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May 21, 2013

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
RE: IND 63,384; Form 1571, Serial No. 0038

Response to FDA Advice Letter on MAA-1 submission, dated April 30, 2013

Dear Division of Psychiatry Products/CDER,

Please find below our responses to the FDA Advice Letter, dated April 30, 2013, on the submission of the study protocol MAA-1, "A Placebo-controlled, Randomized, Blinded, Phase 2 Pilot Safety Study of MDMA-assisted Therapy for Social Anxiety in Autistic Adults."
We are responding to comments 2, 3 and 4 based on current scientific literature and current practice in the Sponsor's ongoing clinical trials under the same U.S. IND #63,384.

1. We appreciate the FDA Advice Letter stating that the reviewers determined the study is reasonably safe to proceed as currently written.

2. Risk of Serotonin Syndrome

The reviewer states "Because of the risk of serotonin syndrome, we recommend that patients treated with serotonergic drugs undergo a washout period of longer than 5 half-lives of the drug; the pharmacodynamic effects of such drugs are longer-lasting than the pharmacokinetic effects. Patients treated with fluoxetine should have a washout period of at least one month, because the active metabolite norfluoxetine has a longer half-life than fluoxetine."

The accompanying revision to the protocol now has additional information on medication washout in Section 9.0 Concomitant medications. A table containing information on commonly used psychiatric drugs and their half-lives has been added and protocol text has been revised to indicate that a "washout period of at least 5 half lives of the drug and active metabolites plus one week for stabilization" would be required for pre-study medications in order to overcome any withdrawal effects and minimize the chance of interfering with MDMA effects from secondary brain changes, such as receptor down regulation.

We would like to bring to the reviewers attention that at least four teams of investigators, three of them independent of each other, and using different compounds (paroxetine, citalopram, duloxetine and fluoextine respectively), have administered selective serotonin reuptake inhibitors (SSRIs) prior to MDMA [1-7]. These drugs mainly attenuated the acute effects of MDMA,

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possibly including those of therapeutic value, such as increased interpersonal closeness and changes in recognizing facial expressions of emotion. The literature does not currently support deleterious drug-drug interactions such as Serotonin Syndrome caused by combining SSRIs and MDMA. Hence the main issue for this study is competition of SSRIs with MDMA for the 5HT transporter eliminating potentially beneficial effects of MDMA, and not producing Serotonin Syndrome. Please see p. 10 of the Sponsor's Investigator Brochure (IB) in Section 7.1.1 for further information.

Monoamine oxidase inhibitors, and not SSRIs, have been associated with reports of serotonin syndrome and death in combination with MDMA [8, 9]. Findings from preclinical research on the impact of SSRIs on the effects of MDMA also supported a reduction in many acute MDMA effects [10]. The current protocol as written includes several features that address these findings.

a. Subjects who require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs are excluded from the study.

b. The physician should not prescribe an SSRI, SNRI, or MAOI as a rescue medication, unless it has been determined that the subject will be withdrawn from the study. See Protocol, p. 54 under Section 9.0 for more details.

3. CYP2D6 Inhibition by MDMA

The reviewer states, "MDMA is a potent inhibitor of CYP2D6. Furthermore, it is a sensitive substrate of CYP2D6. Thus, MDMA significantly inhibits its own metabolism. Patients who require treatment with a drug that is a CYP2D6 inhibitor must be excluded from the study. Patients requiring treatment with a drug primarily metabolized through CYP2D6 must also be excluded from the study. Patients who are CYP2D6 poor metabolizers must be excluded from the study. The protocol must be amended to include these requirements."

We have considered the reviewer's concerns about the effect of CYP2D6 inhibition by MDMA on study subjects. We agree with the reviewer that patients who require ongoing treatment with any drug that inhibits CYP2D6 or is metabolized by CYP2D6 should be excluded from the study. This is already stated regarding psychiatric drugs in Exclusion Criterion Number 14: "Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs." We have also added a requirement to Section 9.0 Concomitant Medications that any atypical antipsychotic medications used as a "rescue medication" within a week after experimental sessions should not be primarily metabolized by CYP2D6, such as quetiapine instead of risperidone.

Only in regards to the use of psychostimulants in the treatment of ADHD, due to the short half-life of these drugs, have we used the procedure listed in Inclusion 8 in this protocol and in studies of MDMA-assisted psychotherapy in people with PTSD. With the accompanying revision inclusion 8 now states, subjects to be enrolled must be "willing to refrain from taking any psychiatric medications for at least 5 half-lives of the drug and active metabolites plus one week

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for stabilization prior to the experimental session. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue at least 5 half-lives and one week before the experimental session and do not restart for 10 days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician." The extended period of abstention from medication was arrived at on the basis of recent studies of MDMA pharmacokinetics [11, 12].

Unfortunately there is no scientific literature available on potential drug-drug interactions of MDMA with atypical antipsychotics, some of which are also metabolized by CYP2D6. In a previous study, the typical antipsychotic haloperidol was administered prior to MDMA exposure and this had no effect on MDMA-induced physiological changes. The moderate dose ranges to be used in the current protocol are within the range of the doses used in a study of 1.5mg/kg MDMA demonstrating these results [13]. In order to ensure drug interactions are not a concern, we have improved upon concomitant medication restrictions in the accompanying revision to the protocol as discussed in Section 9.0 of the protocol.

We think that the literature we cite below indicates that it is not necessary to screen for or exclude subjects who are CYP2D6 poor metabolizers.

Starting in 2004, de la Torre and colleagues demonstrated that an active dose of MDMA inhibits CYP2D6 in people with functioning enzyme, and that administration of MDMA to a single poor metabolizer had relatively minor effects on physiological function [3, 18-20]. Later research has confirmed these effects via examining the effects of MDMA on dextromethorphan metabolism [11, 12]. These findings led de la Torre to state in the abstract of a recent review, "The fraction of metabolic clearance regulated by CYP2D6 for both drugs is substantially lower than expected from in vitro studies. Other isoenzymes of cytochrome P450 and a relevant contribution of renal excretion play a part in their clearance. These facts tune down the potential contribution of CYP2D6 polymorphism in the clinical outcomes of both substances." [15] To date, this team is also the only group to report testing participants for CYP2D6 enzyme function prior to enrollment and sometimes excluding participants on the basis of test results [e.g. 20, 21]. Approximately 755 individuals in completed and ongoing Phase 1 and Phase 2 studies have received MDMA without incident in studies to date where no genotyping for CYP2D6 was performed. The references for these studies are included in the study protocol on p. 12, Section 2.2.5. Furthermore, researchers examining MDMA-related fatalities failed to find an association between likelihood of death and variations in CYP2D6 function[22].

The FDA currently recommends, but does not require, genetic testing prior to initiating a treatment with many SSRIs [14] . MDMA, administered at moderate doses on 2 occasions scheduled one month apart, is the active ingredient in the proposed study. Like SSRIs, MDMA is one of many compounds metabolized by the enzyme P450 CYP2D6 (or CYP2D6). However, it is also metabolized by other cytochrome P450 CYP enzymes, including CYP1A2, CYP3A4, and CYP2D6 [11, 15]. This is discussed on pp. 11-12 under Section 7.1.2 in the Sponsor's IB. CYP2D6 poor metabolizers have been reported to experience trends towards increased adverse events and often discontinue use of the atypical antipsychotic risperidone which is primarily

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metabolized by CYP2D6[16]. A recent systematic literature review of clinical outcomes of risperidone treatment in CYP2D6 poor metabolizers found that outcomes were not significant and does not recommend CYP2D6 genotyping for screening [17].

The current data suggests that it is unnecessary to test for or to exclude people with variations in CYP2D6 phenotype. Our current investigations of MDMA-assisted psychotherapy in subjects with PTSD do not exclude people on the basis of variation in CYP2D6 function. We therefore request that we not be required to conduct screening for CYP2D6 enzyme function.

4. The reviewer states, "Patients with cardiac valvular disease should be excluded from the study. During screening, the examining physician must assess for a history of cardiac valvular disease and signs and symptoms of cardiac valvular disease."

Subjects with valvular heart disease (VHD) and significant cardiac conditions are now excluded from the study under the revised exclusion criterion #5. Because of its activity at $5HT_{2B}$ receptors, some researchers have hypothesized that MDMA could increase risk of VHD[23, 24]. (See p. 37 under Section 9.2.3.2 of the IB). This risk was not considered significant by Dr. John Mendelson, the senior author of the only published study to investigate the acute cardiovascular effects of MDMA in healthy volunteers using 2-dimensional quantitative Doppler echocardiography (see letter provided with this submission in regards to ongoing studies of MDMA-assisted psychotherapy for treatment of PTSD). Note that to date, there is only a single case of VHD reported in an extremely heavy ecstasy user [25], and a comparison of heart abnormalities in a sample of ecstasy and polydrug users suggests that such indications may occur only after very high exposures (equal to or greater than 900 exposures [26]). However, excluding people with VHD is in line with excluding people with serious heart conditions and will reduce any potential exacerbation of an existing condition.

Summary of Response to Advice Letter

In response to the advice offered from the FDA in the letter dated April 30, 2013, we now provide additional information on medication washout and state that washout will be for "*at least 5 half lives of the drug and active metabolites plus one week for stabilization*" for SSRIs and other common psychiatric drugs, and we will specify that diagnosis with VHD is an exclusionary factor for study participation. After examining the literature, we request that the recommendation concerning excluding participants with variants in the CYP2D6 gene be withdrawn since it would unnecessarily exclude subjects. We have not made any changes in inclusions addressing CYP2D6 genotype in the submitted revised Protocol Version 2. Other changes have been made that address reviewer concerns in line with current scientific literature and ongoing clinical trials with the study drug.

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