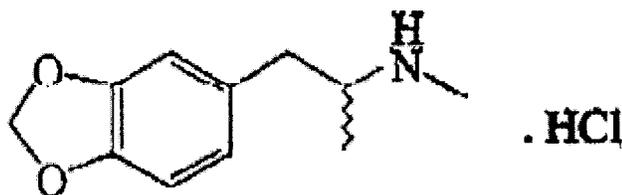
[REDACTED] On January 30, 2006, a quality control analysis was performed by [REDACTED]. This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no.94.1 B5.5 with no decomposition products detectable and a HPLC purity >98%.

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

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

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

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



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

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

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

It is water soluble.

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

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

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

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

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

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

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

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

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

S.2.3 Control of Materials

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

S.3 Characterization:

Batch number is [REDACTED]

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by [REDACTED]

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

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

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

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

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

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

S.3.2 Impurities

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

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder

Identity: IR

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

ϵ_{mol} = 3800 +/- 500

Melting Point: 149 +/- 3 C

Purity HPLC = 98.5%

Free base content = > 82.5%

Water content: 0.3 +/- 0.3%

Calculated hydrochloride content: 15.81%

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

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

HPLC

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

Injection volume: 10 μL

Detection: 198 nm

Identification: DAD spectrum 192-350 nm vs. standard

GC/MS

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

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

Carrier gas: He 1.2 mL/min

Derivatization: MBTFA

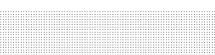
Injection: 250 C, splitless 1 μL

Detection: full scan

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

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

S.4.3 Validation of Analytical Procedures

Validation upon request from 

S.4.4 Batch Analysis:

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

Provided on manufacturer's data sheet

Appearance: Conforms to appearance

Identity: IR identical to reference

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

$\epsilon_{mol.1} = 3939$

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

$\epsilon_{mol.2} = 3688$

Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%

Freebase content: 83.51%

Water content: 055%

Calculated hydrochloride content: 15.81%

Residual solvents: Isopropyl alcohol < 100 ppm

Isopropyl ether < 2000 ppm

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

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

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

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

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

S.4.5 Justification of Specification

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

S.6 Container Closure System

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

S.7 Stability

S.7.1 Stability Summary and Conclusions

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

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

S.7.2 Stability protocol and stability commitment

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

S.7.3 Stability Data

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

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

P. Drug Product

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

Kerrisdale Pharmacy, a Vancouver-area pharmacist. The capsules and lactose are certified BSE/TSE free.

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

P.3 Manufacture

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

P.3.1 Manufacture(s)

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

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

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

P.3.3 Batch Formula

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

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

Experimental initial dose: 125 mg

Experimental supplemental dose: 62.5 mg

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

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

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

P.4 Control of Excipients

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

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

P.4.1. Specifications

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

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

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

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

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

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

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

P.7 Container Closure System

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

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

A Attachments:

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

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

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

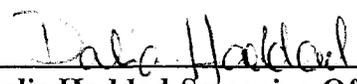
	Health Canada / Santé Canada	Office of Clinical Trials
Screening Template for CTA - 30-day default review		
CR File #: 9427-M2544-21C Date received in OCT : 2009.02.16 Review 1 Start Date: 2009.02.16 Study Phase: Phase II-30 day Study Population: Males, Females Document I.D. #: <i>520609</i>	DSTS Control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

Product Name : MDMA	
Protocol # or Identifier: MP-4	
Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4 methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada	
Therapeutic/Pharmacological Classification: Monoamine releaser and uptake Inhibitor [Clinical Group II : CNS]	
Sponsor Name : Multidisciplinary Association for Psychedelic Studies	Country: USA

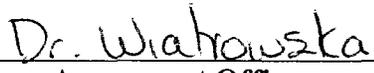
#	Form	Route	Medicinal Ingredients	Strength / Unit	Basic Unit	F#
1	CAP	ORL	UNASSIGNED	12.5 mg	CAP	1
2	CAP	ORL	UNASSIGNED	20 mg	CAP	2
3	CAP	ORL	UNASSIGNED	62.5 mg	CAP	3
4	CAP	ORL	UNASSIGNED	125 mg	CAP	4

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

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



Dalia Haddad-Screening Officer



Assessment Officer

2009.02.16 / 2009.02.16

 Screening start date / Completion date

Feb 17, 2009 /

 Assigned date / Review Hours



Health Canada
Santé Canada

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

Your file Votre référence

Our file Notre référence

16 February 2009

9427-M2544-21C

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

ACKNOWLEDGEMENT CLINICAL TRIAL APPLICATION
RE: PROTOCOL# MP-4

Dear Dr. Doblin:

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

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

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

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/en



Health Canada
Santé Canada

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

Your file Votre référence

Our file Notre référence

23 January 2009

9427-M2544-21C

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

Acknowledgement of Withdrawal

Re: Protocol # M-P4

Dear Dr. Doblin:

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

Your application has been withdrawn according to this notice.

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/mh

Canada

DOC ID # 547219



Rick Doblin <rick@maps.org>

2009-01-23 10:07 AM

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

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

bcc

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

Dr. Chafak,

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

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

Sincerely,

Rick Doblin, Ph.D.
MAPS President



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

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

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

Dr. Rick Doblin,

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

without prejudice and resubmit at a later date.

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

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

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

Rick Doblin <rick@maps.org>



Rick Doblin <rick@maps.org>

2009-01-22 05:00 PM

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

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

Dr. Kumarathanan,

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

Attached is information about the capsules and lactose.

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

Sincerely,

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

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

>
> Thanks

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

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

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

>
> To
> rick@maps.org
> cc

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

>
>
>
>
>
> Dear Dr. Doblin,

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

>
> Thanks

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

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

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

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

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

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

January 22, 2009

Protocol Number: MP-4
Control Number: 126833

Dear Dr. Kumarathasan,

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

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

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

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

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

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

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

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

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

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

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

Revision of P.4 would this appear:

“P.4 Control of Excipients

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

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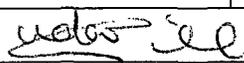
Deleted: 1

Rick Doblin, Ph.D.
MAPS President

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

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

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

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

Evaluator's Introduction/Discussion:

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

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

**PROPOSED COMMENTS TO BE FORWARDED TO THE SUBMISSION
SPONSOR**

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

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

limits for appearance, identity, assay, related substances/degradation products, uniformity dosage units and dissolution.

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

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

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

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

Sponsor's Response

Rick Doblin
<rick@maps.org>

2009-01-23 10:07 AM

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

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

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

Dr. Chafak,

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

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

Sincerely,

Rick Doblin, Ph.D.
MAPS President

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

To Rajkumar Kumarathasan
<Rajkumar_Kumarathasan@hc-sc.gc.ca>
cc Hicham Chafak <Hicham_Chafak@hc-sc.gc.ca>
Subject Re: Clarification Request:MAPS MDMA/PTSD Protocol
t # MP-4, Control Number: 126833

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Attached is information about the capsules and lactose.

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Sincerely,

Rick Doblin, Ph.D.
MAPS President

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> Rajkumar Kumarathasan, PhD.

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

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

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> Office of Clinical Trials, TPD
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>

> Rick Doblin <rick@maps.org>
> 2009-01-14 01:09 AM
>
> To
> Rajkumar Kumarathasan <Rajkumar_Kumarathasan@hc-sc.gc.ca>
> cc
> Ilsa Jerome <ilsa@maps.org>
> Subject
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>
> Sincerely,
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> Rick Doblin, Ph.D.
> MAPS President

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

Lactose_productsafety_303329.pdf  - Certificate of suitability Capsules 2009.pdf