MJP2 Type A Meeting Briefing

Product: Cannabis
IND#: 110513

Version 1: 20 April 2023

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SPONSOR REPRESENTATIVE	Rick Doblin, PhD Founder and President MAPS

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List of Abbreviations

CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CBD	Cannabidiol
IND	Investigational New Drug
MAPS	Multidisciplinary Association for Psychedelic Studies
MAPS PBC	MAPS Public Benefit Corporation
MJP-1	Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
MJP2	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)
NIDA	National Institute on Drug Abuse
PTSD	Posttraumatic Stress Disorder
THC	Tetrahydrocannabinol
U.S.	United States

1.0 Administrative Information

1.1 Application Number

IND # 110513

1.2 Product Name

Cannabis

1.3 Chemical Name, Established Name, and/or Structure.

Marijuana, cannabis sativa or indica (containing 15-25% delta-9-tetrahydrocannabinol (THC) active ingredient or 0% THC placebo)

1.4 Proposed Regulatory Pathway

505(b)(2)

1.5 Proposed Indication(s)

Posttraumatic Stress Disorder (PTSD)

2.0 Meeting Information

2.1 Meeting Type Requested

Type A

2.2 Meeting Date and Time

The Sponsor proposes the following meeting dates for an in-person meeting:

May 15 - 24

2.3 Meeting Background Package Submission

The Sponsor has included the meeting package with this submission.

2.4 Sponsor Attendees, Affiliations, and Titles

Attendee	Title	Affiliation
Rick Doblin, PhD	Founder and President	MAPS
Allison Coker, PhD	Program Manager	MAPS
Josephine Torrente	Director	Hyman, Phelps & McNamara, PC
Suzanne Sisley, MD	President	Scottsdale Research Institute
Anton Harb	Iraqi War Veteran	Michigan Cannabis Regulatory Agency

2.5 Proposed Agenda and Time Estimates

Agenda Item	Estimated Time
I. Introductions	5 minutes
II. Discussion of Questions	50 minutes
III. Conclusions	5 minutes

2.6 Objectives of the Meeting

The objectives of this meeting are to discuss the 16 December 2022 Clinical Hold for Study MJP2 in order to overcome the clinical hold deficiencies. Specifically, to gain agreement from the Agency on the sufficiency of the safety information to support the:

- Proposed dosing paradigm.
- Proposed administration instructions.
- Inclusion of cannabis-naïve participants.

3.0 General Background

3.1 Cannabis Program

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a research and educational organization that is sponsoring clinical trials of whole plant marijuana (cannabis) for treatment of Posttraumatic Stress Disorder (PTSD), conducted under the United States Investigational New Drug Application (US-IND) 110513. Given the increasing prevalence of self-administration of cannabis among US military veterans with PTSD, there is strong public interest in scientific data assessing whether self-administration of whole plant cannabis may be an effective treatment for this indication.

3.2 Study MJP-1

The Sponsor completed the first randomized placebo-controlled trial of smoked cannabis for treatment of PTSD (MJP-1) under this IND using the investigational medicinal product (IMP) developed by the National Institute of Drug Abuse (NIDA). MJP-1 sought to gather preliminary evidence of the safety and efficacy of three formulations of combusted cannabis, each with a different concentration of cannabinoids (THC & CBD), versus placebo on PTSD symptom severity. The formulations of the IMP obtained from the NIDA Drug Supply Program used for MJP-1 were:

Table 1: Formulations of Cannabis IMP in Study MJP-1 Protocol

Formulation Term	THC potency	CBD potency
High THC	~ 12.4% THC	~ 0.03% CBD
High CBD	~ 0.53% THC	~ 13.94% CBD
THC+CBD	~ 7-9% THC	~ 7-9% CBD
Placebo	~ 0 % THC	~ 0% CBD

The study provided n=80 PTSD patients a total of 37.8 g of their randomly assigned formulation for each three-week treatment period along with a metal pipe for treatment delivery (smoked). Each formulation was provided to patients as 21 separate packages of 1.8 g of bulk marijuana for inhalational self-administration with instructions to not consume more than a single 1.8 g package per day. After a two-week cessation period, then were re-randomized into one of the three active treatment groups and were again dispensed 21 packets of 1.8 g bulk marijuana for the second three-week treatment period.

Adverse events were reported by 87.5% of patients across all treatment arms and were mostly mild or moderate and self-limiting. Thirty-seven of 60 patients who received THC, CBD, or THC/CBD during Stage 1 (61.7%) reported at least one treatment-related AE during Stage 1 and 45 of the 74 patients who received THC, CBD, or THC/CBD (60.8%) reported at least one treatment-related AE during the crossover, Stage 2. The most common AEs reported were cough (12.3%), followed by throat irritation (11.7%) and anxiety (10.4%). Most TEAEs (97%) resolved to baseline levels. Three of 80 patients (3.8%) reported an unrelated Serious Adverse Event (SAE) during the study, specifically heart palpitations (n = 1; THC+CBD, Stage 1 cessation period), pulmonary embolism (n = 1, High THC, Stage 2), and abscess (n = 1, High CBD, Stage 2). Across both Stages, 13 total patients terminated from the study early due to an AE (8.4%).

While the study was not powered to detect between-group differences in efficacy, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) was administered and provided useful insight into treatment effects.

In light of the lack of tolerability concerns with whole plant cannabis seen in this study, the Sponsor intends to initiate studies of longer duration that are adequately powered to detect between-group differences. Further given the increasing prevalence of self-administration of higher THC potency cannabis, the Sponsor intends that future research programs utilize IMP that more closely approximate the quality and THC potency of cannabis available within state-sponsored medical cannabis programs.

3.3 Study MJP2

The data from Study MJP-1 were used to inform the design of a second Phase 2 study for the use of inhaled botanical cannabis to treat PTSD, MJP2 Original Protocol Version 2, submitted under US-IND 11053, SN 0015 on 08 March 2021.

3.4 Conversion of IND 110513 to Research IND

MJP-1 and MJP2 are intended to contribute to the general body of scientific knowledge regarding the therapeutic utility of cannabis in individuals with PTSD. Reflective of the research focus of IND 110513, the funding for the development program is through state grants for public research and education as noted below:

Table 2: IND 110513 Cannabis Program Funding

Study	Funding Source
MJP-1	Colorado Department of Public Health and Environment (primary) Internal Sponsor philanthropic funding (secondary)
MJP2	State of Michigan's Veteran Marijuana Research Grant Program (fully funded)

Study MJP2 is intended to build off MJP-1 through use of a larger sample size, a parallel study design, and subjective bias mitigation methods to evaluate the safety and efficacy of combusted higher THC-containing cannabis versus placebo for management of PTSD symptoms in a U.S. Veteran sample. Together these studies are intended to provide valuable insights on the already widespread use of cannabis in individuals with PTSD, for which there is currently a lack of controlled evidence available reflective of this real-world use.

In keeping with these goals, the Sponsor transitioned the IND from a commercial IND to a research IND on 30 September 2022 (SN 0024) and transitioned the management of the IND from MAPS Public

Benefit Corporation, a commercial drug developer, to the non-profit research and educational organization MAPS in January 2023 to better align with the research and public health goals of this clinical program.

3.5 Study Development

The dates of key regulatory interactions related to the Clinical Hold for Study MJP2 are summarized in Table 1 below.

Table 3: Key Regulatory Interactions

Date (Reference ID)	From	Interaction Type	Summary of FDA Interaction
09 MAR 2021 (SN 0017)	Sponsor	Protocol Submission	Sponsor submits MJP2 Original Protocol V2
07 APR 2021	FDA	IR	FDA inquired if MJP2 was intended to demonstrate substantial evidence of effectiveness
07 APR 2021	Sponsor	IR Response	Email confirming that MJP2 is not intended to demonstrate substantial evidence of effectiveness
10 MAY 2021 (4793183)	FDA	Clinical Hold letter	Partial Clinical Hold for MJP2; Clinical issues including on THC max dose
03 JUN 2021 (4806015)	FDA	Clinical Hold letter	Partial Clinical Hold for MJP2; Added CMC issue
10 NOV 2021 (SN 0019)	Sponsor	Clinical Hold response	Complete Response to Clinical Hold lowering max cannabis to 2g / day
23 NOV2021 (4893801)	FDA	Incomplete Hold response notification	Response not considered complete due to lack of Batch CoA
29 NOV 2021 (SN 0020)	Sponsor	Clinical Hold response	Complete Response to Clinical Hold
21 DEC 2021 (4911159)	FDA	Clinical Hold letter	Continued Clinical Hold for MJP2; Clinical and CMC issues
12 AUG 2022 (SN 0023)	Sponsor	Hold response	Complete Response to Clinical Hold lowering cannabis to 20% THC and max cannabis to 1g / 6 hours and 2g / day
30 AUG 2022 (5038185)	FDA	Incomplete Hold response	Response not considered complete due to lack of updated protocol
30 SEP 2022 (SN 0024)	Sponsor	IND submission	IND transitioned from Commercial to Research IND
16 NOV 2023 (SN 0026)	Sponsor	Hold response	Updated protocol to complete the previously submitted Clinical Hold Response
16 DEC 2023 (5095652)	FDA	Clinical Hold letter	Continued Clinical Hold; Clinical and CMC issues

4.0 Meeting Questions and Briefing Information

The proposed meeting questions and associated briefing information are included below.

4.1 Clinical

Question 1: Mode of Administration and Administration Devices

Given the expanding state legalization of medical use of cannabis in the US, the use of cannabis has increased in recent years. While smoking remains a common mode of administration, vaporization has become increasingly popular. As this study intended to gather data on cannabis consumption that mirrors real world use, the sponsor initially proposed flexibility in mode of administration to allow for greater inclusion of participants with different cannabis use preferences and collection of more naturalistic data.

The Division's 16 December 2022 Clinical Hold letter stated that:

> *"You state in your information request response that you intend to use the vaporization device, Mighty Medic, manufactured by Storz and Bickel, as well as the waterpipe device, Eyce Beaker, manufactured by Eyce Molds, for your study. You have not provided supporting information to demonstrate safety of these devices. You have not provided a device description, intended use, risk-benefit analysis, or validation/verification testing. You must provide detailed information for each of your devices for the Agency to review whether they pose undue risks to the patients of your proposed study; see the Center for Devices and Radiological Health, Office of Product Evaluation and Quality, list of requirements attached to this letter. Alternatively, you can provide a Letter of Authorization for an appropriate Device Master File, with descriptions of where relevant safety information can be located."*

In light of the Division's feedback, the Sponsor proposes to remove the provision of the vaporization device, Mighty Medic (manufactured by Storz and Bickel and the waterpipe device, Eyce Beaker (manufactured by Eyce Molds), as well as the option for participants to self-administer the IMP via vaporization from the protocol until such time as device information can be provided and reviewed by the Agency.

In the updated protocol, participants are instructed to self-administer cannabis via smoking the provided pre-rolled cigarettes. Participants will not be provided additional administration devices. Participants will also be provided with a tablet in which they will enter the times of administration and estimates of amounts used on every dosing occasion as Patient Reported Outcomes (PRO). The Sponsor will also collect the route of administration as a PRO to ensure robust data collection in the event of participant noncompliance.

Question 1: Does the Division agree that the removal of the additional administration devices and methods of administration resolves the clinical hold issue related to the administration methods?

Question 2: Dose Justification

The Sponsor recognizes the need to ensure adequate data to support the safety of the proposed exposure to THC to patients enrolled in Study MJP2.

The completed Study MJP-1 provided for administration of up to 1.8 g of smoked cannabis with 12.4% THC "which participants may use at any time that day, with a day defined as a period of 24 hours in this study, from 12:00 AM (midnight) to 11:59 PM of that day." Under a scenario of maximum THC delivery

(*e.g.* use of all 1.8 g of product within a single 60-minute session each day), the amount of THC delivered at one time would be 223.2 mg (1800 mg cannabis x 12.4% THC).

Table 4: Maximum THC and CBD Exposure n Study MJP-1 Protocol

Formulation Term	Max Cannabis	Max THC exposure	Max CBD exposure
High THC	1.8 g	223.2 g THC	0.54 g CBD
High CBD	1.8 g	9.5 g THC	250.9 g CBD
THC+CBD	1.8 g	162.0 g THC	162.0 g CBD
Placebo	1.8 g	0 g THC	0 g CBD

In permitting the previous conduct of Study MJP-1, the Division found that exposure to THC up to 223.2 mg/day via smoking, all of which could be consumed rapidly (potentially in a single 60-minute session), was adequately supported by safety data. This is consistent with data from a published study conducted to assess the safety of ad libitum access to medical cannabis in Canada. There, 215 participants were provided a daily cannabis limit of 5 g containing 12.5% THC for one year (Ware et al. 2015). The median amount used by participants was 2.5 g of cannabis daily, equivalent to approximately 312.5 mg THC daily. A subgroup of 59 participants (27%)[1] consumed between 3 – 5 g/day, equivalent to 375 – 625 mg THC daily. The incidence rate of both SAEs and AEs in participants smoking ≥ 3 g/day of cannabis (≥ 375 mg THC/day) was not greater than the incidence rate for those smoking lower amounts of cannabis (Ware et al. 2015).

For Study MJP2, the first Clinical Hold letter, dated 10 May 2021 stated:

> *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.*

The Agency determined additional safety data was needed because the maximum exposure to THC under the original protocol was 750 mg/day (3000 mg cannabis x 25% THC), all of which could be consumed within a single 60-minute session. In response, and in order to ensure that the maximum THC exposure in Study MJP2 falls within the acceptable limit as determined for Study MJP-1, the Sponsor lowered the daily maximum amount of cannabis that can be administered (SN 0019), decreased the % THC in the IMP (SN 0023), and altered the administration instructions (SN 0023).

[1] The number of participants who consumed > 3 g/day was incorrectly reported as 11 (5% of study sample) in the study publication. The supplementary data correctly reported that 59 participants (27%) consumed >3 g/day. This discrepancy was confirmed with the author in a personal communication dated 10 February 2022 and communicated to the Agency in the MJP2 Clinical Hold Complete Response submitted on 12 August 2022 (SN 0023).

Notwithstanding these changes, the 16 December 2023 Clinical Hold letter continued to hold that the Sponsor has "*not provided adequate data to support the safety of the proposed dose of cannabis with high THC for use as directed in the amended protocol*."

The current protocol for Study MJP2 includes a daily THC maximum of 2.0 grams per day, and dosing limited to no more than of 1.0 gram per any 6-hour period. In addition, the IMP described in the updated IND CMC section is cannabis with a 20% THC concentration. Thus, under a scenario of maximum THC delivery, the maximum amount delivered to a subject in any 6-hour period is 220 mg (1000 mg cannabis x 20% ± 2%[2]THC), and the maximum amount in any day is 400 mg (2000 mg cannabis x 20% THC). The currently proposed calculated maximal exposures in Study MJP2 are comparable to those in the previously completed study MJP-1, outlined in Table 2 below.

Table 5: Dose comparison of Study MJP-1 and MJP2

	Study MJP-1	**Study MJP2**
% THC concentration	12.4%	20% ± 2%
Daily maximum cannabis	1.8 g	2.0 g
Acute (6 hour) maximum cannabis	1.8 g	1.0 g
Calculated acute maximum THC	**223 mg THC**	**220 mg THC**

The 6-hour dosing period was selected in light of data demonstrating that, following inhalation of smoked or vaporized cannabis, concentrations of THC and 11-OH-THC, the primary psychoactive metabolite, peak in whole blood and oral fluid concentrations within 10–30 min, decline rapidly and are no longer detected after 4 hours (Spindle et al. 2019).

Question 2: Does the Division agree that the Sponsor has provided sufficient information to support the safety of smoking 2.0 grams of 20% ± 2% THC-cannabis per day, with dosing limited to no more than of 1.0 gram per any 6-hour period in Study MJP2?

Question 3: Self-Titration

The 16 December 2022 Clinical Hold letter found that "*Self-titration is not an acceptable dosing regimen.*"

Consistent with MAPS' research focus, Study MJP2 is designed to increase understanding of the therapeutic utility of cannabis as used widely by individuals with PTSD. Medicinal cannabis dosing in the PTSD population is highly individualized and relies largely on titration. (Abramovici 2018). The complex pharmacology of cannabis does not align well with the standardized dosing model typical for prescription drugs making it difficult to report or establish precise dosing schedules (Abramovici 2018). In keeping with this, many cannabis studies, including those proposed and completed under this IND utilize self-titration as the dosing paradigm.

There is currently a lack of published evidence available reflective of this real-world use. Patient self-titration of cannabis, within the bounds of the study dosing, permits the collection of key data regarding

[2] To limit the variability in cannabis potency the vendor will ensure product is within 10% of intended potency resulting in a THC range of 20% ± 2% or 18-22% total. This is reflected in the update MJP2 Protocol A1V2, dated 20 April 2023 included with this submission.

the amount they are using and how titration behavior relates to changes in symptoms. Self-titration is therefore a key element of this Phase 2 preliminary study.

The Sponsor's prior study under this IND, Study MJP-1, utilized the same dosing strategy (albeit at lower total THC doses than originally proposed in Study MJP2). As described in Question 2, the Sponsor has amended the study protocol for Study MJP2 such that the maximum exposure of THC delivered to any subject does not exceed that in Study MJP-1 Subjects who chose to self-titrate to lower doses will be exposed to less than 220 mg THC per 6-hour period. Thus, to the extent that the safety of smoking 220 mg THC per 6-hour period is characterized and acceptable, there is no unacceptable risk with self-titration.

IND 110513 is a research IND whose studies will be executed by the non-profit research and educational organization sponsor, MAPS. Therefore, regulatory considerations of eventual product labeling are not germane to evaluation of Study MJP2.

Question 3: In the context of this research IND and the changes in maximum THC dose, does the Division agree that self-titration is an acceptable dosing strategy for Study MJP2?

Question 4: Cannabis Naïve Participants

Study MJP2 eligibility criteria permit enrollment of participants with all levels of cannabis experience, including cannabis-naïve participants. The 16 December 2022 Clinical Hold letter objected to the inclusion of cannabis naïve participants, noting: *"The safety of exposing cannabis naïve participants to your cannabis product with high THC is unknown. To resolve this deficiency, you must characterize the safety and tolerability of your cannabis product with high THC in cannabis naïve subjects."*

Like Study MJP-1, which was conducted under this IND, eligibility criteria for Study MJP2 are silent regarding degree of prior cannabis use. Both studies permit enrollment of cannabis naïve participants and both studies exclude participants with positive THC urine analysis tests or current hazardous marijuana use (defined in MJP2 as moderate or severe cannabis use disorder in the last 12 months).

As outlined in Question 1, the currently proposed maximal THC exposure in Study MJP2 is comparable to that of the previously completed Study MJP-1. The revised protocol limits the acute dose to 220 mg THC / 6-hour period to ensure that the safety and tolerability of the cannabis product with high THC does not exceed the acceptable THC limit for naïve subjects as determined for Study MJP-1 (223 mg within a 60-minute session).

Recognizing that the subjective effects of THC may be disquieting to a cannabis-naive subject, Study MJP2 has been amended to include administration guidance for cannabis naïve subjects that is in keeping with Health Canada's guidance for dosing of smoked or inhaled medical cannabis:

> Patients with no prior experience with cannabis and initiating cannabis therapy for the first time are cautioned to begin at the very lowest dose and to stop therapy if unacceptable or undesirable side effects occur. Consumption of smoked/inhaled […] cannabis should proceed slowly, waiting a minimum of 10 – 20 minutes between puffs or inhalations […] to gauge for strength of effects or for possible overdosing. Subsequent dose escalation should be done slowly, once experience with the subjective effects is fully appreciated, to effect or tolerability. If intolerable adverse effects appear without significant benefit, dosing should be tapered and stopped. (Abramovici 2018).

The Division's prior conclusion, in its review of Study MJP-1, that cannabis-naïve PTSD patients are not exposed to unreasonable risk from participation in a self-titration cannabis study is consistent with available data which does not indicate any increased exposure in cannabis naïve participants over cannabis-experienced participants.

In a NIDA study looking at the pharmacokinetics following smoked and vaporized cannabis, the concentrations of cannabinoids were qualitatively higher in *frequent* cannabis users compared with occasional users (Newmeyer et al. 2016). The Spindle study which looked at very infrequent cannabis users with 30 days or more since the last use reported substantially lower concentrations of cannabinoids than in the occasional or heavy users reported in other studies (Spindle et al. 2019). Based on these data, there is no reason to expect that the exposure in cannabis naïve participants would be higher or that risk would be increased compared to those in patients with prior occasional use.

The authors note that the administration procedures in cannabis inhalation studies typically do not "control for the depth or intensity of inhalation across puffs, which can vary considerably across participants and within individual smoking bouts" and hypothesize that differences in puff duration, puff volume, inhalation depth between infrequent and regular cannabis users could potentially contribute to differential cannabinoid delivery (Spindle et al. 2019).

Question 4: Does the Division agree that Study MJP2 may enroll participants with all levels of cannabis experience, including cannabis-naïve subjects?

5.0 Log of Outstanding Business

None at this time.

References

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Ware, M. A., T. Wang, S. Shapiro, and J. P. Collet. 2015. "Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)." *J Pain* 16 (12): 1233-1242. https://doi.org/10.1016/j.jpain.2015.07.014.