December 17, 2009

[redacted]

RE: MAPS Study MT1 (IRB tracking # [redacted])

Dear [redacted],

I'm writing in response to your email message of December 16, 2009, in which you indicated that, "The Board approved this study conditionally at the meeting yesterday based on the following conditions:

1. Changes to consent form. I have attached this form with the Board's changes tracked for your review. Please let us know if the changes are accepted.

2. The Board has requested written justification to explain why post-treatment EKGs and labs are not being performed."

We accept and appreciate all the Board's changes to the Informed Consent form.

What follows below is our written reply to question #2, with several references.

Justification for Lack of Post-Treatment ECG or Laboratory Tests for Participants in MAPS Study MT1 (IRB tracking # [redacted])

An examination of the literature and our data from the first Phase 2 study do not support performing these tests and assessments. Affects on the heart or organs are rare even in recreational users of ecstasy in unsupervised settings. We do not expect the dose and setting of MDMA used in this study to produce any lasting physiological effects.

There is no need for a post-treatment electrocardiogram (ECG) because MDMA is not expected to produce lasting effects on the heart. The acute effects of MDMA on the cardiovascular system are similar to those of moderate to vigorous exercise. Elevated heart rate and blood pressure

occur for the duration of drug effects, from three to six hours and wane afterwards. Since study participants are screened for presence of major cardiac or cardiovascular conditions, we expect that all participants will be able to tolerate the elevation in heart rate and blood pressure produced by MDMA. If an adverse cardiac event were to be caused by MDMA administration it would occur acutely and would be evaluated at that time based on symptoms or vital sign abnormalities. We do not believe there is any reason to expect that post-treatment ECGs would uncover lasting effects on the heart.

No cardiac abnormalities were reported in samples of ecstasy users reporting moderate to heavy use [1, 2], and transient abnormalities were detected only in a subsample of individuals with an average cumulative exposure greater than 900 ecstasy tablets [1]. Administering either 0.5 or 1.5 mg/kg MDMA did not produce any cardiac abnormalities [2]. It is unexpected that a combined dose of 125 and 62.5 mg MDMA given during this study to require a post-treatment ECG. Although post-treatment ECGs were not performed in our initial Phase 2 study, there were no adverse cardiac events detected either during the MDMA sessions or in follow-up medical examination.

MDMA produced no toxic effects on organs or systems in a 28-day toxicity study in dogs [3]. As has already been determined in Phase 1 studies with MDMA, nearly all unwanted health effects of MDMA, if they are going to occur, are transient and occur soon after administering MDMA. There were no clinically significant abnormalities in laboratory test values after two administrations of MDMA in the study performed by the same principal investigator of 21 participants with posttraumatic stress disorder. When seen in emergency department admissions for ecstasy use, events other than a panic response are generally associated either with acute hyperthermia or hyponatremia [4-6]. Transient liver disease in response to repeated ecstasy use is exceedingly rare and vanishes upon cessation of ecstasy use [7]. It is very unlikely that repeating laboratory tests of thyroid or liver function or metabolism will detect any changes in a sample of up to 20 participants after an administration of 125 and 62.5 mg MDMA.

1. Droogmans, S., et al., Possible association between 3,4-methylenedioxymethamphetamine abuse and valvular heart disease. Am J Cardiol, 2007. 100: 1442-5.

2. Lester, S.J., et al., Cardiovascular effects of 3,4-methylenedioxymethamphetamine. A double-blind, placebo-controlled trial. Ann Intern Med, 2000. 133: 969-73.

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3. Frith, C.H., et al., Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. Fundam Appl Toxicol, 1987. 9: 110-9.

4. Hall, A.P. and J.A. Henry, Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. Br J Anaesth, 2006. 96: 678-85.

5. Liechti, M.E., I. Kunz, and H. Kupferschmidt, Acute medical problems due to Ecstasy use. Case-series of emergency department visits. Swiss Med Wkly, 2005. 135: 652-7.

6. Williams, H., et al., "Saturday night fever": ecstasy related problems in a London accident and emergency department. J Accid Emerg Med, 1998. 15: 322-6.

7. Fidler, H., et al., Chronic ecstasy (3,4-methylenedioxymetamphetamine) abuse: a recurrent and unpredictable cause of severe acute hepatitis. J Hepatol, 1996. 25: 563-6.

Please extend my deep appreciation to the Board for the time they devoted to evaluating our protocol.

Sincerely,

Rick Doblin

Rick Doblin, Ph.D.
MAPS Executive Director

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