Post to Megan Aiken sent Feb 18, 2010 pre-review questions

Re: MAPS Study **MP8**; ""A Randomized, Triple-Blind Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in conjunction with manualized psychotherapy in 16 Veterans with Chronic Posttraumatic Stress Disorder (PTSD)""
IRB Tracking #: **MAP3-10-051**

Hello Megan

Please find our answers to Board queries below. I have also included the following items:

RRPQ Scale and Scoring
CSSRS Baseline and Last Visit measure
Combined CAPS
A paper referring to the PTGI as a validated scale
Copy of the draft training manual
Copy of the telephone script for study MP8
Copy of guidelines for administering the GAF.

I hope these answers reach you in time for the meeting and are helpful. Please let us know if you have any further questions

Ilsa Jerome

On Tue, Feb 16, 2010 at 12:35 PM, Megan Aiken <MAiken@cgirb.com> wrote:

Hi Ilsa,

The Board will review new study MP8 (IRB tracking #MAP3-10-051) at the meeting on Thursday, February 18th. Upon a preliminary review, the Board has asked me to send the following questions/requests:

1. The accompanying information re: CAPS describes the CAPS-Sx, the CAPS-Dx and the later combined "CAPS." What has been provided is the CAPS- Dx. Confirm that the CAPS-Dx is the intended scale to use, as opposed to the later-combined "CAPS." If so, the protocol should qualify the CAPS throughout as CAPS-Dx.

We will be using the combined CAPS. Please see the attached file with combined CAPS.

2. Provide actual copy of the Global Assessment of Functioning for our records.

Please see attached document on the Global Assessment of Functioning, located via internet search and presenting text from the scale as presented within the DSM-IV TR. The scale can be found on p. 32 of the DSM-IV TR, as stated at the top of the Wikipedia entry for the scale sent to the Board with the application. Ratings are made by the clinician and it is a single, 100-point rating scale, there is thus not more detail beyond that described.

3. Is the PTGI-C a validated scale? Is the copy provided what will be used, or will the on-line version be used? If so, please provide copy of on-line version for our records.

It is a validated scale, as noted in Zoellner et al. 2006, also provided (please see attached, first page). The copy provided is the scale. It will not be given on-line but as a pencil-paper self-report measure.

4. Please provide a copy of SCID (pg 19 Section 6.0 Methods)

A hard copy of the SCID will be mailed to the board upon request. it is a lengthy document and not amenable to faxing or easy electronic mailing.

5. Please provide a copy of RRPQ (pg 22 (Section 6.1.2)

Please see attached copy of the RRPQ measure and scoring. This is the same measure used in the first investigation by this PI, MAPS study 63,384 or MP1, IRB tracking number MAPS1-03-077..

6. Please provide a copy of the C-SSRS for our records.

This is the same measure used in the second study CGIRB approved with this PI, MAPS study MT1, IRB tracking number MAP3-09-385. Please see attached Baseline and Sine Last Visit CSSRS scales.

7. Please provide a copy of MAPS' treatment manual (pg 27 Section 6.2.3) for our records.

As with the CSSRS, this was provided previously in reference to MAPS study MT1, IRB tracking number MAP3-09-385. Please see attached copy of training manual.

8. The Investigator's Brochure is over 2 years old. In keeping with 21 CFR 312.55, is a revised IB anticipated?

Yes, as agreed to when reviewing MAPS Study MT1, IRB tracking number MAP3-09-385, we will complete revision of the new IB by June, 2010, with the revised IB supplied as soon as it is completed, at this time or an earlier date if completion occurs earlier.

9. Confirm who will have the code/key to the six different doses used for this study, the compounding pharmacist or the "randomization monitor." Who does the investigator contact should a need to break the blind occurs?

The compounding pharmacist and randomization monitor will be unblinded. Section 5.2 of the protocol (second paragraph) states, "If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, the blind may be broken for an individual participant." There will be sealed envelopes as before, in the first study conducted by the PI (study 63384), made up by the randomization monitor. They'll be in

the safe with the MDMA in the room adjacent to where the experimental sessions are done so the investigators can break the blind immediately if needed.

10. Please identify the Independent Rater and who is the Randomization Monitor?

The independent rater will be Mark Wagner PhD, the same independent rater for the first study conducted by the PI and approved by CGIRB (MAPS study 63,384, IRB tracking number MAPS1-03-077), and/or his assistant. The randomization monitor is to be announced but will be an individual, as a graduate student, working with Mark Wagner.

11. The first paragraph of Section 5.2 ends on the top of pg 16 with an incomplete sentence: Twenty… Please complete.

The word "Twenty" is not meant to be there; the paragraph ends with the sentence concerning the randomization monitor supervising filling of bottles.

12. Please elaborate on the statement in Section 5: There will be preliminary examination of the data before all participants have completed the 12-month follow-up. Is this an interim analysis of some sort; if so, for safety or efficacy?

The interim data analysis will be conducted after the experimental sessions are completed and after the two-month follow-up has been completed. The interim data analysis will be conducted for safety and efficacy.

13. Has a copy of the telephone screening script been provided?

Please see attached copy of the telephone script.

14. Will subjects whose symptoms are controlled on psychiatric medications be allowed in the study, for example persons with depression who are adequately controlled?

Yes. They would have to taper off any medications in time for washout of the drug (5 times the half life of the particular drug) before the first experimental session. People with depression and other psychiatric diagnoses other than the ones specifically excluded in the list of exclusion criteria will be allowed in the study. Information on medication tapering can be found in section 6.2.1, “Prescreening, Screening and Baseline Evaluation”, and inclusion #5 states that participants must be willing to refrain from taking psychiatric medication during the study period. This is the same as for our previous study, MAPS ID 63,384 (MP1), IRB tracking number MAPS1-03-077.

14b. Note--Not all Consent Quiz answers were highlighted for “correct” response.

[I cannot find a case where this was not true.]

15. Confirm that subjects who pose a risk to others are excluded and will be discontinued, should they become such a risk.

Participants who pose a risk to others would be excluded and would be removed from the study if they became a risk to others.

16. Confirm that, as per Section 13.2, further evaluation of carotid US and exercise stress testing is at no cost to subject?

Since such tests would be solely for determining study enrollment, they would be at no cost to study participants.

17. Inclusion # 4 can be interpreted in that subjects who do live within driving distance do not need a therapist. Please confirm.

This is true.

17b. What is considered a “reasonable” driving distance?

Approximately two hours from the study site.

17c. Should subjects in this early phase study have an on-going therapeutic relationship with a psychotherapist or psychiatrist?

It might be ideal but not necessary. Participants will be undergoing a course of psychotherapy with the PI and co-investigator. Veterans are often underserved with respect to supporting psychotherapy.

18. Will any potential subjects be patients of the PI? If so, is there a limit?

It is unlikely that any patients of the PI will be study participants, and no limit on patients of the PI has been determined. At present we expect that no patients of the PI will be enrolling in this study.

19. If the subject cannot be reached for the phone contact, what is the follow-up plan, particularly if this is a call where the C-SSRS is to be administered?

Participants who cannot be reached by telephone are very unlikely to be enrolled in the study, as participants are expected to be reached daily for seven days after each experimental session. As telephone contact occurs not just to assess suicidality but to assess participant well-being, this is an essential part of the study, and is even listed as an inclusion (#12, "are willing to be contacted via telephone for all necessary telephone contacts"

If we were unable to reach a subject by telephone despite repeated attempts, every effort would be made to contact their outside physician or a family member to be sure they

received any support they needed. If we eventually contact the person they would only be allowed to continue in the study if we could be assured that such a problem would not recur.

20. What is the contingency plan if suicidal intent is endorsed?

Seriousness of suicidal intent would first be evaluated by the investigators both informally and through administrations of the CSSRS. Depending upon what is learned from evaluation, the investigator might increase support for and discussion with the participant, increase contacts or if during an experimental session, remain with the subject, consider hospitalization as described as a response to extreme psychological distress described in Appendix A on p. 61.

20b. What if this is with a subject who "does not live within driving distance?"

The same procedures would be in place; increased telephone contact could be used if additional appointments were not a viable option. In addition, since anyone outside driving distance would have to have an outside therapist, that therapist would be enlisted to provide evaluation and support.

20c. When the subject gives the release for the PI to communicate directly with their therapist (Inclusion # 4.), does this allow the PI to communicate with that therapist in instances when suicidal intent is endorsed?

Yes.

21. Section 7.4.1 reports no need for any clinical intervention for elevated BP to date. What criteria would be used to treat BP, in mitigating that potential risk?

First, people with elevated BP above cut-off will have BP assessed more frequently, as stated on p. 21 under "Safety Measures." Medication will be used to lower blood pressure if necessary. This is not explicitly stated but the presence of medications for treating hypertension is described as part of "Medical Emergencies," 7.5, where on pp. 39-40, the text states "The offices are located 2.6 miles from the nearest emergency room. The office will be equipped with a "crash cart" containing the emergency drugs and equipment necessary to respond to any complications. Intravenous fluids, antiarrhythmic drugs, antihypertensive drugs (such as nitroprusside and labetolol), injectable epinephrine and other pressor agents, and other standard emergency drugs and equipment will be available on-site as a means of treating any potential allergic reactions or other medical emergencies. "

The current standard of care is not to administer treatment for acute blood pressure elevations based on any specific blood pressure level, but only if there is evidence of end organ damage associated with severely elevated blood pressure, (usually a diastolic pressure of > 120 mmHg), ie: stroke or subarachnoid hemorrhage, hypertensive encephalopathy, myocardial infarction or unstable angina, acute pulmonary edema or

acute congestive heart failure, aortic dissection. If the blood pressure were to become severely elevated the PI (board certified in emergency medicine and internal medicine as well as psychiatry) would evaluate for signs or symptoms of any of the above conditions and respond accordingly, initiating treatment and/or arranging transport to the hospital if needed. A good summary of criteria for treating acutely elevated blood pressure is found in Flanigan and Vitberg, Hypertensive Emergency and Severe Hypertension: What to Treat, Who to Treat, and How to Treat, Med Clin N Am 90 (2006) 439–451, which states, "Virtually all episodes of hypertensive emergency are associated with a diastolic blood pressure (DBP) O120 mm Hg; however, most patients who present with severe hypertension do not have a hypertensive emergency. It is crucial to recognize that not only will these patients not benefit from aggressive normalization of blood pressure but also there can be substantial morbidity caused by overly rapid decreases in blood pressure in patients who do not have rapidly evolving end-organ damage. Distinguishing between these two groups of patients is the first step in the safe management of significantly hypertensive patients....Hypertensive emergency is defined by acute and rapidly evolving end organ damage associated with significant hypertension, usually a DBP O 120 mm Hg. Controlling blood pressure within hours is desirable and requires admission to a critical care setting."

21b. Section 7.5 pg. 40 refers to “the same contingency plans will be used in this protocol.” This protocol should contain a description of the contingency plans.

The contingency plan referenced within 7.5 is described in full within Appendix A, p. 60 and p. 62

22. Is there a limit to the number of antihypertensive medications a subject can have to control BP and still be on study?

No.

22b. Would someone requiring triple therapy be allowed?

Yes, so long as the investigators determine that none of the medications directly interfere with MDMA, or vice versa. However, the same would be true of a participant on monotherapy.

23. Section 13.0 Informed Consent states “A second informed consent form (ICF) will be obtained from all medium and active-placebo dose subjects who elect to go through the open-label Stage 2 process.” However, only one consent document is provided that appears to capture Stage 2 ‘by default.” Is a second consent form intended or not, particularly as many months can elapse before getting to Stage 2?

That is a holdover from when two consent forms were provided. Signing the single consent form will be considered an indication that a person is willing to enroll in Stage 2. Upon unblinding, they may continue to do so or choose not to do so, and they will be considered completing the study in either case.

24. Given that 48 weeks of therapy is standard of care for Hepatitis C, confirm that: "After this evaluation and completion of any recommended treatment, if the Hepatitis C is judged by this physician to be relatively stable and of mild severity the person may be enrolled if there are no other contraindications."

Yes, whatever course of therapy the hepatitis specialist recommends will need to be completed before someone could be enrolled.

25. Please define, as per Exclusion 8. how a "serious" suicide risk is defined. Is this based off scores from the C-SSRI and/or BDI? Please quantify or qualify this exclusion risk.

Serious suicide risk is determined chiefly through psychiatric interview, responses to CSSRS and through the clinical judgment of the investigator. The BDI does not provide sufficient information for assessing suicide risk and is not meant for that purpose.

Any responses you could provide prior to the meeting (which begins at 1 p.m. EST on Thursday) would be very helpful. If you have any questions regarding this email, please feel free to contact me.