MAPS Public Benefit Corporation
3141 Stevens Creek Blvd. #40547
San Jose, CA 95117 USA
mapspublicbenefit.com | mdmaptsd.org

Tiffany R. Farchione, M.D.
Director, Division of Psychiatry Products
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
5901-B Ammendale Road
Beltsville, MD 20705-1266

10 November 2021

**CLINICAL HOLD COMPLETE RESPONSE**

**RE: IND #110513, Serial No. 0019,** 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. Given the amount of time expected to lapse between the previously supplied COA and obtainment of investigational drug supply intended for the study, we anticipate that the cannabis provided by the supplier for study use may not be from the exact same batch on which this COA was based. Further, it is anticipated that several batches of botanical cannabis as well as resupply of product will be required over the course of the study. The Sponsor accordingly proposes as a regulatory commitment to provide additional COAs to the Agency that at minimum include 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.

Does the agency agree that this ongoing regulatory commitment is sufficient to resolve this deficiency?

Please also see the below responses to the Division's non-hold comments.

**Clinical Non-Hold Comment 1**

FDA communication: "*We strongly recommend a fixed-dose study design to characterize the dose-response relationship for THC in the treatment of patients with PTSD. The amount of cannabis product administered each day, the route of administration (smoking versus vaping), and the timing of administration should be prespecified for each treatment arm. As currently designed, there is a potential for considerable variability in administered dosage of THC; this may make the resulting data uninterpretable."*

**Sponsor response:** The Sponsor appreciates the Agency's recommendation to implement a fixed-dose study design in order to establish a dose-response relationship for THC in the treatment of patients with PTSD. While the Sponsor recognizes the potential benefit of such a design, fixed-dose assignment are likely to result in tolerability issues in participants for whom the assigned dose is too high and may also negatively impact study efficacy findings given the highly individualized nature of optimal cannabis dosing. Additionally, the Sponsor anticipates that the *ad libitum* dosing specified in the current protocol will more closely align with real-world use, similar to certain anxiolytics that are prescribed as *p.r.n* (as needed) [34]. Additionally, as described above, the Sponsors proposes to limit the *ad libitum* use to a maximum of 2 g/day. All participants will complete a 3-week Screening Period, a 5-week randomized double blind Treatment Period, and 1-week Follow Up Period.

Participants will track number of puffs and administration method following each self-administration in a mobile device app. This will permit initial characterization of a dose-response relationship based on a measurable self-titrated dose. All participants will be trained on mobile device app use and self-administration tracking according to the arm to which they are assigned. The free choice inhalation of botanical cannabis using smoking and vaporizing devices readily available on the retail market in Study MJP2 will collect important data on current typical cannabis use in the United States.

**Clinical Non-Hold Comment 2**

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

**Sponsor response:** The Sponsor appreciates the Agency's recommendation to expand enrollment beyond an exclusively veteran population in order to increase study generalizability. However, as the funding for the MJP2 study protocol is provided by the State of Michigan's Veteran Marijuana Research Grant Program, which specifically funds research into the efficacy of cannabis in treating the medical conditions of United States armed services veterans and preventing veteran suicide, enrollment in this study will remain limited to Veterans. The Sponsor plans to include a broader sample of patients in future research protocols under this IND.

**Clinical Non-Hold Comment 3**

FDA communication: "*On Days 1 and 2, patients would inhale a very small amount of study cannabis to train them on the use of the vaporization devices, to teach them skills to cope with potential side effects, and for observation over 3 hours to monitor vital signs and for adverse events. An ECG tracing and laboratory tests would be assessed only at screening. Also, the*

*Columbia-Suicide Severity Rating Scale (C-SSRS) would be assessed on Day 1 and Day 35. We have the following recommendations to enhance the safety monitoring in this trial:*

a. *Consider administering a typical dose of study cannabis on Days 1 and 2 to adequately evaluate the anticipated safety profile for each patient during the outpatient phase of the trial.*
b. *Perform a 12-lead ECG tracing on Day 1 or 2 at 15 minutes after self-administration of study cannabis to assess the acute effects of THC on ECG parameters.*
c. *Assess laboratory tests at end-of-treatment (Day 35) to assess the effects of THC on laboratory parameters.*
d. *Assess the C-SSRS on Day 14."*

**Sponsor response:** We thank the Reviewers for their suggestions and agree to the following changes in order to enhance the safety monitoring in study MJP2:

a. Participants will self-administer a "typical dose" on training days (Days 1 and 2) to ensure dosing is in the optimal range for each participant.
b. A 12-lead ECG tracing will be conducted on Day 1 and 2 at 15 minutes after self-administration of study cannabis to assess the acute effects of THC on ECG parameters.
c. Follow-up laboratory tests will be completed at end-of-treatment (Day 35) to assess the effects of THC on laboratory parameters.
d. A C-SSRS assessment will be conducted for all participants on Day 14.

These changes will be incorporated into an amended study protocol following review of the hold response and agreement of the proposed changes.

**Clinical Non-Hold Comment 4**

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

**Sponsor response:** The "Accurate Symptom Reporting Training (ASRT)" and "Placebo Response Reduction Training Program (PRRTP)" referenced in the original MJP2 protocol are trademarked names of the commercial training platforms available through vendor [redacted]. The Sponsor recently conducted an internal review of these services and concluded that use of these specific products would be to the detriment of study MJP2 due to (1) the potential for interference with established and validated bias minimization procedures of the centralized independent rater (IR) pool, which have previously been utilized in the Sponsor's ongoing Phase 3 PTSD program of MDMA-assisted therapy, and (2) the complexity added by incorporation of additional novel technology and training platform, which would notably increase participant burden. The protocol has accordingly been modified to remove reference to these specifically named training programs.

The Sponsor has determined that these activities would be best implemented in conjunction with the established Independent Rater (IR) pool in use for ongoing Phase 3 trials of MDMA-assisted therapy under IND#063384. The sponsor's utilization of clinician administered measures for both the primary and secondary critical endpoints administered by the IR pool is the primary mechanism to ensure symptoms are reported accurately. The trained pool of blinded IRs use

standardized administration methods to ensure accurate symptom reporting by participants and accuracy of the clinician-administered measures. Validity and reliability of these methods are demonstrated through random sampling of completed IR assessments for evaluation by Senior IRs, as well as Central Reliability Reviews wherein each member of the IR pool review and score the same recorded assessment. The Senior IRs are responsible for oversight of the IR pool and provide retraining as needed.

The Sponsor additionally plans to implement training in study MJP2 for both IRs and all study site staff who engage with participants to ensure understanding of the potential for placebo effects and methods for mitigation. Topics to be discussed in these trainings will include:

- How the consent form process can reduce the potential for placebo effects
- How to monitor personal expectations, assumptions, and biases, in order to maintain a neutral stance toward all participants
- The importance of limiting support, advice-giving, or subtle clinical shaping, and maintaining a neutral, objective stance toward participants
- Ways to avoid the development of a therapeutic alliance and instead striving for a research alliance
- The importance of the use of consistent scripts for all participants at all visits

Participants will also receive regular communication to mitigate placebo response and encourage accuracy in symptom reporting through reminders at the time of consent and prior to each IR assessment visit that they have a chance of random assignment to placebo, that their symptoms may improve, worsen, or remain unchanged, and that they are responsible for reporting symptoms as accurately as possible, without seeking to provide perceived "correct" answers.

This overview of the methods to support accurate symptom reporting and placebo response reduction will be incorporated into the Bias Minimization procedures of an amended study protocol following review of the hold response and agreement of the proposed changes.

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

**Sponsor response:** In keeping with the Statistical Non-Hold Comment 3 below, the Sponsor will submit the SAP prior to the trial initiation. The *estimands* and handling of intercurrent events and missing data will be outlined in the SAP rather than the study protocol.

**Statistical Non-Hold Comment 2**
FDA communication: *"SDS: This scale appears to be a self-reported tool comprising three domains. The first domain "work/school" assesses how much "symptoms have disrupted your work/school work." Under this domain, there is a check box for "I have not worked/ studied at all during the past week for reasons unrelated to the disorder." Any subject who checked the box would not be able to respond to the first domain. This type of missing data would be different from other subjects who had worked/studied but did not respond to the first domain. Also, for subjects who did not check this box, clarify how you can determine whether it is because they had worked/studied (hence, not checking the box) or not (hence, resulting in missing data). To be able to reliably identify the two cohorts of missing data, we recommend adding a question to the case*

*report form; the question should ask if the subject did not work during the past week due to reason related to PTSD. You would also need to pre-specify how to handle these two kinds of missing data in analyses. We do not consider it appropriate to impute missing data on the first domain based on data from the other two domains."*

**Sponsor response:** Per the Agency's prior recommendation in the Sponsor's MDMA program with the PTSD population conducted under IND#063384, the Sponsor will utilize a MAPS-adapted version of the Sheehan Disability Scale (SDS) in study MJP2, created with the aid of SDS developer Dr. David Sheehan. In this adapted version, a question has been added to ask if the participant did not work or study during the past week due to reasons related to PTSD. If this question is endorsed by the participant, this domain will be coded as a 10 for maximal impairment. In cases where participants did not work due to reasons unrelated to PTSD, the score for item 1 (work/school) will be imputed by averaging the scores of items 2 (social life) and 3 (family life/home responsibilities). To limit missing data and ensure standardized administration, the SDS will be administered in a clinician- rated format by a centralized Independent Rater Pool.

If item 1 of the SDS is imputed in more than 5% of the participants, multiple imputation methods will be explored as an additional sensitivity analyses. If more than 5% of Item 1 data is missing, the frequency of participants not working due to reasons unrelated to PTSD and related to PTSD will be tabulated for both overall and within each visit. To ensure this imputation does not introduce bias into the data, a sensitivity analysis will be conducted without imputation to explore the effect of the different distributions for average SDS depending on whether the respective checkboxes for item 1 are checked or not. Separate MMRM models for the two types of responses to item 1 will be run and the treatment effect will be the weighted average of the two groups with the weights calculated as the frequency of checked item 1's.

**Statistical Non-Hold Comment 3**

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

**Sponsor response:** The sponsor agrees to submit the SAP which will list all objectives (e.g., early stop for futility or superiority, sample size increase) of the interim analysis, and provide detailed justifications for the overall type I error control for the primary and the key secondary endpoints prior to trial initiation, as well as submitting the DMC charter for review.

MAPS Public Benefit Corporation
3141 Stevens Creek Blvd. #40547
San Jose, CA 95117 USA
mapspublicbenefit.com | mdmaptsd.org

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 10, 2021 14:20 EST

Amy Emerson
Chief Executive Officer
MAPS Public Benefit Corporation

## References

1. Bonn-Miller, M.O., et al., *The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial.* PLoS One, 2021. **16**(3): p. e0246990.
2. Heishman, S.J. and M.L. Stitzer, *Effect of d-amphetamine, secobarbital, and marijuana on choice behavior: social versus nonsocial options.* Psychopharmacology (Berl), 1989. **99**(2): p. 156-62.
3. Ramesh, D., M. Haney, and Z.D. Cooper, *Marijuana's dose-dependent effects in daily marijuana smokers.* Exp Clin Psychopharmacol, 2013. **21**(4): p. 287-93.
4. Kalaba, M. and M.A. Ware, *Cannabinoid Profiles in Medical Cannabis Users: Effects of Age, Gender, Symptoms, and Duration of Use.* Cannabis Cannabinoid Res, 2021.
5. Hazekamp, A., et al., *The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms.* J Psychoactive Drugs, 2013. **45**(3): p. 199-210.
6. Ware, M.A., et al., *Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS).* J Pain, 2015. **16**(12): p. 1233-1242.
7. VA_Canada. *Reimbursement Policy for Cannabis for Medical Purposes*. 2019 [cited 2021 September 14th]; Available from: https://www.veterans.gc.ca/eng/about-vac/legislation-policies/policies/document/2461.
8. Cash, M.C., et al., *Mapping cannabis potency in medical and recreational programs in the United States.* PLoS One, 2020. **15**(3): p. e0230167.
9. Ohlsson, A., et al., *Single dose kinetics of deuterium labelled Δ1‐tetrahydrocannabinol in heavy and light cannabis users.* Biomedical Mass Spectrometry, 1982. **9**(1): p. 6-10.
10. Heuberger, J.A., et al., *Population pharmacokinetic model of THC integrates oral, intravenous, and pulmonary dosing and characterizes short- and long-term pharmacokinetics.* Clin Pharmacokinet, 2015. **54**(2): p. 209-19.
11. Cooper, Z.D. and M. Haney, *Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts.* Drug Alcohol Depend, 2009. **103**(3): p. 107-13.
12. Huestis, M.A., J.E. Henningfield, and E.J. Cone, *Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana.* J Anal Toxicol, 1992. **16**(5): p. 276-82.
13. Marsot, A., et al., *Population pharmacokinetics model of THC used by pulmonary route in occasional cannabis smokers.* J Pharmacol Toxicol Methods, 2017. **85**: p. 49-54.
14. Huestis, M.A., *Human cannabinoid pharmacokinetics.* Chem Biodivers, 2007. **4**(8): p. 1770-804.
15. Lucas, C.J., P. Galettis, and J. Schneider, *The pharmacokinetics and the pharmacodynamics of cannabinoids.* Br J Clin Pharmacol, 2018. **84**(11): p. 2477-2482.
16. Grotenhermen, F., *Pharmacokinetics and pharmacodynamics of cannabinoids.* Clin Pharmacokinet, 2003. **42**(4): p. 327-60.
17. Hunault, C.C., et al., *Delta-9-tetrahydrocannabinol (THC) serum concentrations and pharmacological effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg THC.* Psychopharmacology (Berl), 2008. **201**(2): p. 171-81.
18. Newmeyer, M.N., et al., *Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake.* Clin Chem, 2016. **62**(12): p. 1579-1592.
19. Abrams, D.I., et al., *Vaporization as a smokeless cannabis delivery system: a pilot study.* Clin Pharmacol Ther, 2007. **82**(5): p. 572-8.

20. Černe, K., *Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol.* Arh Hig Rada Toksikol, 2020. **71**(1): p. 1-11.
21. Maroon, J. and J. Bost, *Review of the neurological benefits of phytocannabinoids.* Surg Neurol Int, 2018. **9**: p. 91.
22. Bennici, A., et al., *Safety of Medical Cannabis in Neuropathic Chronic Pain Management.* Molecules, 2021. **26**(20).
23. Iversen, L., *Cannabis and the brain.* Brain, 2003. **126**(Pt 6): p. 1252-70.
24. Lachenmeier, D.W. and J. Rehm, *Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach.* Sci Rep, 2015. **5**: p. 8126.
25. Ware, M.A., et al., *Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS).* J Pain, 2015. **16**(12): p. 1233-1242.
26. Lucas, P., et al., *Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors.* Drug Alcohol Rev, 2016. **35**(3): p. 326-33.
27. Lucas, P., et al., *Cannabis Significantly Reduces the Use of Prescription Opioids and Improves Quality of Life in Authorized Patients: Results of a Large Prospective Study.* Pain Med, 2021. **22**(3): p. 727-739.
28. Russo, E.B., G.W. Guy, and P.J. Robson, *Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine.* Chem Biodivers, 2007. **4**(8): p. 1729-43.
29. St Pierre, M., E.B. Russo, and Z. Walsh, *No Evidence of Altered Reactivity to Experimentally Induced Pain Among Regular Cannabis Users.* Clin J Pain, 2020. **36**(8): p. 589-593.
30. Walsh, Z., et al., *Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use.* Int J Drug Policy, 2013. **24**(6): p. 511-6.
31. Baer, R.A., et al., *Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples.* Assessment, 2008. **15**(3): p. 329-42.
32. Barrowclough, C., et al., *Does change in cannabis use in established psychosis affect clinical outcome?* Schizophr Bull, 2013. **39**(2): p. 339-48.
33. Barrowclough, C., et al., *The impact of cannabis use on clinical outcomes in recent onset psychosis.* Schizophr Bull, 2015. **41**(2): p. 382-90.
34. Vaismoradi, M., et al., *PRN Medicines Management for Psychotropic Medicines in Long-Term Care Settings: A Systematic Review.* Pharmacy (Basel), 2019. **7**(4).