Development Safety Update Report
Marijuana (cannabis)
IND# 110513
Sequential Number 08

Reporting Period: 15 November 2022 to 14 November 2023
Date of Report: 08 January 2024

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SPONSOR REPRESENTATIVE	Rick Doblin, PhD Founder and President MAPS
USE	In conjunction with relevant regulatory and ethical guidance

Executive Summary

This is the eighth annual report submitted by or on the behalf of the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization that is sponsoring clinical trials of real-world use of whole plant marijuana (cannabis) for treatment of Posttraumatic Stress Disorder (PTSD), conducted under the United States Investigational New Drug Application (US-IND) 110513. Cannabis is a Schedule 1 controlled substance in the US. This report covers the period from 15 November 2022 through 14 November 2023. There were no MAPS-sponsored studies for cannabis conducted during the reporting period. During the reporting period, there were no Serious Adverse Events (SAEs) reported. No IND actions have been taken for safety reasons. Cumulatively as of the reporting period, 80 individuals were exposed to cannabis under this US-IND. The sponsor does not have marketing approval for whole-plant cannabis for the treatment of PTSD anywhere in the world.

There is a pressing need for development of novel pharmacology for the treatment of PTSD. Given increasing prevalence of self-administration of cannabis among US military veterans with PTSD, there is strong public interest in whether cannabis may be an effective treatment for this indication. To date, one Phase 2 pilot study, MJP-1, has been completed for this indication using the investigational medicinal product (IMP) developed by the National Institute of Drug Abuse (NIDA). Data from this study has been published and the clinical study report is in progress. These data were used to inform the design of a second Phase 2 study of the real-world use of inhaled botanical cannabis to treat PTSD, MJP2 Original Protocol Version 2, dated 26 February 2021, first submitted under US-IND 11053, Serial Number 0015 on 08 March 2021, currently on clinical hold.

Cannabis is a botanical drug substance that is known to include at least two active ingredients based on nonclinical and clinical evidence. The active compounds in cannabis, delta-9-tetrahydrocannabinol (THC, Marinol® (dronabinol), and Cesamet® (nabilone), differs in federal scheduling and delivery method based on potency and original source. The latter two are FDA-approved artificial THC formulations available as a tablet or capsule and an oral solution. Cannabidiol (CBD, Epidiolex® a purified plant-derived oral solution) is FDA-approved for indications other than PTSD. A THC:CBD combination cannabinoid analgesic, Sativex® (nabiximols), is a 27mg/ml THC and 25mg/ml CBD buccal spray indicated for pain relief and Multiple Sclerosis (MS) spasticity, is approved in Canada, Switzerland, Norway and Turkey while undergoing Phase III clinical trials in the United States.

Nonclinical studies support the potential of cannabis to treat PTSD in humans. Administration of CBD in rats and mice reduces cue-elicited fear responses, while administration of THC and THC+CBD appears to block reconsolidation of fear memory. Likewise, both THC and CBD when administered alone effectively facilitate fear extinction learning, a critical component for recovery from PTSD.

The sponsor has completed the first randomized placebo-controlled trial of smoked cannabis for treatment of PTSD under this US-IND. The formulations of the IMP (obtained from the NIDA Drug Supply Program) in MJP-1 included: High THC=approximately 12% THC and <0.05% CBD; High CBD=11% CBD and 0.50% THC; THC+CBD=approximately 7.9% THC and 8.1% CBD, and placebo=<0.03% THC and <0.01% CBD, packaged at doses up to 1.8 g per day, for inhalational self-administration. Although the study failed to find a significant group difference between smoked cannabis preparations containing High CBD, High THC, and THC/CBD against placebo cannabis, results from this pilot study provided valuable information for future cannabis clinical trials for treatment of PTSD. All treatment groups, including placebo, showed good tolerability and significant improvements in PTSD symptoms after three weeks of treatment. Higher powered studies that attempt to mitigate the effect of pronounced placebo response and extend duration of the treatment period beyond three weeks appear warranted.

These data were used to inform the design of a second Phase 2 study of the real-world use of inhaled botanical cannabis to treat PTSD, MJP2. To more closely approximate the potency of cannabis available within state-sponsored medical cannabis programs, the planned formulation of the IMP for MJP2 will include: active cannabis, THC-rich=approximately 20% THC and <0.05% CBD, which is planned to be imported from an international supplier; and placebo cannabis=<0.03% THC and <0.01% CBD, planned to be obtained from the NIDA Drug Supply Program. The daily allotment of cannabis product is planned to be 1.5 g per day, provided in the form of three 0.5 g pre-rolled cannabis cigarettes containing dried, milled cannabis flower for inhalational self-administration by smoking the provided cannabis cigarettes or placing the dried milled cannabis flower in a provided dried botanical vaporizer (PAX vaporizer).

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List of Abbreviations

AE	Adverse Event
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CB1	Cannabinoid Receptor Type 1
CB2	Cannabinoid Receptor Type 2
CBD	Cannabidiol
CMC	Chemistry, Manufacturing, and Controls
COA	Certificate of Analysis
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FDA	Food and Drug Administration
IB	Investigator's Brochure
IND	Investigational New Drug Application
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LTFU	Long-Term Follow-Up
MAPS	Multidisciplinary Association for Psychedelic Studies
MPBC	MAPS Public Benefit Corporation
MWC	Marijuana Withdrawal Checklist
NIDA	National Institute on Drug Abuse
PCL-5	PTSD Checklist for DSM-5
PTSD	Posttraumatic Stress Disorder
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
THC	Δ-9-tetrahydrocannabinol
US	United States

1.0 Introduction

This is the eighth annual report submitted by or on behalf of MAPS, a research and educational organization that is sponsoring clinical trials of whole plant marijuana (cannabis) for treatment of PTSD, conducted under US-IND#110513. Cannabis is a Schedule 1 controlled substance in the US. This report covers the period from 15 November 2023 through 14 November 2023. There were no MAPS-sponsored studies for cannabis conducted during the reporting period. The sponsor does not have marketing approval for whole-plant cannabis for treatment of PTSD anywhere in the world.

The principal active component in the complex mixture of cannabinoids present in the cannabis plant is THC, which acts primarily as an agonist at the Cannabinoid Receptor Type 1 (CB1), as well as Cannabinoid Receptor Type 2 (CB2) receptors in the periphery, particularly within the immune system. These recently discovered receptors are activated by at least three endocannabinoids and endogenous fatty acids related to arachidonic acid. CB1 receptors are found at high concentrations throughout the human brain, including the basal ganglia and cerebellar regions, and also in the hippocampus and hypothalamus. THC has been shown to inhibit the release of a wide spectrum of neurotransmitters including L-glutamate, gamma-aminobutyric acid, norepinephrine, dopamine, serotonin, and acetylcholine. Anecdotally reported changes in symptoms after cannabis or THC support the use of cannabis to reduce PTSD symptoms, including reducing nightmares and improving sleep quality.

In addition to THC, whole plant cannabis contains a number of other active constituents, most notably CBD. Research indicates that THC acts upon receptors in brain areas involved in memory and fear processing, and nonclinical studies in rodents suggest cannabinoids reduce fear. Research in mice found that CBD was comparable to the antidepressant imipramine in tests of antidepressant-like effects. Findings of reduced PTSD symptoms, by orally administered THC or comparable synthetic cannabinoids, including nightmares and sleep difficulties suggest a potential role for cannabinoids in the alleviation of PTSD symptoms. Furthermore, CBD may oppose anxiogenic effects of THC in humans, and a naturalistic study found smoking cannabis with higher CBD levels was associated with less memory impairment and lower anxiety during intoxication. These studies suggest that it is worth investigating the effects of cannabis that varies in THC and CBD content on the ability to suppress symptoms of PTSD. Following these reports, MAPS conducted a study of the therapeutic effects of smoked cannabis varying in THC and CBD content in the treatment of PTSD symptoms.

There is an extensive literature on the risks of habitual cannabis use in humans, and a sizeable but considerably smaller literature on the acute safety profile of cannabis. Most risks associated with ingesting or inhaling cannabis relate to its psychoactive effects, though cannabis can also produce acute effects on the cardiovascular system and continued use can produce effects on the pulmonary system. Psychoactive and acute cardiovascular effects are transient and dissipate after the effects of the substance have waned, and in other short-term cannabis studies, pulmonary function has not been impacted. The risks of cannabis are addressed by careful screening of study participants prior to enrolling them, preparing participants during two supervised introductory sessions during which participants will learn how to self-administer their inhaled cannabis and what to expect during the study. Any suicidal ideation is assessed through administering the Columbia Suicide Severity Rating Scale (C-SSRS) and referral for further management if significant, or if any suicidal behavior is detected.

The investigational medicinal product (IMP) in this US-IND is dried plant material from the cannabis plant. *Cannabis* refers to the genus within the *cannabacae* family, containing possibly two species c. *sativa* and *c. indica*. They are hardy annual flowering plants, and dioecious, meaning there are male and female plants. This plant or extracts from this plant have been used medicinally for thousands of years and were legal in the US until 1937, when cannabis was removed from the United States Pharmacopeia and National Formulary.

The sponsor has completed the first randomized placebo-controlled trial of smoked cannabis for treatment of PTSD under this US-IND. The formulation of the IMP (obtained from the NIDA Drug Supply Program) in Study MJP-1 included: High THC=approximately 12% THC and <0.05% CBD; High CBD=11% CBD and 0.50% THC; THC+CBD=approximately 7.9% THC and 8.1% CBD, and placebo=<0.03% THC and <0.01% CBD, packaged at doses up to 1.8 g per day, for inhalational self-administration.

Although the study failed to find a significant group difference between smoked cannabis preparations containing High CBD, High THC, and THC/CBD against placebo in regard to their impact on PTSD symptoms, results from this pilot study provided valuable information for future cannabis clinical trials about real world use of cannabis for the treatment of PTSD. All treatment groups, including placebo, showed good tolerability and significant improvements in PTSD symptoms after three weeks of treatment. The failure to differentiate treatment groups from placebo is likely attributable to the higher than average treatment response in the placebo condition and to the shorter than average duration of treatment. Higher powered studies that attempt to mitigate the effect of pronounced placebo response and extend duration of the treatment period beyond three weeks appear warranted. Future studies would greatly benefit from access to high quality THC-rich cannabis which would more closely mirror what is available to patients within state-sponsored medical cannabis programs. During the reporting period, there were no SAEs reported. No IND actions have been taken for safety reasons within the reporting period.

To more closely approximate the potency of cannabis available within state-sponsored medical cannabis programs, the planned formulation of the IMP for Study MJP2 will be THC-rich =approximately 20% THC and <0.05% CBD, which is planned to be imported from an international supplier; and placebo cannabis=<0.03% THC and <0.01% CBD, planned to be obtained from the NIDA Drug Supply Program. The daily allotment of cannabis product is planned to be 1.5 g per day, provided in the form of three 0.5 g pre-rolled cannabis cigarettes containing dried, milled cannabis flower for inhalational self-administration by smoking the provided cannabis cigarettes or placing the dried milled cannabis flower in a provided dried botanical vaporizer (PAX vaporizer).

2.0 Worldwide Marketing Approval Status

There have been no foreign or domestic marketing approvals for cannabis for treatment of PTSD during the reporting period.

3.0 Actions Taken in the Reporting Period for Safety Reasons

No actions were taken for safety reasons during the reporting period.

4.0 Changes to Reference Safety Information

“Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids”, an October 2018 document issued by Health Canada, serves as the Investigator’s Brochure (IB). The most recent version of the IB was previously submitted to the IND (SN 0013).

5.0 Inventory of Clinical Trials Ongoing, Completed and Planned During the Reporting Period

The following table is a cumulative listing of all studies of cannabis under the MAPS US-IND#110513.

Table 1: Summary of Clinical Trials

Protocol	Study Title	Phase	Country	Participant Population	# of Participants Planned/Actual	Relevant Product	Status During Reporting Period
MJP-1	Placebo-Controlled, Triple-Blind, Randomized Crossover Multi-Site Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic Posttraumatic Stress Disorder	2	US	Veterans with service-related PTSD over the age of 18	76 Planned/ 80 Actual	(20) Low THC/Low CBD "placebo" for three weeks of self-administration, followed by two-week cessation period, followed by High THC, High CBD, or THC/CBD marijuana for three weeks. (20) High CBD marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High THC or THC/CBD marijuana for three weeks. (20) High THC marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High CBD or THC/CBD marijuana for three weeks. (20) THC/CBD marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High THC or High CBD marijuana for three weeks.	Concluded, Clinical Study Report in progress
MJP2	Phase 2 Multicenter Randomized Placebo-Controlled, Double-Blind, Parallel Study to Assess the Safety and Efficacy of Inhaled Cannabis in Veterans for Treatment of Posttraumatic Stress Disorder	2	US	Veterans with PTSD over the age of 18	320 Planned	(240) THC-rich cannabis for five weeks of self-administration, followed by one-week cessation period. (120) Placebo for five weeks of self-administration, followed by one-week cessation period.	Clinical Hold

5.1 Protocol MJP-1

Title: Placebo-Controlled, Triple-Blind, Randomized Crossover Multi-Site Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic PTSD

Purpose: This study was designed to test the safety and efficacy of smoked whole-plant marijuana, comparing varying ratios of THC and CBD to placebo, for treatment of PTSD symptoms using standard clinical measures.

First Participant First Visit: 6 February 2017

Last Participant Last Visit: 22 January 2019

Amendments During the Reporting Period: The protocol was not amended during the reporting period.

Participant Population: Military veterans 18 years and older with chronic service-related PTSD were eligible to enter the study. Study status through the reporting period is detailed below.

Number of Participants Planned	76
Number of Participants Enrolled	80
Number of Participants Who Completed Stage 1 Treatment (up to V5)	76
Number of Participants Who Discontinued Stage 1 Treatment (prior to V5)	4
Number of Participants Who Completed Stage 2 Treatment (up to V12)	67
Number of Participants Who Discontinued Stage 2 Treatment (prior to V12)	9
Number of Participants who Participated in Stage 3 (any visits 15-23)	31
Number of Participants Completed Study	67

Status: This study is concluded and the Clinical Study Report is in preparation.

5.2 Protocol MJP2

Title: 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)

Purpose: This study is intended to examine the use of inhaled high THC-containing cannabis versus placebo for management of PTSD symptoms in a U.S. Veteran sample and provide valuable insight on the patterns of real-world use, safety in the PTSD population, as well as gathering data on the effectiveness of cannabis in managing PTSD symptoms using standard clinical measures.

First Participant First Visit: N/A

Amendments During the Reporting Period: MJP2 Protocol Amendment 1, Version 1, dated 16 November 2022, was submitted to the FDA on 16 November 2022 under SN 00226. MJP2 Protocol Amendment 1, Version 2, dated 20 April 2023, was submitted to the FDA on 28 April 2023 under SN 0031. A final amendment was made just after the close of this reporting period: MJP2 Protocol Amendment 2, Version 1, dated 17 November 2023 was submitted to the FDA on 30 November 2023.

Participant Population: Military Veterans over the age of 18 with a diagnosis of at least moderate PTSD that is confirmed by a PTSD Checklist for DSM-5 (PCL-5) Total Score of 33 or greater at baseline are eligible to enroll. Study status through the reporting period is detailed below.

Number of Participants Planned	320
Number of Participants Enrolled	0
Number of Participants Treated	0
Number of Participants Dropped Treatment	0
Number of Participants Completed Study	0

Status: The study is currently on Clinical Hold.

6.0 Estimated Cumulative Exposure

Estimates of overall cumulative participant exposure are provided in Table 2: Cumulative Participant Exposure in the Development Program to Each Dose. The table is based upon exposure data from completed studies. Cumulatively as of the reporting period, 80 participants were treated in one study, MJP-1, which comprises the total cumulative participant exposures to cannabis for research purposes in studies under US-IND 110513.

6.1 Cumulative Participant Exposure in the Development Program

Table 2: Cumulative Participant Exposure in the Development Program to Each Dose

Study	Phase	Country	Study Population	Placebo	High THC/ Low CBD	Low THC/ High CBD	High THC/ High CBD
MJP-1	2	US	PTSD	20	20	20	20
Total Participants Exposed at Any Dose to IMP: 80*							

*Adjustment in planned enrollment to account for non-evaluable dropouts

Total exposure to smoked cannabis was lower than anticipated in the MJP-1 study and might not equate to a full therapeutic dose. In Stage 1, cannabis use in grams ranged from 8.2 g (THC/CBD) to 14.6 g (High THC) over three weeks (0.39 g/day to 0.69 g/day on average), despite all participants having access to up to 37.8 g over the three week self-administration period (1.8 g/day).

The findings from a large prospective examination of Canadian medical cannabis patients (N=1145) focused on the impacts of cannabis on prescription opioid use and measured cannabis use over 6 months. Mean flower cannabis use per week at Month 1 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, remaining quite stable over the first five months of use. (Lucas et al., 2021. “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 Mar 18;22(3):727-739). We suspect that participants might have used less cannabis in the current study because of differences between the cannabis available for research trials and the quality of cannabis sold commercially in the U.S. and internationally. Several participants spontaneously reported to study staff that the smoke from the cannabis that was provided was “harsher” than they were used to. This observation reinforces the importance of studying the safety and potential benefits of THC-rich botanical cannabis in the context of planned clinical trials under this US-IND.

6.2 Cumulative Participant Exposure from Marketing Experience

The investigational medicinal product (IMP) is not marketed by the sponsor.

7.0 Data in Line Listings and Summary Tabulations

7.1 Reference Information

Relevant reference safety information has been provided in Section 4.0 Changes to Reference Safety Information.

7.2 Line Listings of Serious Adverse Reactions During the Reporting Period

None occurred during the reporting period.

7.3 Cumulative Summary Tabulations of Serious Adverse Events

Cumulatively, 3 primary SAE cases have occurred across the one MAPS-sponsored study. For a cumulative summary of all SAEs in the Clinical Development Program, see Appendix Table 4.

No SAEs occurred during the reporting period.

8.0 Significant Findings from Clinical Trials During the Reporting Period

8.1 Completed Clinical Trials

There was one completed clinical trial under this US-IND, MJP-1. The MJP-1 Clinical Study Report is in preparation.

8.2 Ongoing Clinical Trials

No clinical trials are ongoing. One study is planned, a randomized, placebo-controlled double-blind study of inhaled cannabis in a population of Veterans with PTSD (MJP2) under the same US-IND (110513). The study is currently on clinical hold.

8.3 Long-Term Follow-up

There is no long-term follow-up (LTFU) data available during this reporting period.

8.4 Other Therapeutic Use of Investigational Drug

The sponsor has not conducted other programs that follow a specific protocol with solicited reporting as per ICH E2D during this reporting period.

8.5 New Safety Data Related to Combination Therapies

The IMP under development is not being evaluated as a component of a fixed-combination product or multi-drug regimen during this reporting period by the sponsor.

9.0 Safety Findings from Non-Interventional Studies

No new safety information was obtained from non-interventional studies during the reporting period.

10.0 Other Clinical Trial/Study Safety Information

No new safety information was obtained from randomized clinical trials not supported by the sponsor during the reporting period.

11.0 Safety Findings from Marketing Experience

The IMP has not been approved for marketing for medical use in any country.

12.0 Nonclinical Data

No new nonclinical studies with the IMP were performed by the sponsor during the reporting period.

13.0 Literature

No new literature with the IMP was published during the reporting period.

14.0 Other Annual Reports or DSURs

No other Annual Reports with the IMP were submitted by the sponsor during the reporting period.

15.0 Lack of Efficacy

No studies were ongoing during the reporting period under US-IND.

16.0 Region-Specific Information

16.1 IND Safety Reports Submitted During the Reporting Period

No IND safety reports were submitted during this reporting period under US-IND 110513.

16.2 Participants Who Died During Reporting Period

There have been no deaths during the reporting period, see Appendix Table 6: Cumulative List of Deaths.

16.3 Participants Who Dropped Out of Study Due to An Adverse Event During the Reporting Period

There have been no participants who dropped out of study due to an AE during this reporting period, see Appendix Table 5: Cumulative Line Listings of Treatment Dropouts.

16.4 Phase 1 Protocol Modifications

There are no Phase 1 protocols under this US-IND.

16.5 Significant Manufacturing Changes

There have been no significant changes to the manufacturing of the IMP during this reporting period. The IMP for MJP-1 was supplied by the NIDA Drug Supply Program. The active botanical cannabis for the upcoming MJP2 trial will be supplied by an international cannabis manufacturer and the placebo cannabis will be supplied by the NIDA Drug Supply Program.

16.6 Investigational Plan

This Investigational Plan is intended to contribute to the general body of scientific knowledge regarding the therapeutic utility of cannabis in individuals with PTSD. The sponsor completed the first randomized placebo-controlled trial of smoked cannabis for treatment of PTSD under this US-IND. Although the study failed to find a significant group difference between smoked cannabis preparations containing High CBD, High THC, and THC/CBD against placebo cannabis, results from this pilot study provided valuable information for future cannabis clinical trials for treatment of PTSD.

These data were used to inform the design of a second Phase 2 study, MJP2, for the use of inhaled cannabis to treat PTSD, initially submitted to the Agency on 09 March 2021 for review. Study MJP2 is intended to contribute to the general body of scientific knowledge regarding the therapeutic utility of cannabis in individuals with PTSD. This research is critical to better understanding the already

widespread use of cannabis in individuals with PTSD, for which there is currently a lack of controlled evidence. Study MJP2 is intended to examine the use of inhaled high THC-containing cannabis versus placebo for management of PTSD symptoms in a U.S. Veteran sample and provide valuable insight on the patterns of real-world use, safety in the PTSD population, as well as gathering data on the effectiveness of cannabis in managing PTSD symptoms.

Study MJP2 was initially put on clinical hold on 10 May 2021. In this reporting period, the sponsor submitted a Complete Response to Clinical Hold to US-IND 110513 for Agency review under Serial No. 0026 on 16 November 2022 in response to the Agency's incomplete response to hold letter, which was received from the FDA on 30 August 2022 requesting a revised protocol. A Continued Partial Clinical hold letter was received from the FDA on 16 December 2022. In order to gain agreement from the Agency on the sufficiency of the safety information to support the proposed dosing paradigm, proposed administration instructions, and inclusion of cannabis naïve participants, the sponsor submitted a Type A meeting request on 28 April 2023 under Serial No. 0031. The Agency granted the meeting on 09 May 2023. The Agency and sponsor had a productive discussion in the Type A Meeting held on 15 June 2023, as reflected in the meeting minutes. While the Division of Pulmonology, Allergy, and Critical Care (DPACC) did not attend the June 15th meeting, it provided comments in a separate post-meeting communication on 11 August 2023. Taking these responses into account, the sponsor submitted a Complete Response to the Clinical Hold, along with a protocol amendment under Serial No. 0032 on 30 November 2023.

Below is a table of completed, ongoing, and planned MAPS-sponsored clinical trials of Cannabis across indications.

Table 3: Investigational Plan of Concluded, Ongoing, and Planned Clinical Trials of Cannabis

Study / Phase	Start -End (Year)	Country	Study Population	Cannabis	Placebo
MJP-1 / Phase 2	2017-2019	US	PTSD	60	20
MJP2 / Phase 2	2024-2027	US	PTSD	214	106

16.7 Log of Outstanding Business

At the time of this report there is no outstanding business.

17.0 Late-Breaking Information

No late-breaking information was reported during the reporting period.

18.0 Overall Safety Assessment

18.1 Evaluation of the Risks

During this reporting period no new SAEs were reported as no studies were ongoing. Overall, the risks of exposure have been addressed and constrained by limited exposure to the IMP to participants who have undergone adequate screening according to eligibility criteria defined in study protocols. There have been no newly identified safety issues during this reporting period.

18.2 Benefit-Risk Considerations

The MJP-1 study served as the first randomized placebo-controlled trial of smoked cannabis for symptoms of PTSD in US military veterans. The study failed to detect a significant effect of treatment condition on the primary efficacy outcome (change in total PTSD severity on the Clinician-Administered PTSD Scale for DSM-5 [CAPS-5] from Baseline to End of Stage 1) after three weeks of self-administration of cannabis on an outpatient basis. All treatment groups (placebo, High CBD, High THC, THC/CBD) achieved statistically significant within-subject reductions in PTSD severity on the CAPS-5 in Stage 1, with effect sizes for change in mean PTSD severity ranging between d=0.83 (High CBD) and d=1.34 (High THC). These effect sizes are much larger than effect sizes reported for symptom change in other psychopharmacology trials for PTSD. For example, a 2018 meta-analysis reported standardized mean differences between 0.33 and 0.97 across PTSD pharmacology trials. The average length of trials reported in the 2018 meta-analysis lasted approximately ten weeks, whereas the current trial's primary endpoint was evaluated after only three weeks of treatment. Additional studies with longer duration of self-administration are warranted.

The MJP-1 study is unique in that it trialed whole plant cannabis preparations, rather than single molecule extracts or synthetic pharmaceutical cannabinoids. In addition to reporting changes in structured assessments of symptoms, the study results provide critical information about participant preference for cannabinoid preparations when exposed to different whole plant THC and CBD ratios. Consistent with previous observational studies, participants in the MJP-1 study reported a general preference for cannabis types that included significant quantities of THC.

19.0 Summary of Important Risks

In the Phase 2 study MJP-1, the number of participants who reported at least one Adverse Event (AE) did not significantly differ by treatment group. Thirty-seven of 60 participants who received THC, CBD, or THC/CBD during Stage 1 (61.7%) reported at least one treatment-related AE by the end of Stage 1. In Stage 2, 45 of the 74 participants who received THC, CBD, or THC/CBD (60.8%) reported at least one treatment-related AE during the crossover, Stage 2. Of 188 treatment-related AEs reported in the study, five did not resolve to baseline levels: irritability, weight gain, tightness in jaw, cough, and exacerbation of pre-existing peripheral neuropathy. Three of 80 participants (3.75%) reported an SAE in Stage 1, specifically heart palpitations (n=1), pulmonary embolism (n=1), and abscess (n=1). These SAEs were reported in the Annual Report for this IND# 110513 dated 09 November 2018.

There were 8 participants who reported a total of 14 severe AEs that were deemed related to treatment by the Site CI. These participants reported anxiety (3 of 80 or 3.8%), nausea (3 of 80 or 3.8%), agitation (1 of 80 or 1.2%), insomnia (1 of 80 or 1.2%), dizziness (1 of 80 or 1.2%), chest discomfort (1 of 80 or 1.2%), headache (1 of 80 or 1.2%), emesis (1 of 80 or 1.2%), suicidal ideation (1 of 80 or 1.2%), and disorientation (1 of 80 or 1.2%). The latter two AEs caused two separate participants to withdraw from study participation. In all participants who reported a treatment-related AE that was severe, there were no reported hospitalizations and all AEs returned to baseline levels.

The most common treatment-related AEs reported throughout the study periods (i.e., those with >10% frequency) were throat irritation (17 of 80 or 21.2%), anxiety (16 of 80 or 20.0%), cough (15 of 80 or 18.8%), headache (14 of 80 or 17.5%), nausea (11 of 80 or 13.8%), and paranoia (9 of 80 or 11.2%). Three participants reported emesis (3 of 80 or 3.8%).

One participant (THC/CBD) discontinued treatment during the introductory session in Stage 1 due to an AE, and two participants discontinued treatment during the introductory session in Stage 2 due to an AE (High CBD and High THC). Of 80 participants, 13 total participants terminated from the study early prior to the optional Stage 3 period, and 9 were due to AEs (11.25%). One participant withdrew from the

optional Stage 3 period due to logistical reasons. Five participants withdrew from the study due to treatment-related AEs. None of the participants withdrew from the Placebo cannabis group during Stage 1. A comprehensive list of participants who dropped out of clinical trials in association with an AE is presented in Appendix Table 5: Cumulative Line Listings of Treatment Dropouts.

One participant with a Lifetime C-SSRS Suicidal Ideation score of 1 who received THC/CBD in Stage 1 (1 of 80 in Stage 1) reported treatment-related suicidal ideation that was deemed not serious in the opinion of the Site CI. AE onset occurred on 16 February 2018, 4 days after randomization, and fully recovered to baseline levels 12 days after discontinuation of study cannabis. This AE was categorized as severe and the participant withdrew from study participation. One participant with Lifetime C-SSRS Suicidal Ideation score of 4 and no history of suicidal behavior who received High THC (same day of self-administration) cannabis and one participant with a Lifetime C-SSRS Suicidal Ideation score of 2 and Suicidal Behavior score of 2 who received High CBD (1 day after self-administration) cannabis reported treatment-related suicidal ideation in Stage 2 (2 of 74 in Stage 2). Both were deemed not serious in the opinion of the Site CI, rated as mild (C-SSRS Suicidal Ideation score 1), and resolved on the day of onset. The participant in the High CBD group, however, withdrew from study participation as a result of this AE. The cumulative prevalence of AEs of suicidal ideation was 3 of 80 (3.75%) participants in this study.

AE terms that reflect abuse liability or acute intoxication were reported with low prevalence in this study. Among treatment-related AEs, participants reported drug craving (1 of 80 or 1.25%), intoxication (1 of 80 or 1.25%), and visual hallucinations (1 of 80 or 1.25%). As measured by the Marijuana Withdrawal Checklist (MWC), all treatment groups showed a significant reduction in cannabis withdrawal symptoms from Baseline to the end of treatment in Stage 1. Only participants assigned to High THC in Stage 1 reported a significant increase in mean self-reported withdrawal symptoms after one week of cessation from the assigned treatment in Stage 1 (Δ=12.6, SD=11.41, p=0.0004). Total cannabis withdrawal symptoms were mild to moderate by the end of treatment in Stage 1, despite access to study cannabis. Participants who received High THC in Stage 1 reported a significant increase in withdrawal following one week of cessation from Stage 1 treatment, which averaged in the moderate range following cessation. There was no significant change in withdrawal symptoms from the end of Stage 2 to one-week follow-up.

20.0 Conclusions

To date, one Phase 2 study, MJP-1, has been concluded under this IND. In the first randomized, blinded, placebo-controlled clinical trial of whole plant cannabis, the overall rates of AEs were low and generally reversible upon discontinuation, although 5 of 80 (6.2%) participants withdrew due to treatment-related AEs (3 High CBD, 1 High THC, 1 THC/CBD). The introductory sessions where cannabis self-administration was conducted on site under direct observation were successful in mitigating risks as three participants (THC/CBD, High CBD, High THC) discontinued treatment during the introductory sessions due to AEs prior to receiving significant exposure to study cannabis as a take-home medication. In addition, there was a low rate of AEs supporting abuse liability and acute intoxication in PTSD participants, although withdrawal symptoms were evident after one week of cessation of High THC cannabis. Most of the AEs that occurred were mild to moderate in severity and resolved without intensive medical attention. There does not seem to be significant cause for concern in continuing the current research and conducting future studies of whole plant cannabis to treat PTSD using an outpatient treatment model, however as with any drug this treatment is not without risks.

These data informed the development of the Phase 2 study, MJP2, which intends to contribute to the general body of scientific knowledge regarding the therapeutic utility of cannabis in individuals with PTSD. Study MJP2 intends to examine the use of inhaled high THC-containing cannabis for management of PTSD symptoms in a U.S. Veteran sample and provide insight on the patterns of real-world use, safety in the PTSD population, as well as gathering data on the effectiveness of cannabis in managing PTSD symptoms.

Appendix

Appendix Table 1: Cumulative Listing of All Clinical Research Studies Using Cannabis Under the Sponsorship of MAPS or Subsidiaries

Protocol	Study Title	Phase	Country /IND	Participant Population	Number of Participants Planned	Relevant Product	Status During Reporting Period
MJP-1	Placebo-Controlled, Triple-Blind, Randomized Crossover Multi-Site Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic PTSD	2	US/ US-IND 110513	Veterans with service-related PTSD over the age of 18	76 planned/ 80 actual	(20) Low THC/Low CBD "placebo" for three weeks of self-administration, followed by two-week cessation period, followed by High THC, High CBD, or THC/CBD marijuana for three weeks. (20) High CBD marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High THC or THC/CBD marijuana for three weeks. (20) High THC marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High CBD or THC/CBD marijuana for three weeks. (20) THC/CBD marijuana for three weeks of self-administration, followed by two-week cessation period, followed by High THC or High CBD marijuana for three weeks.	Concluded, Clinical Study Report in progress
MPJ2	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)	2	US/ US-IND 110513	Veterans with PTSD over the age of 18	320 planned/ 0 actual	(240) THC-rich cannabis for five weeks of self-administration, followed by one-week cessation period. (120) Placebo for five weeks of self-administration, followed by one-week cessation period.	Clinical Hold

Appendix Table 2: Cumulative Summary Tabulations of Demographic Data

	Number of Participants		
Age Range	**Male**	**Female**	**Total**
20-29	7	1	8
30-39	22	5	27
40-49	21	0	21
50-59	8	2	10
60-69	11	0	11
70-79	3	0	3

Racial Group	**Number of Participants**
Asian	1
Black	3
Caucasian	53
Latino/Hispanic	11
Native American	2
Other/Multiple	10
Total	80

Appendix Table 3: Cumulative Line Listings of Serious Adverse Reactions

Study ID	Participant Number	Country / Gender / Age	Serious Adverse Drug Reactions (SARs)	Outcome	Date of onset / Date of Treatment	Suspect Drug	Daily dose / Route / Formulation	Dates of Treatment / Duration of Treatment	Comments
N/A	N/A	N/A	None to report	N/A	N/A	N/A	N/A	N/A	N/A

Appendix Table 4: Cumulative Summary of Serious Adverse Events by Body System

System Organ Class Preferred Term*	Placebo	High THC / Low CBD	Low THC / High CBD	High THC / High CBD	Total
Cardiac disorders Palpitations		1			1
Respiratory, thoracic, and mediastinal disorders Pulmonary embolism	1				1
Infections and infestations Abscess	1				1

Appendix Table 5: Cumulative Line Listings of Treatment Dropouts

Study	Investigator	Participant #	Reason for Not Completing Treatment	Condition Assignment	Relationship to Study Drug
MJP-1	Sisley	1119	AE: throat irritation	Withdrawn at V7, evaluable, High THC	Probably Related
MJP-1	Sisley	1120	AE: exacerbation of depression	Withdrawn at V3, not evaluable, High CBD	Probably Related
MJP-1	Sisley	01121	SAE: heart palpitations	Withdrawn at V6; evaluable, THC/CBD	Not Related
MJP-1	Sisley	01124	Moved to Israel	Withdrawn at V4; not evaluable, High THC	N/A
MJP-1	Sisley	01126	SAE: pulmonary embolism	Withdrawn at V9; evaluable, High THC	Not Related
MJP-1	Sisley	01136	Did not want to complete cessation period	Withdrawn at V13; evaluable, THC/CBD	N/A
MJP-1	Sisley	01137	Because of new requirement at job	Withdrawn at V10; evaluable, High THC	N/A
MJP-1	Sisley	01142	AE: suicidal ideation	Withdrawn at V2; not evaluable, THC/CBD	Possibly related
MJP-1	Sisley	01145	AE: pneumonia	Withdrawn at V5; not evaluable, THC/CBD	Not related
MJP-1	Sisley	01153	AE: disorientation, exacerbation of anxiety, unpleasant body high, increased awareness of musculoskeletal pain	Withdrawn at V10; evaluable, High CBD	Probably related
MJP-1	Sisley	01154	AE: recurrence of syncopal episode	Withdrawn at V6; evaluable, THC/CBD	Not related
MJP-1	Sisley	01165	Discontinued treatment without reason	Withdrawn at V6; evaluable, THC/CBD	N/A
MJP-1	Sisley	01166	AE: recurrence of anxiety, recurrence of insomnia, suicidal ideation	Withdrawn at V10; evaluable, High CBD	Possibly related

Based on final data received from the sites

Appendix Table 6: Cumulative List of Deaths

Study	Dose	Participant #	Adverse Event	Date Last Drug Admin	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Outcome	Relationship to Drug
MJP-1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No Deaths	N/A

Based on final data received from the sites