IND 110513

CONTINUE PARTIAL CLINICAL HOLD

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Amy Emerson
Chief Executive Officer
3141 Stevens Creek Blvd #40563
San Jose, CA 95117

Dear Ms. Emerson:

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 amendments dated November 29 and December 10, 2021, that provide a response to our May 10 and June 3, 2021, letters which cited the reasons for placing 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.

We have completed the review of your submissions and have concluded that removal of the clinical hold from the following proposed study is not warranted. Specifically, the following issues have not been resolved:

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

CHEMISTRY, MANUFACTURING, AND CONTROLS

Microbiology

1. You submitted an amendment to this IND in 2017 to revise the storage conditions of the cannabis to frozen conditions (-20°C) until immediately prior to dispensation, and you stated in that amendment that the participants would receive a new supply each week from frozen storage to ensure a fresh product to limit the likelihood of yeast and mold being present. However, in the December 10, 2021, information request (IR) response, these storage conditions have changed, and no explanation is provided.

   To resolve this deficiency:

a. Confirm that this same dispensing process of giving participants a new supply of frozen cannabis material each week will occur as defined in the 2017 amendment. If the dispensing process had changed, provide an explanation for the change.

b. Justify the change in storage conditions of the cannabis prior to dispensing to participants, as described in the December 10, 2021, IR response. Include an explanation of whether the likelihood of yeast and mold growth under these storage conditions remains a concern.

Drug Product

2. We acknowledge your submission dated November 10, 2021, SN 0019, which lists [redacted] as a new drug product supplier. Additional information is needed.

   To resolve this deficiency:

   Provide quantitative composition of the drug product including excipients. Include any processing aids added during manufacturing.

3. We acknowledge your submission dated December 15, 2021, SN 0022, which states, “The Sponsor commits to supplying an additional CoA containing all requested elements to the Agency reflective of the alcohol washed placebo product once the alcohol wash has been completed on this batch.” Additional information is needed.

   To resolve this deficiency:

   a. Provide a certificate of analysis for the placebo showing testing for cannabinoids, pesticides, residual solvents, elemental impurities, mycotoxins (at least aflatoxins and ochratoxins) and microbiological testing.

   b. Clearly state if the placebo will be prepared from a single cannabis batch or if several batches will be blended.

   c. Provide a brief outline of the manufacturing process including all solvents used.

   d. Provide stability data for the placebo which includes testing for cannabinoids, mycotoxins (at least aflatoxins and ochratoxins) as well as microbiological testing.

   e. These requirements may be satisfied by obtaining and submitting a letter of authorization to reference an existing IND, NDA, or supplier's drug master file (DMF) that contains the required information.

Botanical

4. You have not provided information on the manufacturing of the placebo. It is unclear what your post-harvest processing steps are prior to the placebo's use by participants in the study.

   To resolve this deficiency:

   Provide the full manufacturing process for the placebo, starting from plant harvest. For the placebo proposed for use in your study, per the guidance for industry, *Botanical Drug Development* (December 2016), provide the following: Post-harvest processing (e.g., washing, drying, and grinding procedures); control of foreign matter (i.e., inorganic and organic contaminants such as soil, insects, and algae/fungi); preservation procedures; handling, transportation, and storage conditions; tests for elemental impurities; microbial limits; tests for residual pesticides, including parent pesticides and their major toxic metabolites; and tests for adventitious toxins (e.g., aflatoxins), foreign materials, and adulterants.

5. We acknowledge your statement "the Sponsor no longer intends to use hemp product Catalog [redacted], Lot [redacted] as placebo in MJP2. The placebo product will instead come from an older lot of the [redacted] cultivar of cannabis obtained from supplier [redacted] on which an alcohol wash will be completed in order to remove cannabinoids. This batch failed the d9-THC specification as it had converted into THC-A and is an ideal lot to be converted into a placebo control." However, we are unaware of any literature or research demonstrating delta-9 THC converting back to THC-A in botanical raw material. This proposed conversion may signal a botanical raw material control issue.

   To resolve this deficiency:

   Provide scientific references or data to justify the statement "d9-THC converting to THC-A" in your botanical raw material (i.e., [redacted] cultivar). If data exists of this conversion in your cultivar proposed for use, provide it for assessment. If no data exists, consider use of a cultivar with adequate botanical raw material controls as your placebo; refer to the *Botanical Drug Development* guidance for industry.

CLINICAL

You have not provided 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. The information submitted does not inform 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).

The scientific literature submitted does not support the safety of use of cannabis products with 25% of THC by inhalation in human subjects, for the following reasons:

Daily dose of cannabis products with 25% of THC

The Division had requested specific information on the expected safety for the entire proposed dose range for this particular formulation. We acknowledge your proposal to reduce the maximum daily intake up to 2 grams (g) per day of cannabis product. However, under a scenario of maximum THC delivery (e.g., use of all 2 g of product within a single 60-minute session each day via vaporization), the amount of THC delivered would be about 500 mg. This dose is higher than maximum doses reported in the submitted scientific literature. The study reported by Ware et al. in 2015, for example, with a median daily dose of 2.5 g cannabis containing 12.5% of THC, produced a daily exposure of approximately 312.5 mg THC. Although the study permitted 5 g of cannabis per day, only 11 patients (5% of study population) received >3 grams of cannabis per day. Also, in the Ware et al. study, there was a report of convulsions that led to treatment discontinuation and was judged to be probably related to cannabis, which is a serious safety concern that you have not adequately addressed in your submission. Also, because baseline characteristics between the control group and the cannabis group were different, results should be interpreted with caution.

As you noted, while epidemiological surveys report that cannabis users smoke or vaporize an average of 3 g of cannabis daily, these surveys do not contain enough detailed information on cannabis potency and routes of administration to support the safety of high doses of THC administered through a specific route (vaping versus smoking versus oral administration).

Method of administration

The articles you cited do not support the contention that there would be comparable PK between smoking and vaping. There are several articles in the scientific literature reporting both PK and PD differences between smoking and vaporization (Spindle et al., 2018; Spindle et al., 2019).[1]

In addition, irrespective of differences in PK and PD between smoking or vaping, recent literature on combusted methods of cannabis administration raises serious concerns about the association between cannabis smoking/vaping and adverse outcomes on pulmonary function and increased respiratory symptoms (Dai and Richter, 2019),[2]

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[1] Spindle TR, et al. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: A crossover trial. JAMA Netw Open. 2018; 1(7): e184841.
Spindle TR, et al. Acute pharmacokinetic profile of smoked and vaporized cannabis in human blood and oral fluid. J Anal Toxicol. 2019; 43(4):233-58.
[2] Dai H, Richter KP. A national survey of marijuana use among US adults with medical conditions, 2016-2017. JAMA Netw Open. 2019;2(9):e1911936.

including the E-cigarette or Vaping Use-Associated Lung Injury (Layden et al., 2019).[3] Recent recommendations by the American Thoracic Society echoed these serious concerns (Neff et al. 2021).[4] The Ware et al., 2015, study you cited reports that medical cannabis users had a higher rate of developing respiratory AEs during 1 year of follow-up compared with controls.

To resolve this deficiency:

a. Modify the proposed maximum possible dose or provide scientific evidence that supports the safety of the currently proposed maximum dose. It is important to clearly specify the starting dose, dose titration and frequency of administration of cannabis in the proposed study.

b. Change the route of administration to a route without the aforementioned safety concerns or provide scientific evidence that the proposed routes of administration do not place the participants, who may not have had a history of smoked or vaped cannabis, at undue risk.

Therefore, the clinical hold on Protocol MJP2 remains in effect until you have submitted the required information and we notify you that you may initiate this clinical study, you may not legally conduct this study under this IND.

Please identify your response to the clinical hold issues as a "**CLINICAL HOLD COMPLETE RESPONSE**."

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

We remind you of the non-hold issues in our May 10 and June 3, 2021, letters. In addition, we have the following additional recommendations and requests that are not clinical hold issues. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Microbiology

1. We acknowledge the details of the manufacturing process of the THC-rich cannabis material. However, because of concerns about potential growth of microorganisms, especially yeast and mold, you should submit additional information:

[3] Layden JE, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. N Engl J Med. 2019;382(10):903-16.
[4] Neff S, et al. Inhaled marijuana and the lungs. Am J Respir Crit Care Med. 2021;204(5):9-10.

a. Identify any bioburden reducing steps that will be used in the manufacturing processes for the THC-rich cannabis and placebo cannabis material that will be used in the clinical study, such as gamma irradiation. The microbiological test results of [redacted] for Yeast and Mold Counts and [redacted] for the Total Aerobic Counts are surprising if there are no bioburden reducing steps, given the drying and storage conditions that are described for the manufacturing process.

b. We note that the drying process for the flower is performed at room temperature until a water activity value of "below 0.62" is achieved. You should clarify what is meant by "below." Note that water activity slightly below 0.62 can still support microbial growth, whereas a much lower water activity value is less likely to support microbial growth. See USP <1112> *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* for additional information.

c. You should confirm that the same drying processes and conditions that have been described for the THC-rich cannabis material will be used for the manufacture of the placebo cannabis.

Drug Product

2. We acknowledge your submission dated December 10, 2021, SN 0021, which states:

   - The drug product is bulk-packaged and vacuum sealed in Mylar bags for bulk transfer or for further packaging in secondary retail packaging. The product is stored in a secure, licensed storage room and maintained at a temperature of 17 to 22°C.

   - The study drug would be dispensed to participants in individual packets containing 2 grams of cannabis or placebo for ad libitum use up to 2 grams per day.

   We note stability data provided in your submission dated December 15, 2021, SN 0022. You should state how the cannabis was packaged and stored for this stability study and whether there are any differences between how the cannabis was packaged and stored for the stability study and how it would be packaged for and stored by study participants. If there are significant differences in packaging and/or storage, an in-use stability study looking at cannabinoids, mycotoxins (at least aflatoxins and ochratoxins) as well as microbiological testing may be needed.

3. We acknowledge your submission dated December 10, 2021, SN 0021, which states, "The Sponsor commits to placing each cannabis batch used in the clinical trial on stability with testing at intervals of initial, 1 month, 3 months, 6 months, 12

months, and every 6 months thereafter according to the schedule recommended by the Agency. The stability testing of cannabinoid levels will be performed for the length of time that the material is used in the trial." You should also commit to testing for mycotoxins (at least aflatoxins and ochratoxins) as well as microbiology testing at appropriate intervals including at least at the Initial and final stability study timepoint.

CLINICAL PHARMACOLOGY

1. Given the formulation and the dose level of cannabis product that you plan to use in the proposed study are different from those reported in literature, we recommend that you adequately characterize the pharmacokinetics of THC, CBD, and their major metabolites and determine the maximum tolerable dose of the cannabis product through single ascending dose, multiple ascending dose, and safety and tolerability studies following administration of the proposed cannabis product through the specific delivery methods that you intend to use.

2. Given there is a lack of dose-response information of cannabis for the treatment PTSD, you should conduct a fixed-dose study to evaluate a range of doses of cannabis for the treatment of PTSD in the proposed phase 2 study. This information is critical for the selection of optimal dose of cannabis for the treatment of PTSD in the phase 3 studies.

3. THC is mainly metabolized by CYP3A4/5, CYP2C9, and CYP2C19. THC has been reported as an inhibitor of CYP3A4/5, CYP2C9, and CYP2C19 and an inducer of CYP1A2. Therefore, we recommend that you provide evidence that supports the drug interaction liability of cannabis at the dose levels that would be evaluated in the proposed phase 2 study. Also, we recommend that you exclude drugs that are strong and moderate inhibitors/inducers of CYP3A4/5, CYP2C9, and CYP2C19, and drugs that are substrates of CYP1A2 in the proposed study to minimize the drug interaction risks associated with cannabis.

CLINICAL

There is evidence from your previous study (Bonn-Miller et al., 2021) that the study blind was not upheld when participants were assigned to high THC. This new study, as proposed, is not adequately designed to address the potential for unblinding. You should determine how you might modify the protocol to provide adequate blinding to meet study objectives and include an assessment of blinding in the protocol.

CONTROLLED SUBSTANCE STAFF

1. You propose to obtain the cannabis plant material containing a delta-9 tetrahydrocannabinol (THC) concentration of 25.0 ± 0.8% THC from [redacted] which appears to be licensed to distribute cannabis in Canada. We refer you to Drug Enforcement Administration (DEA) guidance regarding the Import/Export Permits

and Declarations (Controlled Substances) under 21 CFR 1312, which is available at https://www.deadiversion.usdoj.gov/21cfr/cfr/2112cfrt.htm. We recommend that you contact DEA directly regarding guidance for the importation/exportation of your product.

2. The dosing regimen for cannabis in the proposed study poses a risk of developing physical dependence and acute withdrawal symptoms after drug discontinuation, and the proposed 1-week follow-up period after cannabis cessation is not adequate to assess that risk. We recommend that you revise the clinical protocol to include a 4-week follow-up period with regular assessments after cannabis cessation. Specifically, we recommend cannabis withdrawal be assessed daily for the first 2 weeks after the last dose of cannabis and then every 3 days for the last 2 weeks. Also, you should describe in the protocol how you intend to manage and mitigate the risks of severe withdrawal symptoms.

3. During all phase 1, 2, and 3 studies, capture adverse events (AEs) that may be indicative of abuse potential (e.g., CNS-related, drug abuse-related) and provide detailed narratives for these AEs. The incidence of these AEs in comparison to placebo in trials should be reported by study, population, and dose and should be displayed in tabular format, including study number and type of study, subject ID number, narratives, case description and details. Tables should be created for higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE. Also, you should provide a list of terms that will prompt these reports, including AE terms such as euphoria, dissociative effects, impaired cognition and attention, psychomotor effects, inappropriate affect, overdose, misuse, or lost or unaccounted for medication and unjustified dose increases.

   Narratives describing these events should be provided, including time to onset in relation to drug administration, duration of the event, dose of drug, severity, medical outcome, and disposition of the subject (e.g., if the AE resulted in discontinuation from the study); also, indicate if more than one event was observed simultaneously, and if other drugs were taken by subjects at the time of the event. In addition, if available, provide pharmacokinetic measures for subjects reporting the event to understand if there is a temporal correlation between drug plasma levels and these AEs.

   Refer to section V.B. of the guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017), for additional details and recommendations.

4. We also recommend that you monitor for possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials. Additionally, you should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was used, as compared to expected use). Towards this end:

- Train investigators to capture cases of abuse, misuse, addiction and to monitor for drug accountability discrepancies before starting trials. In addition, instruct investigators to obtain more information and explanations from the subjects when there are drug accountability discrepancies.

- Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials (phase 1, 2, and 3). These data should include study number and type of study, subject ID number, narratives, case description, and other available details.

- Provide narratives for cases where the patients drop out from studies for reasons that might be coded as “protocol violation”, “lack of efficacy” (to eliminate the possibility of aberrant behaviors behavior in patients who drop out of the study supposedly due to lack of efficacy), “lost to follow up”, “non-compliance to study medication or procedures,” “over compliance” or for “other.” Case reports should be provided separately.

- Report any use of the investigational formulation by individuals other than the patients (e.g., family members, health care practitioners).

- Report any instances of drug accountability discrepancies that may have occurred at the study site level and identify the origin of the discrepancy and individuals involved.

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

Sincerely,

{See appended electronic signature page}

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

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.

/s/

BERNARD A FISCHER on behalf of TIFFANY R FARCHIONE
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