IND 110513

PARTIAL CLINICAL HOLD

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Amy Emerson
Chief Executive Officer
3141 Stevens Creek Blvd #40547
San Jose, CA 95117

Dear Ms. Emerson:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for marijuana, cannabis sativa (containing delta-9-tetrahydrocannabinol and cannabidiol).

We also refer to your amendment(s) dated March 8, 2021 and to our partial clinical hold letter dated May 10, 2021, which cited the reasons for placing the study you proposed, protocol MJP2, titled "Phase 2 Multicenter Randomized Placebo-controlled, Double-blind, Parallel Study to Assess the Safety and Efficacy of Inhaled Cannabis in Veterans for Treatment of Posttraumatic Stress Disorder (PTSD)," on clinical hold and the information needed to resolve the clinical hold issues.

On further review of your submission, we have identified a second deficiency and reason for placing protocol MJP2 on clinical hold (shown below in italics).

The following are the specific deficiencies and the information needed to resolve the deficiencies.

21 CFR 312.42(b)(2)(i): Insufficient information to assess risks to human subjects

CHEMISTRY, MANUFACTURING, AND CONTROLS
We note you have provided a representative certificate of analysis (COA) for a batch of cannabis material. This is not adequate.

To resolve this deficiency, you must provide the COA for the batch of cannabis material to be used in the clinical trial. The COA should include at least an assay of all cannabinoids, moisture content, pesticides, mycotoxins, elemental impurities testing, and microbial testing.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CLINICAL
Study MJP2 will use a cannabis product with a THC concentration up to twice the concentration of the product used in the completed Study MJP1 (15% to 25% versus 12.4%). Study MJP2 will permit subjects to decide how much cannabis product is consumed each day (up to 3 g/day), the method of administration at any inhalation session (inhalation from cigarettes or from a vaporizer), and the timing of inhalations each day (for example, once daily versus four times throughout a 24 hour period). These variables may produce wide variation in the amount of THC delivered, both within subjects and between subjects. Because the assessment of the safety of this study depends primarily on the amount of THC delivered, we do not have sufficient information to assess the risk to human subjects under the dosing conditions described in the protocol. Under a scenario of maximum THC delivery (e.g., use of all 3 grams of product within a single 60-minute session each day via vaporization), you have provided no data to show that such use would be reasonably safe and well-tolerated.

To resolve this deficiency, you must provide data to support that the delivered amount of THC would be reasonably safe and well-tolerated under the conditions of use described in the revised protocol (particularly at the highest dose proposed). We need specific information (e.g., published literature) on the expected safety (nonclinical and clinical) for the entire proposed dosing range for this particular formulation and for the proposed delivery methods (i.e., smoked and vaporized).

Until you have submitted the required information, and we notify you that you may initiate the clinical study, you may not legally conduct the identified clinical study under this IND.

Please identify your response to the clinical hold issues as a "**CLINICAL HOLD COMPLETE RESPONSE**." To facilitate a response to your submission, submit this information in triplicate to the IND. In addition, send a copy of the cover letter to CDR Sarah Seung.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

In addition, we have the following recommendations and requests that are not clinical hold issues.

CLINICAL

1. We strongly recommend a fixed-dose study design to characterize the dose-response relationship for THC in the treatment of patients with PTSD. The amount of cannabis product adminstered each day, the route of administration (smoking versus vaping), and the timing of administration should be prespecified for each treatment

arm. As currently designed, there is a potential for considerable variability in administered dosage of THC; this may make the resulting data uninterpretable.

2. We recommend that you enroll a broader sample of patients with post-traumatic stress disorder (PTSD; e.g., including non-Veterans with PTSD). This would allow greater generalizability of the study results.

3. On Days 1 and 2, patients would inhale a very small amount of study cannabis to train them on the use of the vaporization devices, to teach them skills to cope with potential side effects, and for observation over 3 hours to monitor vital signs and for adverse events. An ECG tracing and laboratory tests would be assessed only at screening. Also, the Columbia-Suicide Severity Rating Scale (C-SSRS) would be assessed on Day 1 and Day 35. We have the following recommendations to enhance the safety monitoring in this trial:

    a. Consider administering a typical dose of study cannabis on Days 1 and 2 to adequately evaluate the anticipated safety profile for each patient during the outpatient phase of the trial.

    b. Perform a 12-lead ECG tracing on Day 1 or 2 at 15 minutes after self-administration of study cannabis to assess the acute effects of THC on ECG parameters.

    c. Assess laboratory tests at end-of-treatment (Day 35) to assess the effects of THC on laboratory parameters.

    d. Assess the C-SSRS on Day 14.

4. The protocol indicates that Accurate Symptom Reporting Training (ASRT) would be conducted to improve awareness of symptoms. Also, a Placebo Response Reduction Training Program (PRRTP) would be implemented to reduce the placebo response. However, the protocol provides only limited information on these two activities. You should describe these measures in sufficient detail in the study protocol to ensure that they are uniformly performed for all subjects.

STATISTICAL

1. The protocol should pre-specify each attribute of the estimand for the efficacy of primary interest, with the rationale to support the proposed estimand, including strategies to handle intercurrent events and missing data. For details, please refer to ICH E9(R1) Addendum on https://www.gmp-compliance.org/guidemgr/files/E9-R1_Step4_Guideline_2019_1203.pdf

2. SDS: This scale appears to be a self-reported tool comprising three domains. The first domain “work/school” assesses how much “symptoms have disrupted your work/school work.” Under this domain, there is a check box for “I have not worked/ studied at all during the past week for reasons unrelated to the disorder.” Any subject who checked the box would not be able to respond to the first domain. This type of missing data would be different from other subjects who had worked/studied but did not respond to the first domain. Also, for subjects who did not check this box, clarify how you can determine whether it is because they had worked/studied (hence, not checking the box) or not (hence, resulting in missing data). To be able to reliably identify the two cohorts of missing data, we recommend adding a question to the case report form; the question should ask if the subject did not work during the past week due to reason related to PTSD. You would also need to pre-specify how to handle these two kinds of missing data in analyses. We do not consider it appropriate to impute missing data on the first domain based on data from the other two domains.

3. Because of the planned interim analysis for potential sample size re-estimation, you should submit the SAP before trial initiation. The SAP should be finalized before the planned interim analysis. The SAP should clearly list all objectives (e.g., early stop for futility or superiority, sample size increase) of the interim analysis, and provide detailed justifications for the overall type I error control for the primary and the key secondary endpoints. You should also submit the DMC charter for our review.

CONTROLLED SUBSTANCE STAFF

If you intend to develop your product commercially with the goal of submitting an NDA, we recommend that you submit an overview of your plan for addressing abuse and dependence in your marketing application for our review and comment. Refer to guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017), as you develop your plan. We acknowledge that some of the requirements outlined in the guidance may be addressed through analysis of published literature. Therefore, include any plans for doing so in your proposal.

If we have additional comments or information requests not related to this clinical hold, we will notify you. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

Please cite the IND number listed above at the top of the first page of any communications concerning this application

SUBMISSION REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[2]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[3]

SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [redacted]. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact CDR Sarah Seung [redacted]

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

[2] http://www.fda.gov/ectd
[3] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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