Tuesday, September 16, 2008

Mr. Rick Doblin
Multidisciplinary Association for Psychedelic Studies (MAPS)
3 Francis Street
Belmont, MA 02478 USA

Dear Mr. Doblin

Re: MAPS Final Protocol No: M-P4 dated 09/03/08

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

The above protocol, plus MDMA Investigator's Brochure Dated December 2007, CAPS-DX Scale dated December 1995, Subject Units of Distress, Script for Phone Screening, PDS Questionnaire, Reactions to Research Participation Questionnaire – Short Form, Beck Depression Inventory, Informed Consent Quiz, Informed Consent Form Quiz Answer Key, Dear Dr. Letter and Informed Consent Document undated, were reviewed by the British Columbia Institutional Review Board (BC IRB) of Institutional Review Board Services on September 10, 2008. The IRB complies with Health Canada Regulations, ICH GCP Guidelines, FDA 21 CFR Parts 50 & 56, DHHS 45 CFR 46, and the Tri-Council Policy Statement.

Attending the meeting and constituting a quorum were:

Dr. Valia Lestou, Ph.D., Scientist Representative (knowledgeable in research ethics), Acting Chairman
Dr. Jonathan Willmer, MD, FRCPC, (neurology) Medical Representative
Dr. David Sinclair, MD, FRCPC, CITI, Medical Representative (Alternate)
Mr. Robert Sarrazin, B.Pharm, Pharmacy/Scientific Representative (Alternate)
Dr. Stephen Hoption Cann, Ph.D., Scientist Representative (knowledgeable in alternative and complementary medicine)
Ms. Vanessa Silverberg, B.Sc., Scientist Representative (Alternate)
Ms. Christine McDermott, BA, JD, Legal Representative/Community Representative
Ms. Karen Low Ah Kee, CMA, Non-Scientist /Community Representative
Mr. Bill Ornstein, BSc., M.Sc. (Health Planning), Scientist/Alternate Ethicist

The committee unanimously withheld approval of the study, as numerous concerns were raised regarding the protocol and consent document, as described below. As you are aware, under Good Clinical Practices (GCP), the study may not begin until final, unconditional approval has been granted by the IRB for the study and information to subjects. In addition, you are reminded that it is a violation of Canadian federal regulations to commence a study prior to it receiving a no objection/authorization letter from Health Canada; **you must not begin the study until the sponsor has been so notified by Health Canada.**

GENERAL ISSUES:

Information Card: As the study involves the administration of a controlled substance, the committee recommends that subjects be provided with an information card, which explains that the subject is enrolled in a research study involving MDMA, and provides contact information for the Investigator(s). Please submit this card for review.

No Objection Letter: The committee recommends submitting this protocol to Health Canada for review, in order to expedite the approval process. When available, please submit to us the No Objection Letter for our files.

PROTOCOL ISSUES:

Open-Label Sessions: The Committee cannot approve at this time the Open-label Sessions for Non-Responders ("Stage 2") or the Optional Open-Label Session, before the results from the main portion of the study are available. Please revise the consent form accordingly.

Age Limit: The Committee recommends that the lower age limit for subjects enrolled in this study be set at 25 years instead of 18, because of possible drug interference with the ongoing brain development in younger individuals. Please also revise the consent documents accordingly.

Exclusion Criteria:

- On page 14 of the protocol, it is noted that people with hypertension are excluded from the study (exclusion criteria 5). Please clarify the criteria for determining whether or not an individual is hypertensive.
- On page 17 of the protocol, exclusion criterion No. 8 "*People who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.*" Please clarify how suicide risk will be assessed in patients (i.e. which psychometric scales will be used).
- On page 17 of the protocol, exclusion criterion No. 10 notes the exclusion of "*People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.*" Please confirm that the phrase "*in the past 60 days*" refers only to caffeine or nicotine, and that individuals with any history of abuse of or dependence to controlled substances will be excluded from the study.

Medical Examination: The Committee recommends that a medical examination be performed at the end of the study, in addition to the one at screening, to ensure subject safety.

Access to Hospital: The protocol indicates that the study site is a five-minute drive from the University of British Columbia and St. Paul's Hospital. The committee is of the opinion that the travel time to either hospital is in fact longer. Please revise, to provide more accurate information.

Study Costs: Please clarify whether or not non-Canadian subjects are to be enrolled. If so, please indicate who will pay for health care costs arising from study-related injury (e.g., for Emergency Room visits) for subjects not covered by the provincial health plan.

Study Environment: As subjects will be supervised only intermittently during their overnight stays at the study site, the committee is concerned about the potential for self-harm in the event of an adverse reaction to the study drug. Please clarify if/what measures are in place to prevent such an event from happening.

Attendant Qualifications: On page 31 of the protocol it is noted, "*The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs*." Please clarify what qualifications and experience the attendant will possess, in order to ensure that they are able to provide the appropriate care in the case of an adverse event.

PATIENT INFORMATION AND CONSENT FORM:

The changes to the informed consent document were made directly to the electronic copy included with your submission. Suggested deletions are shown as strike through. Suggested additions in the electronic version are in colour. Wording that needs clarification/revision is highlighted in yellow.

In addition, please note/complete the following:

- The study title was revised to match the study title found on the protocol.
- A version date was added to the footer of the document.
- The consent document was found to contain a good deal of duplicated information. Unnecessarily lengthy consent documents may be a barrier to fully informed consent, as the prospective subject may not read the form thoroughly and/or find it confusing. Please revise and simplify, removing duplicate information where appropriate.
- Throughout the document, the investigator(s) is referred to alternately as *"study doctor(s)," "investigator(s)," "researcher(s)," "therapist-investigator(s),"* and *"therapist-researcher(s)."* Please revise all references to the investigator(s) to read "*study doctor(s),"* to avoid confusion.
- The committee considers referring to the study doses as "*experimental*" and "*active placebo*" to be potentially confusing to subjects, as both doses contain investigational medication. It is suggested that the terms "*high study dose"* and *"low study dose"* be used instead.
- In the section titled, "Purpose and Background," please include a brief and simple description (in lay language) of the way MDMA is thought to work and how it might help treat post-traumatic stress disorder.
- In the section titled, "Experimental Sessions":
    - It is noted: "*If you cannot find anyone to take you home, the researchers will find someone to drive you*." Please clarify who will be appointed to drive the subjects home.
    - Please include the expected duration of the telephone calls.
    - Stating in the consent form that the study or form have been "approved" by a Research Ethics Board may serve as an endorsement or "good seal of approval." The word "approved" has been therefore been marked for deletion.
- In the section titled, "Possible Risks or Discomforts," please include the frequency in percent terms, or some other quantitative indication of probability, of the less commonly reported side effects associated with MDMA-assisted psychotherapy.

- In the section titled, "Other Risks," the sentence indicating that subjects should be careful driving after the experimental sessions has been revised and bolded for emphasis.
- In the section titled, "Reproductive Risks," please include some examples of allowed birth control methods.
- ICH guidelines state that the amount of reimbursement to patients should be specified in the informed consent document. Suggested wording for this purpose has been added to the revised form. *Please note that IRB Services will personalize this section, as per the information provided to us by you or by the investigators in the study.*
- In the section titled, "Alternatives," please include some specific examples of other medications that are available as an alternative to participation, including the class or type of drug, and the generic and brand names of one or two most representative compounds.
- In the section titled, "Confidentiality":
    - Please indicate the duration and manner of storage of the audio and video recordings.
    - Please indicate how subjects' faces will be obscured, if they request it. Also, please clarify if subjects could be identified or not after their face is obscured.
    - It is noted, "***You may be asked to give an additional consent at the end of the study*** *in order for your audio or video recordings to be viewed by others, such as therapists learning how to perform MDMA-assisted psychotherapy, but you do not have to agree to this in order to participate in the study.*" Please submit this additional consent document for review, in order for the complete study related documentation to undergo ethics review.
    - Checkboxes were added, allowing a place for subjects to indicate whether or not they request their faces be obscured in video recordings.
- Please note that this IRB normally requires three signatures - subject, person obtaining consent, and the investigator. A signature line for the person administering consent has been added.

Please review the revised consent form for accuracy of the information, to ensure that any revised/added information correctly reflects the protocol; also, please check for any typographical, formatting, or related errors, and complete any missing information as requested.

Budget. Please forward a copy of the study budget to IRB services when it becomes available.

ADVERTISEMENT/RECRUITMENT MATERIAL:

If you intend on advertising we ask that you forward all proposed advertising/recruitment material to IRB Services for review prior to use.

Thank you for submitting this study for review. I look forward to your reply so that the approval process may be continued. If you have any questions or concerns, please do not hesitate to contact the undersigned at 905-727-7989 ext. 261 or via email at fweatherill@irbservices.com.

Sincerely,
Institutional Review Board Services

Filomena Weatherill
Senior Coordinator
Protocol Review
(Phase II-IV Team)

Enclosure

Cc Dr. V. Lestou, BC IRB Acting Chairman
Mr. Jack Corman, IRBS President
Mrs. Marianne Vanderwel, Director HRPP