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October 21, 2014

Y. Jennifer Ahn, Pharm D.
RAPC
455 Golden Gate Avenue, Suite 11000
San Francisco, CA 94102

Re: Protocol # MDA-1, PR #1424C

"A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated with a Life-Threatening Illness"

Dear Dr. Ahn,

Please find below our response to the Panel's concerns as outlined in their letter from September 17, 2014. We have preserved your requests and comments in italic print and provide our responses below each item.

We submitted our IRB-approved protocol to the FDA on October 7. We should hear from the FDA prior to your next meeting on November 19 and will write again to inform you of the outcome of the FDA review. The PI, Dr. Phil Wolfson has also contacted the DEA to initiate the DEA Schedule 1 license.

1. *The ICF does not adequately describe MDMA. Define MDMA at a laymen's level.*

   We have added the following text to the ICF on Page 3:

   "MDMA is a drug that can influence people's emotions by making difficult, fearful feelings easier to experience and think about. MDMA helps most people feel more connected to others, more accepting of themselves, and more peaceful. MDMA has some stimulant-like effects such as raising your heart rate and body temperature making you feel more alert, and reducing hunger. It has few perceptual effects, on vision, smell, hearing or taste but touch can feel better. MDMA's effects last between 4-6 hours in most healthy adults.

2. *MDMA's adverse effects of psychosis and mania should be included in the ICF, in the protocol, and in the IB.*

   To our knowledge, no cases of mania induced by MDMA administration exist in controlled clinical studies in which over 900 subjects have been administered MDMA. Most of these subjects were healthy volunteers but also include 2 cancer patients with anxiety, about 79 PTSD patients and 3 adults on the autism spectrum. There are also no reports in PubMed of mania as a result of uncontrolled

recreational use of Ecstasy (illicit material purported to contain MDMA). Without a reference in the literature, we don't think it's appropriate to add mania as a potential adverse effect of MDMA to the protocol or Investigator's Brochure. If RAPC can provide us with a reference to mania as a result of the clinical use of MDMA or uncontrolled recreational use of MDMA/Ecstasy/Molly, we will add it to the ICF, protocol and IB.

There is no evidence of psychosis occurring in the controlled clinical studies mentioned above. Some cases do exist of psychotic reactions related to the use of ecstasy (illicit material purported to contain MDMA) in uncontrolled settings; we report this on page 22 of the Investigator's Brochure. *"Psychiatric problems after uncontrolled, non-medical ecstasy use were reported in 22.1% of 199 case reports from the early 1990s to 2001, and are the most common reason for appearance at an emergency department [83]. Psychiatric symptoms included affective responses, such as dysphoria, anxiety, panic, and psychotic response, as well as cases with mixed psychotic and affective features."* We require all investigators to read the IB and sign a Read and Received document verifying that they have read it so they are informed of this risk even though it's not in the protocol.

The information related to this risk of ecstasy use is represented more specifically and simply in the informed consent where we list paranoia on page 20. The decision to list paranoia was based on the literature referenced in the IB which indicates that the most common psychotic features reported in psychotic reactions subsequent to illicit ecstasy use were paranoid—i.e. delusions of persecution or ideas of reference. These reports can be found in:

> Cohen, R.S., Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. Prog Neuropsychopharmacol Biol Psychiatry, 1995. 19(7): p. 1137-45.
>
> McGuire, P.K., H. Cope, and T.A. Fahy, Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('Ecstasy'). Br J Psychiatry, 1994. 165(3): p. 391-5.

Since this study is a controlled clinical trial using pure MDMA in a safe, supportive setting and the risks mentioned are related to uncontrolled ecstasy use, we do not feel it is necessary to include more information on psychosis to the IC or protocol. An ongoing MDMA-assisted therapy study in autistic adults with social anxiety, currently being conducted at Harbor-UCLA/Los Angeles Biomedical Research Center, was reviewed and approved by the RAPC board without mention of psychosis or mania in the protocol or ICF, and all of our MDMA-assisted psychotherapy studies to date have passed IRB and FDA review without referencing these issues. We therefore request that you accept the ICF, protocol, and Investigator's Brochure as is with regard to this issue.

Should you decide that something should still be said about the risk of psychosis, we propose that the text on Page 20 of the ICF be modified to read "Though over 900 people have been administered pure MDMA in controlled clinical settings without any reports of psychosis (losing touch with reality), there is still some risk of psychosis since some reports of psychotic reactions have been reported from the use of Ecstasy (which may or may not be pure MDMA) used in uncontrolled settings."

3. *The role of the medical provider monitoring the medical problems during MDMA treatment is missing in the protocol.*

   We have text in the protocol describing the procedures for monitoring for medical problems during experimental sessions, indicating that the PI, who is a licensed physician, will be on-site for all experimental sessions and available for monitoring and addressing any emergent medical problems. We have added additional text to section 5.2.3 as follows:

   "The Principal Investigator will monitor all experimental sessions for medical issues in his capacity as a licensed physician. If the PI is the treating therapist for a subject, he will conduct this monitoring concomitant to the session therapy. If the subject is being treated by another therapist team, the PI will be available to supervise the session via closed-circuit camera system from an adjacent room."

   These changes have also been added to the Informed Consent document, reflected in the following language on page 5:

   "If the Principal Investigator (Dr. Wolfson) is not one of the therapists on your therapy team, he will still be available to monitor your study sessions by video from an adjacent room and can respond in moments in case of any medical problems."

   All Adverse Events and safety information is reviewed by the Sponsor's Medical Monitor during study monitoring.

4. *There is a conflict of interest of consent. Since the PI is the psychiatrist and doing the consent himself in his private office, there appears to be a lack of oversight.*

   We have previously received IRB approval for this protocol, which contains text regarding the procedures for administering informed consent.
   To our knowledge, there is no stipulation against the PI administering the informed consent process in a private office. In several of our other studies with MDMA, the PI's administer the informed consent in their private offices. Section 4.8 of ICH GCP guidelines does not require that someone other than the PI should conduct the informed consent process, or specify where that process should take place. We do not feel that the informed consent discussion taking place in the PI's office intrinsically constitutes a conflict of interest. Subjects in this study are not in a

vulnerable patient population and, per the exclusion criteria outlined in the protocol, must be deemed capable of providing adequate informed consent.

To respond to your concerns, we have added text to section 14.0 of the protocol stating: "The informed consent document will be provided to the subject in advance of the informed consent discussion, with enough time provided for the subject to review the document in an environment of their own choosing. The informed consent discussion must be conducted by a person who is qualified according to FDA regulations. The subject should have the opportunity to inquire about details of the MDMA session and to consider participation. A witness must be present for the informed consent process, and must sign the informed consent document as well."

We have included a line in the informed consent document for a witness's signature.

The Sponsor will provide oversight of Informed Consent documentation per GCP guidelines.

5. *Although the protocol on page 52 states that the experimental sessions will be conducted in a private practice setting, the protocol does not adequately describe the site where the sessions will be conducted.*

The following text will be added section 8.4 of the protocol, on page 52:

"Experimental sessions will take place in the PI's home therapy office, located 3.3 miles from Marin General hospital in a residential area. The Study Coordinator will have an office on-site. The treatment room will be comfortably furnished, with an adjacent restroom. An overnight room will also be used following experimental sessions, and there will be space for both the co-therapy team and a night attendant to remain on-site overnight if necessary. The PI will also remain on-site overnight."

In addition, the following text will be added to page 10 of the ICF:

"Experimental sessions will take place in Dr. Wolfson's home psychotherapy office, located 3.3 miles from the Marin General Hospital. The treatment room will be comfortably furnished, with a bed in which you will sit or lie on during the MDMA experience along with chairs for both co-therapists. The treatment room has a restroom nearby. The treatment room will be equipped with video cameras to record the sessions and stereo and speakers for music during the sessions. The treatment room has windows from which only trees, bushes and landscaping is visible and is in a quiet location. A nearby overnight room will also be used following experimental sessions, and there will be space for both the co-therapy team and a night attendant to remain on-site overnight if necessary. Dr. Wolfson will also remain on-site overnight."

Should any of these responses prove unsatisfactory, we will have Amy Emerson, MAPS Director of Clinical Research, available to respond via phone during the RAPC meeting should you be willing to call us at 510-393-7224 so that we can address any additional concerns immediately. Should you decide to require the optional text that we have proposed, we can send you all revised documents within a day or two after we receive comments from your meeting on November 19, 2014.

We will let you know prior to your November 19, 2014 meeting what we hear from the FDA regarding our protocol.

Sincerely,

Benjamin Shechet
Clinical Research Associate
and
Amy Emerson
Director of Clinical Research