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CONTINUED CLINICAL HOLD COMPLETE RESPONSE

RE: IND #110513, Serial No. 0023, MJP2 Continued Clinical Hold Response Letter

Dear Division of Psychiatry Products,

Please see the below response to the hold issues in the Agency's Continued Partial Clinical Hold Letter dated 27 December 2021 for the MAPS-sponsored protocol MJP2, entitled "*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),*" submitted under IND#110513, Serial No. 0017.

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

Chemistry, Manufacturing, and Controls

Microbiology

FDA communication 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."

Sponsor response 1a: The procedures outlined in the 07 June 2017 addendum regarding frozen storage were implemented in response to microbial testing findings specific to the NIDA-supplied cannabis used in study MJP-1. As stated in the report that was submitted to FDA under IND# 110513 in the 2017 amendment, the concern at the time was based on Total Yeast and Mold Count (TYMC) of the NIDA-supplied cannabis based on secondary testing conducted per the MJP-1 study protocol. TYMC testing based on two different methods found a range of 23,000-44,000 CFU/g (3M plates) and 38,000-64,000 CFU/g (Neofilm plates) in 2017. At the time, independent research teams utilizing NIDA cannabis had also indicated that refrigerated storage was a concern based on visible mold growth. In response to these reports, additional storage and dispensation testing was conducted using the NIDA-supplied cannabis at Scottsdale Research Institute. The ideal storage conditions to limit yeast and mold growth were found to be frozen storage followed by leaving the jars open to allow the cannabis to dry out, after which it could be dispensed to study participants and stored at room temperature for a week.

For the present study MJP2, the dispensation schedule has been adjusted based on differences in cannabis supply and recommended storage conditions, as well as the need to limit face to face contact between study participants and clinical trial site personnel, in order to minimize potential expectancy bias and placebo response in the MJP2 trial. Participants will return to the clinical site approximately 2.5 weeks after starting treatment to return unused study cannabis and obtain their next dispensation for an additional approximately 2.5 weeks, to cover the 5-week self-administration period. As the recommended storage conditions from the manufacturers support room temperature storage, and TYMC is well below compendial specifications through the duration of shelf-life, there is no reason to believe that room temperature storage at trial sites followed by 2.5 weeks of room temperature storage by study participants will cause concern of yeast and mold growth in study MJP2.

FDA communication 1 (cont.**)**

"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."

Sponsor response 1b: For study MJP2, NIDA has provided the attached Letter of Authorization dated July 27, 2022 to the NIDA Drug Master File, which will be used as the placebo cannabis in the MJP2 clinical trial. Furthermore, the Certificate of Analysis for the placebo cannabis provided by NIDA, also attached for reference, states the recommended storage condition is "At or below room temperature." The specification for both the active drug product and the placebo have also been revised to meet the recommendations for microbial Limits for Botanical Ingredients and Products – Dried or Powdered Botanicals, as per the United States Pharmacopeia (USP).

This documentation justifies the change from previously developed storage conditions for the MJP-1 trial in 2017, at which point NIDA had not yet developed specifications for TYMC. According to the new Certificate of Analysis, the material intended for placebo cannabis meets NIDA and sponsor specifications for TYMC and is substantially lower than the TYMC results reported in 2017. Additional details are available in the NIDA Drug Master File if needed per the attached Letter of Authorization dated July 27, 2022. In addition, the active THC cannabis cultivar intended for the present study MJP2 is also recommended to be stored at room temperature (17-22ºC). All production rooms and storage rooms environmental controls are alarmed and monitored to ensure acceptable temperature and humidity tolerances are or will be maintained by the manufacturers and at clinical trial sites. Under these conditions, the active THC cannabis cultivar also meets sponsor and manufacturer specifications for TYMC.

Similar to the MJP-1 trial, only participants who are not immunocompromised will be enrolled in the MJP2 trial. The protocol will exclude any participant that may have an allergy or a past adverse reaction to cannabis. Potential participants will demonstrate immune system health via routine clinical laboratory testing prior to participation. Each lab result will be reviewed by a physician on the study. If a potential participant presents with abnormal white blood cell counts outside of the normal reference range, the study Medical Monitor will be consulted prior to the inclusion of the subject in the clinical trial. Risk is further limited through a planned adjustment to the daily limit of smoking no more than 2 grams per day during the treatment period and no more than 1 gram in a 6-hour period.

Based on these data and risk mitigation elements, the likelihood of yeast and mold growth under room temperature storage conditions is no longer a concern.

Drug Product

FDA communication 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."

Sponsor response 2: The sponsor intends to provide the placebo and active THC cannabis product in the form of pre-rolled cigarettes (i.e., joints). The pre-rolled cigarettes consist of dried, milled cannabis, rolled into a light paper that **does not contain** tobacco, and are sealed at both ends.

The botanical cannabis forming the active THC pre-rolled cigarettes as well as the placebo cigarettes are both naturally derived from the cannabis plant and contain no excipients. The drug product for the active arm of the clinical trial will be Ghost Train Haze, a THC-rich cannabis cultivar. For each the active and placebo arm, four 0.5 g pre-rolled cigarettes are packaged into a single primary container.

The cannabis forming the active arm does not require the use of any added processing aids. The cannabis forming the placebo arm is washed with solvents to remove any cannabinoids and terpenes from the material. Therefore, the placebo cannabis is subject to testing for these residual solvents using the specifications and methods set forth in USP <467> - Residual Solvents.

FDA communication 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."

Sponsor response 3: NIDA has provided the attached Letter of Authorization to their DMF dated 27 July 2022 that contains the required information for placebo cannabis with authorization specific to study MJP2.

Botanical

FDA communication 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."

Sponsor response 4: NIDA has provided the attached Letter of Authorization to their DMF dated 27 July 2022 that contains the required information for placebo cannabis with authorization specific to study MJP2. Please refer to the NIDA DMF for this information. In addition, NIDA has provided a Certificate of Analysis that lists the data pertaining to the placebo cannabis and the tests and specifications.

FDA communication 5: *"We acknowledge your statement 'the Sponsor no longer intends to use hemp product Catalog #C939, Lot 211019 as placebo in MJP2. The placebo product will instead come from an older lot of the Ghost Train Haze 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., Ghost Train Haze 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."

Sponsor response 5: The sponsor apologizes for this error in communication with the Agency. It is not possible for d9-THC to convert to THC-A. However, THC-A converts to d9-THC through decarboxylation which occurs upon combustion prior to inhalation [1, 2]. As the choice of placebo control has now changed, the sponsor no longer intends to use the older lot of Ghost Train Haze. Instead, the solvent-washed placebo material will be obtained from the NIDA supplier as previously stated.

Clinical

FDA communication 6: *"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).

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), including the E-cigarette or Vaping Use-Associated Lung Injury (Layden et al., 2019). Recent recommendations by the American Thoracic Society echoed these serious concerns (Neff et al. 2021). 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."

Sponsor response 6a: The sponsor proposes to lower the maximum daily intake permitted under the protocol to up to 2 grams (g) per day of a cannabis product containing approximately 20.0% ± 3.0% THC, which is reduced from the previously proposed 25% ± 0.8% THC and results in a daily total maximum intake of 400 ± 60 mg THC. The daily allotment of cannabis product will be provided in the form of four 0.5 g pre-rolled cannabis cigarettes to be administered via smoking. Participants will be informed not to consume more than two of the 0.5 g pre-rolled cannabis cigarettes in any 6-hour period.

Participants will be provided a vaporizer of cannabis flower (distinct from a "vape pen" that uses cannabis oil) and a water pipe. Participants have the option to unroll the cannabis cigarettes and place the cannabis in these devices. Participants will also be provided with a tablet in which they will enter the times, routes of administration, and estimates of amounts used on every dosing occasion as Patient Reported Outcomes (PRO). Self-titration through smoking topography enables patients to control for possible adverse effects, including higher THC-content cigarettes.

In a recently published study, of the 128 users who smoked a single cannabis cigarette (700 mg) with 5.9% or 13.4% THC *ad libitum*, there was one adverse event of anxiety requiring withdrawal from the study [3]. Participants could smoke up to the entirety of the cannabis cigarette and on average smoked about 60% of the cigarette. When controlling their own intake, the 13.4% THC group did not achieve higher blood THC concentrations; in fact, the 5.9% THC group had a significantly higher blood THC concentration [4]. The groups reported a similar level of "highness," a pharmacodynamic (PD) measure, and the lower THC concentration group reported increased levels of highness in comparison to the higher THC concentration group. This study demonstrates that patient self-titration is sufficient to mitigate risk of adverse events and obviates the need to demonstrate comparable PK and PD between the various routes of administration. These findings also suggest that cannabis with higher THC concentration may allow for more precise self-titration to the desired effect, possibly mediated by smaller inhalation volumes and enhanced by greater opportunity to modulate intake when doses were higher. It is important to evaluate the 20% THC in this setting, as it may be safer than low-dose THC.

Although the differences in PK and PD in the Spindle studies were statistically significant, these differences were not clinically meaningful [5, 6]. The Spindle studies also suggest that the differences observed in their study between vaporized and smoked cannabis were a result of the instructions that the participants were given when smoking or vaping. Although cannabis self-administration was labeled *ad libitum* in these studies, participants had to consume the entire amount, just at their own pace, and it was felt that there was more opportunity for product loss in the smoking condition (e.g., side stream, product combustion) vs vaping condition. In a truly *ad libitum* study, where participants smoke to the desired effect, participants may self-titrate, which would avoid this problem. Based on a similar naturalistic study, in which route of administration was chosen by the participant, the vaporized botanical cannabis was found to present no greater safety issues than smoked botanical cannabis [7]. Additional studies supported by MAPS and independent researchers further support this finding [8, 9].

A July 31, 2022 letter from Prof. Dr. Med. Torsten Passie and Dr. Med F. Grotenhermen, two prominent German physicians and researchers, whose practice currently includes ~800 patients who receive cannabis for a range of clinical indications including ~50 PTSD patients, supports the amount and potency to be used in this study, and patient self-titration [10]. Their letter states,

"We have learned in the last years of legal cannabis prescription in Germany that patients need individualized strategies regarding their dosage. This means that patients are not assigned a specific dose in a way that is determined by their clinical picture, for example, but that this dose is adjusted accordingly in coordination with the effects and side effects that are produced individually. We then change the dosage prescription accordingly, as long as the patient's idiosyncrasy allows it and there is no evidence of the development of problematic use. The doses used in treatment of different disorders (e.g. Acne inversa, psoriasis, ADHD, Morbus Crohn [Crohn's disease], colitis ulcerosa [ulcerative colitis]) is usually in the range of 0.5 to 3 gr. Cannabis per day (usually with preparations of 20-25% THC and some CBD). We did not see cases where this leads to significant problems in everyday life performance.

We have treated approximately 50 patients with post-traumatic stress disorder with cannabis to date. Usually, cannabis is then the only medication the patient receives for the PTSD. The dosages range from 0.5 to 2.5g (inhaled via vaporizer) in 3 to 7 applications per day. Our experiences shows that the dosage and the frequency of| intake must be adapted to each patient individually…In many patients, it also turns out that the patients have to adjust the dose individually due to the changing severity of the symptoms on a daily or weekly basis, for which the patients are given appropriate leeway by the doctors (cf Muller-Vahl & Grotenhermen, 2019 [11]). The sorts of cannabis flowers available in Germany which are used primarily for PTSD symptoms have 20-25% THC and usually 1-5% CBD, sometimes up to 9-14% CBD."

As referenced by the Sponsor in the MJP2 Clinical Hold Complete Response submitted on 29 November 2021 (SN 0020), the Canadian COMPASS study (Cannabis Use for the Management of Pain: Assessment of Safety Study) was conducted to assess the safety of *ad libitum* access to medical cannabis, providing 215 participants a daily cannabis limit of 5 g containing 12.5% THC for one year [7]. While the median amount used by participants was 2.5 g of cannabis daily, equivalent to approximately 312.5 mg THC, the sponsor notes that the number of participants who consumed more than 3 g per day was incorrectly reported as 11 (5% of study sample) in the study publication. The related supplementary data correctly reported that 59 participants (27%) consumed >3 g/day, and therefore over a quarter of study participants consumed a minimum of 375 mg THC daily (this discrepancy was confirmed with the author in a personal communication dated 10 February 2022).

The concerns regarding the effects of combusted cannabis on respiratory and pulmonary function are relevant to long-term and habitual combusted cannabis consumption but have not been found to be applicable to short-term clinical trials, such as the proposed study. The proposed study involves a short term (5-week) treatment period with *ad libitum* access of up to a maximum of 2 g/day combusted cannabis, with no more than 1 g consumed within a 6-hour period. While the COMPASS study reported medical cannabis users had a higher rate of developing non-serious respiratory AEs compared with controls, the duration of the study was for one year, during which participants consumed an average of 2.5 g/day of 12.5% THC cannabis. This usage greatly exceeds the proposed treatment period in study MJP2.

With a daily median consumption of 312.5 mg THC and 27% of participants consuming ≥ 375 mg THC daily over a one-year period, the COMPASS study found no increase in risk of serious respiratory adverse events associated with medical cannabis use (1 SAE in the cannabis group, and 7 in the control group) as well as no significant differences between groups on secondary safety assessments, including tests of pulmonary, renal, liver, hematology, biochemistry, and neurocognitive function. The cannabis group did have increased risk of non-serious adverse events such as headache, nausea, and dizziness, which were largely characterized as mild to moderate in severity. In this MJP2 study, participants can judge for themselves the tolerability of

these non-serious AEs, reduce their consumption of study drug if it is intolerable, or continue at a particular dose if they are receiving sufficient clinical benefit.

Although the COMPASS study reports that medical cannabis users had a higher rate of developing respiratory AEs during 1 year of follow-up compared with controls, the authors still concluded, "Medical cannabis users were at increased risk of non-serious adverse events (adjusted incidence rate ratio = 1.73, 95% confidence interval = 1.41-2.13); most were mild to moderate. There were no differences in secondary safety assessments. Quality-controlled herbal cannabis, when used by patients with experience of cannabis use as part of a monitored treatment program over 1 year, appears to have a reasonable safety profile."

In regards to the single report of convulsion in the COMPASS study among 215 participants in the cannabis group referenced by the Agency in the Continue Partial Clinical Hold correspondence dated 27 December 2021, the study publication did not provide any details regarding the amount of cannabis the participant had consumed or whether the participant had any relevant medical history [7]. Though this event was determined to be "probably/likely" related to study cannabis, it is difficult to ascertain the specific relevance to the sponsor's proposed study given that the COMPASS study recommended an upper daily limit of 5 grams of 12.5 ± 1.5% THC cannabis (equivalent to 625 ± 75 mg THC/day) and permitted higher doses when approved by the prescribing physician. Additionally, this study had a one-year duration versus the sponsor's proposed 5-week study. Available evidence regarding the relationship between THC exposure and convulsions is largely preclinical and suggests both pro- and anticonvulsant effects of THC, though proconvulsant effects observed in animal models have been at extremely high or nearly lethal doses (20-100 mg/kg) [12, 13]. Clinical evidence suggestive of proconvulsive effects of THC is sparse, providing "little compelling support for THC having significant proconvulsant properties in humans [14]."

The Layden study cited by the Agency is about e-cigarettes [15], which are not the same as vaporization of plant material intended to be studied in MJP2. Furthermore, "Of the 81 patients who were extensively interviewed, 73% reported use of nicotine products and 89% reported use of THC products." This study is not directly relevant to the proposed approach to vaporization. In recent years, there have been reports of lung injury associated with the use of e-cigarettes and vape pens, collectively termed EVALI (E-cigarette, or Vaping, Product Use-Associated Lung Injury), which has been attributed to the vitamin E acetate, an additive in some THC-containing products (Blount et al, 2020). EVALI is commonly caused by contaminated concentrate, or untested homemade e-liquid, and faulty electronic vaporizer equipment. When researchers evaluated the national incidences in 2019, the data showed that the states with higher rates of e-cigarette and cannabis use in earlier years prior to the rise in cases demonstrated a lower EVALI prevalence overall during the outbreak [16]. Ultimately, these results indicate that EVALI cases are more closely linked to locally distributed e-liquids or additives most prevalent in the affected areas and did not arise from e-cigarette or cannabis use exclusively. Since unregulated manufacturers operate outside the quality standards and regulatory requirements of legal cannabis markets, these illicitly produced extracts are adulterated additives intended as diluents [17]. The sponsor is acquiring legally produced whole flower cannabis from a licensed grower with operational compliance to national quality standards.

Common causative contaminants of EVALI include Vitamin E acetate, propylene glycol, vegetable glycerol, or another filler used in an illicitly processed oil or extract that does not adhere to Good Manufacturing Practices (GMP). Vitamin E acetate, also known as tocopherol acetate, is a commonly used diluent in e-cigarettes between 2018 and 2019 which causes respiratory impairment and may alter lung surfactant function. Heating Vitamin E acetate

produces a highly reactive lung irritant compound known as ketene [18]. Predominantly reported EVALI cases involved tainted distillate products that did not successfully undergo sterile compounding or processing: heated vegetable glycerin and propylene glycol decompose into potentially harmful carbonyl compounds such as formaldehyde, acrolein, and acetaldehyde [19]. The sponsor's study design minimizes the risk for EVALI by ensuring that all botanical cannabis product is fully qualified and meets release specifications based on the Certificates of Analysis provided, prior to distribution to study participants.

The Dai and Richter study cited by the Agency is a survey study that concluded, "This study found that marijuana use was more common among adults with medical conditions than those without such conditions… adults aged 18 to 34 years with COPD had almost 3 times higher odds of reporting current marijuana use than their peers without COPD (AOR, 3.4; 95% CI, 2.3-4.9). It is possible that long-term marijuana use was a contributing factor to their comorbid condition. It is also possible that these adults were using marijuana for relief from pain, anxiety, stress, or depression [20]." As this was only a survey study, it was only designed to study association and not causation. Nevertheless, the survey data does not raise serious concerns about the association between cannabis smoking/vaping and adverse outcomes on pulmonary function and increased respiratory symptoms. Given the risk of leaving ongoing psychiatric symptoms untreated in the midst of a mental health crisis, these studies are in fact supportive of generating controlled safety data and exploring the potential benefits of the inhalation of botanical cannabis as this use is already happening throughout most of the United States and the world.

The reference to the American Thoracic Society cited by the Agency is not a study but a patient education document [21]. It says, "We recommend against smoking marijuana for anyone, particularly in people with an existing lung disease, such as COPD or asthma." It also says, "Marijuana smoke may increase the risk of lung cancer." The use of the word "may" is telling. There is no direct evidence that smoking marijuana causes lung cancer, or increases risk of exacerbation of COPD or asthma, based on the analysis of multiple studies: "habitual use of cannabis does not appear to lead to significant abnormalities in lung function when assessed either cross-sectionally or longitudinally, except for possible increases in lung volumes and modest increases in airway resistance of unclear clinical significance. Therefore, no clear link to chronic obstructive pulmonary disease has been established [22]." In a meta-analysis of the health effects of cannabis, the National Academies of Science, Engineering, and Medicine also came to the conclusion that there was no significant association between smoking cannabis and incidence of lung cancer [23]. It is notable that NIDA no longer considers the risk of lung cancer to be increased due to cannabis inhalation. On NIDA's website on cannabis effects on lung health, this statement appears, "well-designed population studies have failed to find an increased risk of lung cancer associated with marijuana use [24]."

Cannabis use in individuals with PTSD is widespread [25-27]. Further, cannabis is the most commonly used federally illegal drug in the general U.S. population and its use is increasing [28]. Cannabis is currently legal for medical use in 37 states, legal for recreational use in 19 states, and decriminalized in 13 states [29]. According to results from the U.S. Department of Health and Human Service's National Survey on Drug Use and Health, 48.2 million people (18%) in the United States used cannabis at least once in 2019, compared to 25.8 million people (11%) in 2002 [28]. A 2020 cross-sectional study found that in a sample of 17,048 Americans aged 16-65, 20% reported at least monthly cannabis use and 14% reported daily or almost daily use [30].

Despite the increasingly widespread use and acceptance of cannabis, there is a lack of safety data on cannabis that models real-world consumption. Most cannabis studies to date do not reflect the average daily dose and percent composition of THC cannabis consumed by medical and

recreational cannabis users cited above. Clinical research on the safety, as well as potential risks and benefits, of typical consumption patterns of cannabis should be viewed as a public health priority as the legalization and cultivation of cannabis continues to evolve and more Americans become cannabis users.

The proposed study design of MJP2 will model real-world consumption in order to adequately characterize the safety of cannabis use among participants. The sponsor's proposal to modify the MJP2 protocol to reduce the THC content of the cannabis product to 20.0% ± 3.0% THC is in alignment with the national average of THC content reported in large epidemiological surveys of legal cannabis products sold in dispensaries. An analysis of cannabis potency in nine states where cannabis was legalized reported the average THC content in medical cannabis products is 19.2% ± 6.2%, comparable to recreational cannabis product at 21.5% ± 6.0% [31]. A survey of over 30 million Washington State cannabis sales reported an average of 20.59% ± 4.19% THC content [32].

As discussed in the sponsor's MJP2 Clinical Hold Complete Response submitted on 29 November 2021 (SN 0020), several epidemiological surveys of cannabis use report >2 g/day of cannabis flower smoked [33-35] and Veterans Affairs Canada currently implements a 3 g maximum daily reimbursement limit of cannabis products for medical purposes, irrespective of potency [36]. Although many of these epidemiological surveys do not report cannabis potency, it is reasonable to extrapolate the findings from these studies to the sponsor's proposed THC content of 20%, given alignment with reported averages. In addition, the sponsor hypothesizes that self-titration will lead study participants to limit their overall intake to a greater degree when smoking or vaporizing botanical cannabis with higher potency. As such, the proposed study design is indicative of real-world consumption patterns of both medical and recreational cannabis.

Thus, the sponsor proposes up to 2 grams (g) per day, supplied in the form of four 0.5 g pre-rolled cannabis cigarettes, containing approximately 20.0% ± 3.0% THC, in order to gather robust safety data on real-world cannabis consumption and test its efficacy on the treatment of PTSD. Participants will be informed not to inhale more than two of the 0.5 g pre-rolled cannabis cigarettes in any 6-hour period.

FDA communication 6 (cont.)

"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."

Sponsor response 6b: To simplify the protocol design, the cannabis product will be supplied to participants in the form of four 0.5 g pre-rolled cannabis cigarettes, containing approximately 20.0% ± 3.0% THC. Participants will be provided a vaporizer of cannabis flower (distinct from a "vape pen" that uses cannabis oil) and a water pipe. Participants have the option to unroll the cannabis cigarettes and place the cannabis in these devices. Participants will also be provided a tablet in which they will enter the times, routes of administration, and estimates of amounts used on every dosing occasion. The sponsor has selected smoking as the route of administration in the study design, with the option to vaporize the cannabis, as smoking is the most commonly utilized method of cannabis inhalation [20, 37]. Administration through ingestion would present additional challenges around appropriate dose titration as users of edibles commonly ingest larger than intended doses of THC due to the delayed and variable effects of gastrointestinal absorption [38].

The sponsor's previous cannabis trial, MJP-1 conducted under this IND, provided preliminary safety evidence of the safety of short-term *ad libitum* smoked botanical cannabis [39]. The blinded cross-over study design consisted of two 3-week periods during which participants smoked treatment or placebo cannabis *ad libitum*, separated by a 2-week cessation period, resulting in a total duration of 6 weeks of daily smoked inhalation. The study allowed a similar daily maximum amount of cannabis (1.8 g) of a lower THC concentration (12.4%) and participants smoked an average of 0.69 g per day. The Agency's concerns regarding potential respiratory and pulmonary effects of the proposed study appear to be regarding the volume of combusted cannabis consumed and not the potency. Cannabis users down-regulate consumption of cannabis as THC content increases [40]. While this does not alleviate concerns regarding the safety of possible maximum exposure, it is relevant to note that participants of the proposed study may consume a lesser volume of the higher potency cannabis (20% THC) than the average amount of 0.69 g/day reported in MJP-1, resulting in a similar safety profile.

In two short-term randomized controlled trials on Crohn's disease, cannabis-naïve participants smoked a prescribed amount of 1 g/day for 8 weeks without reported respiratory or pulmonary adverse effects [41, 42]. Participants in these studies received either study cannabis (23% and 16% THC, respectively) or placebo cannabis (<0.04% THC) in the form of 0.5 g pre-rolled cannabis cigarettes, similar to the proposed study design.

The Dai and Richter article cited by the Agency regarding adverse outcomes on pulmonary function and increased respiratory symptoms is from a national survey of medical cannabis users that does not list duration of cannabis use other than whether they used cannabis within the last 30 days [20]. Additionally, it does not include data on tobacco use, a common confound as more cannabis users also smoke tobacco compared to non-cannabis users [43]. Contrary to the acute effects of tobacco smoke as a bronchoconstrictor, there is some evidence that short-term cannabis smoking can improve airway dynamics, specifically causing bronchodilation, but not with chronic use [44, 45]. It should also be noted that cannabis-naïve users were also allowed to participate in the COMPASS year-long *ad libitum* cannabis use study, although they comprised a small portion of the cannabis group (n=16, 7%) [7]. Additionally, similar to MJP-1, the proposed study excludes participants with a diagnosis or evidence of significant or uncontrolled pulmonary disease (alongside many other significant diseases), who may be at risk of consuming combusted cannabis, as mentioned in the American Thoracic Society web page referenced [21]. Due to the short-term treatment period of 5 weeks and study exclusion criteria, acute inhalation of cannabis is unlikely to place participants, who may not have had a history of smoked cannabis, at undue risk.

Given the findings from previous short-term and acute cannabis use studies, it is unlikely the proposed short-term study design will induce long-term effects on pulmonary and respiratory function in study participants, regardless of their cannabis use history. The proposed MJP2 study from the sponsor will bolster the nascent cannabis safety literature and contribute to a more robust safety profile of cannabis by modeling real-world consumption, particularly route of administration, dose, and % THC content. The proposed study is important not only to identify a potential treatment option for the underserved veteran PTSD population, but also to provide data to better characterize the safety of cannabis for the millions of cannabis users in the United States.

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If you have any questions or requests regarding this submission, please do not hesitate to contact Sponsor Designee, Amy Emerson, by email at [redacted] or Associate Director of Regulatory Affairs, Allison Coker, by email at [redacted]

Sincerely,

Amy Emerson

Electronically signed by: Amy Emerson
Reason: I am the approver of this document
Date: Aug 15, 2022 15:51 PDT

Amy Emerson
Chief Executive Officer
MAPS Public Benefit Corporation

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