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29 November 2021

CLINICAL HOLD COMPLETE RESPONSE

RE: IND #110513, Serial No. 0020, MJP2 Partial Clinical Hold Response Letter

Dear Division of Psychiatry Products,

Please see the below response to the Agency's Partial Clinical Hold Letters dated 10 May 2021 and 03 June 2021 for the new 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 1: 21 CFR 312.42(b)(2)(i): Insufficient information to assess risks to human subjects

FDA communication: *"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)."

Sponsor response: The Sponsor proposes to reduce the maximum daily intake permitted under the protocol to up to 2 grams (g) per day of a cannabis product containing approximately 25.0 ± 0.8% THC[1]. In the Sponsor's previous cannabis trial, MJP1, a similar daily maximum amount of cannabis (1.8 g) was permitted, however participants consumed on average 0.69 g per day. This was safe and well-tolerated [1]. While the THC concentration was lower in the cannabis used for

[1] Per stability of cultivar over last 10 batches from supplier, [redacted]

study MJP1 (12.4%) due to constraints on cannabis supply available from the [redacted], prior studies suggest individuals self-titrate their THC exposure, smoking less as cannabis potency increases [2-4].[2]

While it is difficult to estimate average cannabis consumption in current medical users due to differences in cannabis potency and route of administration, epidemiological surveys report medical cannabis users smoke or vaporize an average of 3 g of cannabis daily [5, 6] and Veterans Affairs Canada currently implements a 3 g maximum daily reimbursement limit of cannabis products for medical purposes, irrespective of potency [7]. A recent analysis of cannabis potency in the U.S. reported the average THC content in medical cannabis products is 19.2% ± 6.2%, comparable to recreational cannabis product at 21.5% ± 6.0% [8]. The reduced maximum daily limit of 2 g is intended to provide sufficient cannabis for treatment of PTSD symptoms while also allowing for individual variation in typical consumption per session.

The clinical pharmacokinetics of smoked cannabis are well documented [9-13], (for review, see [14-16]). A clinical study on the dose-dependent effects of smoked cannabis reported a linear relationship between THC concentration in botanical cannabis by weight and THC serum concentration, even at high doses [17]. There is significant variability in THC absorption from smoked cannabis, ranging from 2 to 56% dependent on factors such as combustion and side-stream smoke, as well as depth, duration, and frequency of inhalation [14] and evidence suggests the pharmacokinetic properties of THC are comparable between smoking and vaporization delivery methods [18, 19]. Due to this variability, the average bioavailability of THC, from smoked or vaporized cannabis, is estimated at 25%.

THC and CBD act through the activation of cannabinoid receptors CB1 and CB2 [20]. When administered via inhalation, THC and CBD differ pharmacologically with limited risk of fatal overdose [16, 21]. THC acts as a partial agonist at CB1 receptors [22]. CBD is an allosteric modulator with minimal activity at CB1 and CB2 receptors [16, 22]. Notably, there is minimal risk of cardiorespiratory depression, or an acute lethal overdose caused by these cannabinoids, due to the lack of CB1 receptors in the brain stem [20, 21, 23].

When a comparative risk assessment of drugs including alcohol and tobacco using the margin of exposure (MOE) approach was conducted, the MOE is defined as the ratio between toxicological threshold (benchmark dose) and estimated human intake [24]. The benchmark dose was derived using median lethal dose values from animal experiments and the human intake was calculated for individual and population-based scenarios. While the other agents (i.e., opiates, cocaine, amphetamine-type stimulants, and benzodiazepines) had MOEs > 100, cannabis had an MOE > 10,000. The toxicological MOE approach validates epidemiological and social science-based drug ranking approaches especially when considering alcohol and tobacco categorized as high-risk and cannabis as low-risk [24].

A previous safety study provides a basis for the expected safety profile of the Sponsor's proposed dosing range. 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

[2] It is not expected that consumption of the 2.0 g maximum daily allotment of cannabis will be typical of participant use in study MJP2, based on MJP1 daily use data [1].

year [6]. The median amount used was 2.5 g of cannabis daily and 27% of participants used >3 g daily. The study found no difference between the cannabis and control group for risk of incidence of serious adverse events, although 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. There were also no differences between groups on secondary safety assessments, including pulmonary, renal, liver, hematology, biochemistry, and neurocognitive function.

A secondary outcome measured in the COMPASS study showed a significant improvement in pain intensity and quality of life after one year for the cannabis group compared to the control. The results of this study suggest that the adverse events with cannabis for medical use are modest and that an average dose of 2.5 g per day can be included in pain management programs safely with careful monitoring if conventional treatments have been considered inappropriate or inadequate [22, 25].

While the potency of cannabis used in the COMPASS study contained 12.5% THC, the daily limit of 5 g results in a scenario of greater maximum THC delivery than the Sponsor's proposed dose, *ad libitum* use of up to 2 g per day of THC-rich (25%) cannabis in MJP2 (see Table 1) and reported a reasonable safety profile. Together these findings demonstrate that existing clinical pharmacokinetic data derived from cannabis with a lower concentration of THC can be extrapolated to the THC-rich cannabis product proposed for use by the Sponsor in study MJP2 with a reasonable safety profile.

Table 1: Estimated Daily Maximum Amount of THC

Protocol	Max. Daily Cannabis (g)	THC (%)	Average Estimated Bioavailability (%)	Estimated Max. daily THC (mg)
MJP2	2.0 g	25 %	25 %	125.0 mg
MJP1	1.8 g	12 %	25 %	54.0 mg
COMPASS	5.0 g	12.5 %	25 %	156.3 mg
VA Canada Medical	3.0 g	19.2 %[a]	25 %	144.0 mg

a. Estimated THC concentration using findings from Cash et al. 2020

Additionally, in the Cannabis Access for Medical Purposes Survey (CAMPS) among 473 self-identified current users of cannabis for medical purposes, over 80% of respondents self-reported substituting cannabis for prescription drugs, over 51% for alcohol, and over 32% for illicit substances. According to the survey participants, the most endorsed reasons for substitution were "less adverse side effects" and "better symptom management." The median weekly amount of cannabis used was 14 g (or 2 g per day) [26].

The Tilray Observational Patient Study analyzed 1,145 patients who had at least one post-baseline visit, with follow-up at 1, 3, and 6 months and took place at 21 medical clinics throughout Canada [27]. The findings from this large prospective examination of Canadian medical cannabis patients focused on the impacts of cannabis on prescription opioid use and quality of life over 6 months. Regarding cannabis use, flower use was reported by 38.3% of participants at baseline (n = 438), increasing to 93.6% (n = 392) by month 6. Mean flower cannabis use per week at M1 was 6.2 g (SD = 6.2), increasing to 6.9 g at month 6 (SD = 6.5) or just below 1 g per day, therefore remaining quite stable over the first five months of use [27].

Considering quality of life, statistically significant improvements were noted in the mean scores for the four domains of the World Health Organization Quality of Life Short Form (WHOQOL-

BREF) at all follow-up visits relative to baseline, with the most significant changes seen in physical health (13.9 points [36% increase]; 95% CI, 11.7–15.0) and psychological health (9.2 points [17% increase]; 95% CI, 6.6–9.7) [27]. The finding that cannabis use did not increase significantly over a 6-month period is encouraging from both a therapeutic and a public health perspective and adds to the growing body of evidence suggesting that although patients appear to develop a tolerance to some of the side effects of cannabis-based medicines, they do not seem to develop a tolerance to many of the primary therapeutic effects [27-29].

A Canadian cross-sectional study surveyed 628 self-selected participants reporting current cannabis for therapeutic purposes (CTP) and gathered data from 2011–2012 [30]. The survey queried access, perceived effectiveness, patterns and history of cannabis use, medical diagnoses and symptoms, mood, and demographics. Aggregate analyses indicated that 40% (n = 167) of users fell into the modal quantity of use category of more than 14 grams per week, and that 42% (n = 226) fell in the modal frequency of use group reporting 2–3 uses per day [31].

In 2013, Barrowclough et al. found no association between cannabis use and positive symptoms in patients with non-affective psychotic disorders, as assessed by the Positive and Negative Syndrome Scale (PANSS) (adjusted coefficient = 0.07; 95% CI = –0.21–0.34). In this study, a cross-sectional analysis of 160 patients with a clinical diagnosis of non-affective psychotic disorder and a diagnosis of drug and/or alcohol dependence or abuse examined the association between cannabis use and symptom, functioning, relapse, and hospital admission outcomes in people with established psychosis [32]. Generalized estimating equation models were used to estimate the effects of cannabis doses on subsequent clinical outcomes and whether a change in cannabis use was associated with a change in results. The notable strengths of this study are its dose-response analysis and its detailed quantification of cannabis use, with mean use in the sample being four days per week and an average of 2.4 grams per day.

Barrowclough et al. found that changes in cannabis dose did not predict changes in positive symptoms severity, even when patients became abstinent. The one hundred and sixty participants who use cannabis were compared with other substance users (n = 167) on baseline demographic, clinical, and substance use variables. The cannabis-using subgroup was examined prospectively with repeated measures of substance use and psychopathology at baseline, 12 months, and 24 months. To overcome several major limitations of previous studies, this study employed a longitudinal analysis over 24 months, with repeated and time-lagged measures of psychopathology, use of cannabis, alcohol, and other substances, and adjusting for a wide range of potential confounds [32]. While the type of cannabis, specifically whether resin or [other botanical forms] was used, which have differing THC content, was not assessed, this study had the advantage of analyzing the frequency and weight of cannabis consumed.

In 2015, Barrowclough et al. conducted a prospective, longitudinal cross-sectional study evaluating THC potency, frequency (percentage days used) and average daily weight per cannabis using day (grams) was assessed for the three months preceding baseline, 4.5-, 9-, and 18-month follow-up assessments. Data on cannabis use was collected for 83 participants (75.5%) at 4.5 months, 79 (71.8%) at 9 months, and 75 (68.2%) at 18 months. The mean frequency of cannabis use was 65% of days in the preceding 90 days (SD 30%), equating to 4–5 days use per week, and when corrected for the type of cannabis, average daily use was 2.3 g per day [33].

The authors found no specific association between cannabis dose and positive symptoms (n = 102; adjusted coefficient, 0.01; 95% CI = −0.24–0.25). For participants whose use was described in joints and who could not provide an estimate of grams used the researchers used the average amount for the sample: 0.3 g per joint. Barrowclough et al. accounted for the potency of the

cannabis smoked by multiplying the weight of the more potent types by 1.5 since the average THC content of sinsemilla found in the UK Home Office Potency Study was 15% THC, compared with 5% THC for resin [33]. This study only examined the relatively long-term and durable consequences of cannabis use. The transient impacts of cannabis on both psychotic symptoms and anxiety have been demonstrated in experimental studies. An increase in the amount of cannabis used was associated with a statistically significant increase in anxiety scores, but not depression [33]. The analyses accounted for an estimate of THC content consumed and found associations between a greater amount of cannabis used and more affective symptoms for both observer-rated affective symptoms (PANSS general symptoms) and self-reports of depression and anxiety. There was a significant relationship between dose of cannabis and subsequent severity of these symptoms over the 18-month period of study [33].

There were no relationships between cannabis use and relapse or admissions, and the positive association between negative symptoms and cannabis was not evident once covariates were considered [33]. One major advantage of this study is that the researchers were able to take account of the differing THC content in the types of cannabis participants reported. This 2015 study was able to take account of cannabis dose more accurately than previous studies since Barrowclough et al. analyzed both the weight and frequency of cannabis used and implemented measures that supported the validity of the self-reports of consumption.

The Sponsor believes the existing clinical literature cited provides sufficient information on the pharmacokinetics and safety profile of the proposed dose and delivery of cannabis, superseding the need for nonclinical data. The changes described above will be incorporated into an amended study protocol following Agency review of the hold response and agreement of the proposed changes.

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

FDA communication: *"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."

Sponsor response: Since the submission of the representative COA from supplier [redacted] provided to the Agency via email on 20 April 2021, the Sponsor has decided to proceed with [redacted] as the supplier of THC-rich cannabis for this study. A COA for the initial batch of botanical cannabis to be used in study MJP2 has been obtained and is included with this submission. Given that several batches of botanical cannabis will be required over the course of the study, the Sponsor commits to also provide additional COAs to the Agency that at minimum includes an assay of all cannabinoids, moisture content, pesticides, mycotoxins, elemental impurities testing, and microbial testing for any new batches used in study MJP2 at least 30 days prior to first administration of each batch, in keeping with the Agency's Incomplete Response to Hold correspondence dated 23 November 2021.

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

Sincerely,

Amy Emerson

Electronically signed by: Amy Emerson
Reason: I am the approver of this document
Date: Nov 29, 2021 16:35 PST

Amy Emerson
Chief Executive Officer
MAPS Public Benefit Corporation

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