Protocol and Synopsis MJP2
US IND #110513

Original Protocol Version 2: 26 February 2021

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)

SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS)
SPONSOR REPRESENTATIVE	Rick Doblin, Ph.D. Executive Director MAPS
SPONSOR DELEGATE & TRIAL ORGANIZER	MAPS Public Benefit Corporation (MAPS PBC)
SPONSOR DESIGNEE	Amy Emerson Chief Executive Officer MAPS Public Benefit Corporation
COORDINATING INVESTIGATOR	Suzanne Sisley, M.D.
SITE INVESTIGATORS	Multisite study
MEDICAL MONITOR	Monica Taing Medical Monitor MAPS Public Benefit Corporation (MAPS PBC)
USE	In conjunction with relevant Food and Drug Administration (FDA) guidance

Disclaimer: This protocol version is for public viewing. Some information has been removed to maintain the integrity of this ongoing study.

MJP2 PROTOCOL SYNOPSIS

Rationale

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to obtain approval for the prescription use of botanical cannabis in patients with posttraumatic stress disorder (PTSD). PTSD is a serious debilitating disorder that negatively impacts a person's daily life, and can result in diminished cognitive and psychosocial functioning, fractured relationships, inability to maintain employment, substance abuse, high-cost healthcare utilization, increased depression, and suicide risk. People who suffer from PTSD relive their traumatic experience(s) through nightmares and flashbacks, have difficulty sleeping, and feel detached or estranged. Symptoms can be severe and long lasting.

The rationale for the use of inhalation of botanical cannabis to treat PTSD symptoms is based on the reports of cannabis attenuating PTSD symptom expression among individuals with PTSD, including veterans[1]. Preliminary findings from assessing current and recalled PTSD symptoms in 80 patients suggest that use of cannabis can reduce PTSD symptoms[2]. An open-label study in 10 people with chronic PTSD showed that sublingual Δ-9-tetrahydrocannabinol (THC) reduced PTSD symptoms, reduced nightmares, and improved sleep quality[3].

Finally, a randomized, placebo-controlled double-blind pilot study conducted by the sponsor in 76 veterans with PTSD, which tested three inhaled cannabis treatments (high THC, high CBD, THC+CBD) and placebo cannabis, showed that inhaled cannabis containing high THC was associated with greater improvement in PTSD symptoms[4]. The study provided preliminary evidence that all three types of inhaled cannabis could improve PTSD symptoms, anxiety, depression, and sleep quality in a clinically significant manner[4]. However, the beneficial effect of inhaled cannabis on PTSD symptoms assessed at the primary endpoint was not statistically significantly different from placebo likely due to the exploratory study design, large placebo effect, and small sample size (N=19) in each treatment group. The present study aims to re-examine use of inhaled cannabis containing high THC against placebo for treatment of PTSD using a larger sample size, a parallel design, and methods to mitigate placebo response.

Protocol Objective

The overall objective of the study is study to assess the safety and efficacy of inhaled botanical cannabis in veterans for treatment of PTSD.

Primary Objective

The primary objective of the study is to compare the efficacy of inhaled cannabis containing high THC cannabis versus placebo cannabis on PTSD symptom severity measured by the change in mean CAPS-5 total severity score.

Secondary Objective

The key secondary objective is to compare the efficacy of high THC cannabis versus placebo cannabis for treating functional impairment associated with PTSD, as measured by the change in mean Sheehan Disability Scale (SDS) score.

Exploratory Objectives

Exploratory objectives are to compare the efficacy of high THC cannabis versus placebo cannabis on depression, anxiety, pain and pain medication use, sleep, sexual function, and overall health.

Safety Objectives

The overall safety objective is to assess differences between high THC cannabis and placebo cannabis in severity, incidence and frequency of AEs, SAEs, AESIs, concomitant medication use, suicidal ideation and behavior, vital signs, and withdrawal symptoms.
The following objectives will evaluate the safety of high THC cannabis compared to placebo cannabis:

1. Compare relative incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) (primary objective).
2. Compare relative incidence of AEs.
3. Compare relative incidence of related AEs.
4. Compare relative incidence of AESIs, defined as a subset of AEs involving abuse liability (cannabis use disorder) and cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, and non-postural syncope. Withdrawal will be recorded as an AESI.

Study Design

This Phase 2 multicenter randomized placebo-controlled, double-blind, parallel study will assess the safety and efficacy of inhaled cannabis containing high THC versus placebo to manage PTSD symptoms and pain among approximately 360 veterans in an outpatient setting. The study will be conducted at roughly 3 sites in Michigan and 3 sites in other locations in the United States (US).
The approximately 9-week study will consist of a Screening Period, randomized double-blind Treatment Period, and Follow-up Period.

Screening: An initial Screening Period will be conducted to obtain participant's informed consent, determine participant's eligibility, and ensure that participants are willing and able to abstain from taking prohibited medications and drugs, attend scheduled appointments, and complete the study procedures. Major eligibility assessments will include severity of PTSD (using the Posttraumatic Symptom Checklist based on DSM-5 [PCL-5]), vital signs, electrocardiogram (ECG), physical examination, clinical laboratory testing, pregnancy testing and urine drug test. Participants with a positive THC qualitative urine analysis test will not be eligible for participation in the study but will be allowed to rescreen (maximum twice) after a 1-month cessation of cannabis use off-study.
Eligible participants will be enrolled and scheduled to return to the clinic for the Baseline Visit.

Baseline Visit and Introductory Sessions: At the Baseline Visit, participants will be trained for reduction of the placebo response using the Placebo Response Reduction Training Program (PRRTP) and assessed for various baseline measures. Participants will be randomized to one of two treatment groups in a double-blinded manner: High THC cannabis or Placebo cannabis at a ratio of 2:1. Participants will then undergo an introductory inhalation session (Introductory Session 1) to train participants on cannabis inhalation techniques and will be observed for 3 hours afterwards to monitor AEs and vital signs. Participants will be provided and trained on a Mobile Device App to record the daily dose (number of puffs) and method of cannabis self-administration (smoke/vape). The Mobile Device App will also allow participants to alert the clinical site in case of an emergency. Participants will return to the clinic to have a second introductory inhalation session (Introductory Session 2) with AEs and vital signs monitored for 3

hours afterwards. Participants will be provided with a supply of study cannabis for at home use and a lock box to store their study cannabis in throughout the duration of the study.

Treatment Period: Treatment will be on an outpatient basis. The Mobile Device App will remind participants to inhale the study cannabis on a daily basis. Participants will record on the Mobile Device App the daily amount of cannabis (number of puffs) and method of cannabis self-administration (smoke/vape). Participants will be provided with a log to track their concomitant medications and any changes in health. Participants will return to the clinic approximately 2 weeks after starting treatment to return unused study cannabis and obtain their next supply of study cannabis to inhale on an outpatient basis (Study Cannabis Resupply Visit). This will be stored in their study provided lock box. Participants will be reminded by the Mobile Device App to stop study cannabis use at bedtime on the day prior to the EoT (so they are not impaired at the visit). Participants will return to the clinic for EoT visit for assessment of PTSD symptoms.

Follow-up Period: An End of Study (EoS) visit will be conducted after cessation of treatment for safety and some efficacy assessments. The procedures of the EoS visit will also be followed in case of a participant's Early Termination (ET).

Recruitment and Participant Population

The study population will be military veterans, ≥18 years of age, with a confirmed diagnosis of moderate to severe PTSD from any cause per the PCL-5 and medical history review at Screening lasting for at least 6 months. Major exclusion criteria are: (i) have evidence or history of significant medical disorder or uncontrolled disease; (ii) positive for THC on a urine drug test.

Participants will be recruited at Veteran Administration sites, various Veteran organizations, through print and internet advertisements, a recruitment website, referrals from other treatment providers, and by word of mouth.

Treatment

The study will assess the safety and efficacy of inhaled cannabis containing high THC versus placebo to manage PTSD symptoms. In the Treatment Period, participants will be randomized to either High THC cannabis or placebo cannabis *ad libitum* daily at up to 3 g/day. Participants will be reminded to stop study cannabis use at bedtime on the day before the EoT Visit. Participants will have the choice of either smoking or vaping the study cannabis and may change between modalities at any time.

Type of Cannabis	THC Content[a]	CBD Content[a]	Dose[b]
High THC	15-25%	<1%	Up to 3 g/day
Placebo	<1%	<1%	Up to 3 g/day

[a.] THC and CBD contents of the study cannabis will be determined by analytical testing prior to the study.
[b.] Participants will be provided with 3 g of study cannabis per day but will choose their daily dose.

Primary Outcome Data Collection by Visit

The Clinician Administered PTSD Scale for DSM-5 (CAPS-5), a 30-item semi-structured clinical interview, is the gold standard for PTSD assessment in clinical trials of PTSD[5]. CAPS-5 (with a recall period of 1 month) will be administered by a qualified blinded independent rater. The change in mean CAPS-5 total severity score will be used as the primary outcome measure and will be the primary determinant of effect size between treatment groups for this study.

Statistical Analysis of Efficacy

Based on a recent meta-analysis conducted with the National Center for PTSD[6], possible effect sizes are estimated to be 0.3 (small to medium effect) for a between-group comparison to ensure an adequately powered study. Thus, in the proposed study, 360 participants (with 240 participants randomized to the MDMA group and 120 to the Placebo group) will have 80% power to detect these or greater differences between groups on the primary outcome measure (change in mean CAPS-5 total severity score).

Primary Efficacy Analysis

The primary endpoint will be the *change in mean CAPS-5 total severity scores*. Analysis of the primary endpoint will be conducted using an ANCOVA model with change from baseline score as the outcome with treatment group and baseline CAPS-5 score as independent variables. Effects on outcome and treatment from potential covariates, will be assessed. The effect size between high THC and placebo groups will be estimated using Cohen's techniques.

Key Secondary Analysis

The key secondary endpoint is the *change in mean SDS score*. The SDS is a brief, 5-item clinician-collected tool that assesses functional impairment in the domains of work/school, social life, and family life. Analysis will be conducted using an ANCOVA model change from baseline score as the outcome with treatment group and baseline SDS as independent variables.

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Table of Contents

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List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASEX	Arizona Sexual Experiences Scale
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CBD	Cannabidiol
CI	Clinical investigator
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
DVPRS	Defense and Veterans Pain Rating Scale
ECG	Electrocardiogram
EDC	Electronic Data Capture
EoS	End-of-study
EoT	End-of-treatment
ePRO	Electronic patient reported outcome
EQ-5D-5L	EuroQol Five Dimensions-Five Levels Questionnaire
ET	Early termination
FDA	Food and Drug Administration
g/day	Grams per day
GCP	Good Clinical Practice
HCV	Hepatitis C virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDAS	Inventory of Depression and Anxiety Symptoms
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
IRDB	Independent Rater Database
ISF	Investigator site file
ISI	Insomnia Severity Index
ITT	Intent to treat
IWRS	Interactive Web Randomization System
MAPS	Multidisciplinary Association for Psychedelic Studies
MINI	Mini-International Neuropsychiatric Interview
MPBC	MAPS Public Benefit Corporation
MWC	Cannabis Withdrawal Checklist
NCT	National Clinical Trial Registry
PCL-5	Posttraumatic Symptom Checklist based on DSM-5
PHI	Protected health information
PRRTP	Placebo Response Reduction Training Program
PTSD	Posttraumatic Stress Disorder
SAE	Serious adverse event
SCID-5-PD	Structured Clinical Interview for DSM-5 Diagnoses - Personality Disorders

SCID-5-SPQ	SCID-5 Self-report Personality Questionnaire
SDS	Sheehan Disability Scale
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent AE
THC	Δ-9-tetrahydrocannabinol
US	United States of America
VA	US Department of Veterans Affairs
WDS	Withdrawal discomfort score

1.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working as a clinical trial sponsor to gain knowledge on the potential benefits of inhaled cannabis as an adjunct to psychotherapy in patients with posttraumatic stress disorder (PTSD). MAPS has delegated trial organization responsibilities to the MAPS Public Benefit Corporation (MAPS PBC).

This study will continue MAPS' investigation into the treatment of PTSD with the second randomized controlled trial (RCT) to test the therapeutic potential of inhalation of botanical cannabis as a treatment for PTSD. This study is essential for understanding potential risks and therapeutic benefits of cannabis for PTSD patients.

1.1 Background

1.1.1 PTSD

PTSD is a serious debilitating disorder associated with increased mortality and cardiometabolic morbidity. PTSD is a stress-related psychiatric condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, and accidents. The four main symptom categories described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), include arousal and reactivity, avoidance of triggers, negative thoughts and feelings, and intrusive thoughts and nightmares. PTSD negatively impacts a person's daily life, resulting in fractured relationships, inability to maintain employment, diminished cognitive and psychosocial functioning, substance abuse, high-cost healthcare utilization, and increased depression and suicide risk. People who suffer from PTSD often relive the experience through nightmares and flashbacks, have poor sleep quality, and feel detached or estranged. Confronting overwhelming internal distress and frightening external environments can also lead to high levels of depersonalization and derealization, which led clinicians to identify a dissociative subtype of PTSD in the DSM-5. Adaptations in normal brain function have been observed in imaging studies of patients with PTSD that underlie alterations in emotional processing and regulation, cognition, and many aspects of behavior, though clinical symptoms and changes in brain activity are not homogenous across patients [7]. The dissociative subtype occurs in 12% to 30% of people with PTSD and is characterized by detachment and emotional numbing and visualized in the brain as overmodulation of affect mediated by midline prefrontal inhibition of limbic regions, while the non-dissociative subtype presents symptoms of hyperarousal and re-experiencing, an emotional undermodulation mediated by failure of prefrontal inhibition of the same limbic regions [8, 9]. Patients suffering from the dissociative subtype of PTSD typically have early childhood trauma and appear to be particularly difficult to treat, with mixed response to existing evidence-based treatments.

Approximately 7% of the population in the United States (U.S.) will have PTSD sometime in their life, but this figure jumps to 10.8% to 13% of veterans with combat experience [10]. For soldiers returning from Iraq and Afghanistan, the incidence of PTSD is 17.1% with 400,000 to 500,000 U.S. Iraq/Afghanistan veterans reportedly having PTSD. In 2004, the Defense Department and U.S. Department of Veterans Affairs (VA) spent $4.3 billion on PTSD disability payments to approximately 215,000 veterans [11]. In 2012 alone the VA spent $294 million and $3 billion, respectively, on care for veterans with the disorder and disability payments, even with this funding the demand for services far outreached the availability of VA doctors and services. As of June 30, 2016, more than 868,000 veterans with a diagnosis of PTSD were receiving disability compensation for service-connected mental disorders, with an estimated cost of about $17 billion per year [12]. There are an estimated 20 to 22 suicides per day by veterans [13].

Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration. This indicates a need to develop treatments targeting durable remission of PTSD. The Food and Drug Administration (FDA) has approved only two pharmacotherapies for PTSD, both of which are selective serotonin reuptake inhibitors (SSRIs). Paroxetine and sertraline (Paxil and Zoloft) both demonstrated statistically significant superiority over placebo on the CAPS in 12-week confirmatory clinical trials with daily dosing, but some studies were less effective in treating combat-related PTSD and sertraline demonstrated gender differences with minimal efficacy in men [14, 15]. PTSD rarely remits after 12 weeks of SSRIs, and many patients who are placed on maintenance treatment experience partial relief of symptoms, which fully return upon discontinuation of treatment. Adverse effects of maintenance SSRI treatment that contribute to discontinuation include sexual dysfunction, weight gain, and sleep disturbance. Variable SSRI treatment outcomes have led to recommendations of trauma-focused psychotherapy as routine first-line treatment by the VA's National Center for PTSD in the U.S., as well as by the World Health Organization. An extensive list of medications, namely antipsychotics, anxiolytics, antidepressants, and sleep aids, are frequently prescribed off-label but have only small effect sizes in reducing PTSD symptoms. PTSD brings a high public burden, both economically and socially, by increased use of health and social services, lost wages, and disability payments [16, 17]. Given the chronicity of PTSD, low compliance evidenced by high dropouts, and limited recovery with current medications contributing to serious outcomes, PTSD patients suffer from unmet medical need.

One treatment approach is to develop medications and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal axis associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure therapy and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing have also proven to be effective in treating some symptoms of PTSD [18, 19], although some patients may need more than one type of treatment to reduce or resolve those symptoms. A meta-analysis concluded that all "bona fide" psychotherapies, including those listed above, are similarly effective with PTSD [20]. In the past decade, there has been a growing amount of research into medications and other methods that may augment the effectiveness of psychotherapy for PTSD (see [21] for a review). Examples of this are virtual reality-assisted exposure therapy [22, 23] and D-cycloserine-assisted psychotherapy [24].

1.1.2 Cannabis as a Treatment for PTSD

1.1.2.1 *Cannabis Use in PTSD*

The principal active component in the complex mixture of cannabinoids present in the cannabis plant is Δ-9-tetrahydrocannabinol (THC), which acts primarily as an agonist at the CB1 cannabinoid receptor. This receptor is found at high concentrations in the brain, including the basal ganglia, cerebellum, hippocampus, and hypothalamus. THC has been shown to inhibit the release of a wide spectrum of neurotransmitters including L-glutamate, GABA, norepinephrine, dopamine, serotonin, and acetylcholine [25].

The rationale for the use of inhaled cannabis to treat/relieve PTSD symptoms is based on the many reports of cannabis attenuating PTSD symptom expression among individuals with PTSD, including veterans [26]. Preliminary findings from assessing current and recalled PTSD symptoms in 80 patients suggest that use of cannabis can reduce PTSD symptoms [27]. An open-label study in 10 people with chronic PTSD showed that sublingual THC reduced PTSD symptoms, reduced nightmares, and improved sleep quality[28]. Finally, a randomized, placebo-controlled double-blind pilot study (MJP1) conducted by the sponsor in 76 veterans with PTSD,

which tested three concentrations of THC and cannabidiol (CBD) versus placebo cannabis, showed that inhaled cannabis containing high THC was associated with greater improvement in PTSD symptoms [29]. However, the primary outcome measure of PTSD (ie, reduction in total severity scores in the CAPS-5 [Clinician Administered PTSD Scale for DSM-5]) in the high THC group was not statistically significantly different from that in the placebo group.

As of January 2020, 33 states have legalized medical cannabis, and 11 have fully legalized cannabis. Twenty-six of the 33 states with medical cannabis legislation list PTSD as a qualifying condition for medical cannabis [30]. In many states, PTSD is the primary condition for patients to enroll in the medical cannabis program [31-33].

1.1.2.2 *Cannabis Mechanism of Action in PTSD*

Research indicates that THC acts upon receptors in brain areas involved in memory and fear processing, and preclinical studies in rodents suggest cannabinoids reduce fear[34, 35]. 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 [36, 37].

Another potential mechanism by which cannabis may confer benefit in the treatment of PTSD relates to reductions in inflammation. A longitudinal study in US Marines reported an association between higher pre-deployment levels of C-reactive protein (CRP) and post-deployment development of PTSD [38]. In other research, reduction in PTSD symptoms following treatment with SSRIs was associated with a reduction in interleukin-1beta (IL-1β) [39], and women whose PTSD symptoms were in remission exhibited lower levels of CRP and interleukin-6 (IL-6) compared with those with current PTSD [40]. Further, a meta-analysis supported a link between IL-1β and IL-6 and exposure to trauma [41], with stress-related elevation in IL-6 potentially higher among those with PTSD [40, 42]. Because both THC and CBD have potent anti-inflammatory and immunomodulatory properties [43, 44], cannabis use may have therapeutic benefit in PTSD treatment simply via reductions in inflammation.

1.2 Rationale for the Study

The rationale for the use of inhalational cannabis to potentially treat PTSD symptoms is based on the many reports of cannabis attenuating PTSD symptom expression among individuals with PTSD, including veterans (see Section 1.1.2 above).

A pilot crossover double-blinded placebo-controlled study (MJP1) was conducted by MPBC to assess the effects of three inhaled cannabis treatments (high THC, high CBD, THC+CBD) and placebo cannabis in 76 veterans with chronic PTSD. The study provided preliminary evidence that all three types of inhaled cannabis could improve PTSD symptoms, anxiety, depression, and sleep quality in a clinically significant manner [29]. However, the beneficial effect of inhaled cannabis on PTSD symptoms (primary endpoint of reduction in CAPS-5 total score) was not statistically significantly different from placebo, likely due to the exploratory study design, large placebo effect, and small sample size in each treatment group. MJP1 study demonstrated that all three types of inhaled cannabis were safe and well tolerated. Across both stages, 63.3% of participants who received THC, CBD, or THC+CBD reported at least one treatment-related adverse event (TEAE) compared to 70% in the placebo group. There were no significant differences between groups reporting at least one AE in Stage 1. Across both Stages, 11.2% of participants enrolled discontinued from the study early due to an AE. The most common AEs reported 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%). There were no AEs indicative of

drug dependence, intentional drug misuse, or substance abuse, and a low rate (<2%) of secondary terms that reflect acute intoxication in PTSD patients. There were 3 serious AEs (SAEs) and these were deemed unrelated to study drug by the Investigator. Although AEs of special interest (AESIs) were not tracked in MJP1, AESIs will be tracked in MJP2 study and will be defined as a subset of AEs involving abuse liability (cannabis use disorder) and cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, and non-postural syncope. Withdrawal will be recorded as an AESI.

The present study proposal aims to re-examine the use of inhaled cannabis containing high THC against placebo for treatment of PTSD using a larger sample size, one active cannabis group only (High THC), a parallel design, and methods to mitigate placebo response.

2.0 Protocol Objectives

The overall objective of the study is to assess the safety and efficacy of inhaled botanical cannabis in veterans for treatment of PTSD.

2.1 Primary Objectives

The primary objective of the study is to compare the efficacy of inhaled cannabis containing high THC versus placebo cannabis on PTSD symptom severity measured by the change in mean CAPS-5 total severity score.

2.2 Key Secondary Objective

The key secondary objective is to compare the efficacy of high THC cannabis versus placebo cannabis for treating functional impairment associated with PTSD, as measured by the change in mean Sheehan Disability Scale (SDS) score.

2.3 Exploratory Objectives

Exploratory objectives are to compare the efficacy of high THC cannabis versus placebo cannabis on suicidal ideation and behavior, depression, anxiety, pain and pain medication use, sleep, sexual function, overall health, and dropout rate.

2.4 Safety Objectives

The overall safety objective is to assess differences between high THC cannabis and placebo cannabis in severity, incidence and frequency of AEs, SAEs, AESIs, concomitant medication use, suicidal ideation and behavior, vital signs, and withdrawal symptoms.

1. Compare relative incidence of AEs.
2. Compare relative incidence of related AEs.
3. Compare relative incidence of AESIs, defined as a subset of AEs involving abuse liability (cannabis use disorder) and cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, and non-postural syncope. Withdrawal will be recorded as an AESI.
4. Compare relative incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).

3.0 Study Population

The study population will be military veterans ≥18 years of age with a confirmed diagnosis of moderate to severe PTSD from any cause per the PCL-5 and medical history review at Screening. Major exclusion criteria are: (i) have evidence or history of significant medical disorder or uncontrolled disease; (ii) positive for THC on a urine drug test.

Participants will be recruited at Veteran Administration sites and various Veteran organizations, through print and internet advertisements, a recruitment website, referrals from other treatment providers, and by word of mouth.

3.1 Inclusion Criteria

Eligible individuals based on initial screening criteria must:

1. Be at least 18 years old.
2. Be a Veteran with PTSD lasting 6 months in duration.
3. Be able to provide written, informed consent.
4. Meet DSM-5 criteria for PTSD with symptoms (as assessed by the MINI).
5. Have PTSD (as assessed by the PCL-5) at the time of screening.
6. If of childbearing potential, must agree to use an effective form of birth control during study participation and may only be allowed to enroll and continue in the study based on a negative pregnancy test. Adequate birth control methods include intrauterine device, injected or implanted hormonal methods, abstinence, oral hormones plus a barrier contraception or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e. condom + diaphragm, condom or diaphragm + spermicide, oral hormonal contraceptives + spermicide or condom). Not of childbearing potential is defined as permanent sterilization, postmenopausal, or assigned male at birth.
7. Be willing to commit to medication dosing and delivery method, to complete evaluation instruments, and attend all study visits.
8. Agree to use only cannabis provided by site staff and agree to required follow up periods for the duration of the study.
9. Agree to keep all cannabis provided by site staff securely stored in the provided lock box and not to share/distribute cannabis to any other individual.
10. Be proficient in reading and writing in English and able to effectively communicate with site staff.
11. Agree not to participate in any other interventional clinical trials during the study.
12. Must agree to inform the investigators within 48 hours of any medical conditions and procedures.
13. Must provide a contact (relative, spouse, close friend or other support person) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal or unreachable.

3.2 Exclusion Criteria

Individuals who meet any of the following criteria will not be eligible for participation:

1. Are not able to give adequate informed consent.
2. Are pregnant, nursing, or are of childbearing potential who are not practicing an effective means of birth control.
3. Participants with a positive THC urine analysis tests are excluded from the study but will

be allowed to rescreen (maximum twice) after a 1-month cessation of cannabis use.
4. Have a history of arrhythmia at any time, other than occasional premature atrial contractions (PACs) and PVCs in the absence of ischemic heart disease.
5. Have evidence or history of significant medical disorder
6. Have any current problem, which in the opinion of the CI or Medical Monitor, might interfere with participation.
7. Have any known allergies to cannabis or contraindication for inhalation of cannabis.
8. Are not able to attend required face-to-face visits or those who plan to move out of the area within the treatment period.

3.3 Lifestyle Modification

Participants with a positive THC urine analysis tests are excluded from the study but will be allowed to rescreen (maximum twice) after a 1-month cessation of cannabis use.

Participants will not be allowed to use the following prohibited medications/drugs during the entire study:

- Cannabis (other than study cannabis) in all its forms
- THC and CBD in all its forms

Participants will be required to adhere to contraception requirements (see Section 9.2.2 for details).

4.0 Study Design

This Phase 2 multicenter randomized placebo-controlled, double-blind, parallel study will assess the safety and efficacy of inhaled cannabis containing high THC versus placebo to manage PTSD symptoms and pain among approximately 360 Veterans in an outpatient setting. The study will be conducted at roughly 3 sites in Michigan and 3 sites at other states in the United States (US). The approximately 9-week study will consist of a Screening Period, a randomized double-blind Treatment Period, and a Follow-up Period.

Screening: An initial Screening Period will be conducted to obtain participants' informed consent and determine participants' eligibility and ensure that participants are willing and able to abstain from taking prohibited medications and drugs, attend scheduled appointments, and complete the study procedures. Eligibility assessments will include diagnosis of PTSD (using the Posttraumatic Symptom Checklist based on DSM-5 [PCL-5]), vital signs, electrocardiogram (ECG), physical examination, clinical laboratory testing, pregnancy testing, urine drug test. Participants with a positive THC urine analysis tests will not be eligible for participation in the study but will be allowed to rescreen (maximum twice) after a 1-month cessation of cannabis use off study.

Eligible participants will be enrolled and scheduled to return to the clinic for the Baseline Visit.

Baseline Visit and Introductory Sessions: At the Baseline Visit, participants will be trained for reduction of the placebo response using the Placebo Response Reduction Training Program (PRRTP) and assessed for various baseline measures. Participants will be randomized to one of two treatment groups in a double-blinded manner: High THC cannabis or Placebo cannabis at a ratio of 2:1. Participants will then undergo an introductory inhalation session (Introductory Session 1) to train participants on inhaling cannabis and will be observed for 3 hours afterwards to monitor AEs and vital signs. Participants will be provided with a Mobile Device App to record the daily dose (number of puffs) and method of cannabis self-administration (smoke/vape). The

Mobile Device App will also allow participants to alert the clinical site in case of an emergency. Participants will return to the clinic to have a second introductory inhalation session (Introductory Session 2) with AEs and vital signs monitored for 3 hours afterwards. Participants will be provided with approximately a 2-week supply of study cannabis for home use.

Treatment Period: Treatment will be on an outpatient basis. The Mobile Device App will remind participants to inhale the study cannabis on a daily basis. Participants will record on the Mobile Device App the daily amount of cannabis inhaled (number of puffs) and method of cannabis self-administration (smoke/vape). Participants will be given a log to track daily use of concomitant medications and changes in health, in order to provide to clinical staff during on-site visits for collection of AEs and concomitant medications. Approximately 2 weeks after starting treatment, participants will return to the clinic for the Study Cannabis Resupply Visit to return unused study cannabis and obtain their next supply of study cannabis to inhale at home. Participants will be reminded by the Mobile Device App to stop study cannabis use at bedtime on the day prior to the EoT visit (so they are not impaired at the visit). Participants will return to the clinic for the EoT visit for assessment of PTSD symptoms.

Follow-up Period: An EoS visit will be conducted after cessation of treatment for safety assessments. The schedule of procedures is provided in Section 7.3.

4.1 Planned Duration of the Study

The study will consist of a Screening Period, a randomized double-blind Treatment Period, and a Follow-up Period. Therefore, each participant will be in the study for ~9 weeks.

4.2 Interruptions and Accommodations Due to COVID-19 Pandemic or Any Other Unforeseen Emergency at Clinic Locations

This clinical trial may be interrupted by the Coronavirus Disease 2019 (COVID-19) global pandemic. Accommodations may be required for study continuation and participant and study site staff safety due to this emergency or any other unforeseen emergency in the future. The following accommodations in the protocol will be allowed, captured, and noted in the Clinical Study Report as COVID-19 deviations:

- Delaying Introductory Sessions
  (ex. participants whose Introductory Session(s) is delayed by the COVID-19 pandemic should be rescheduled when the visits resume).
- Skipping Introductory Sessions
  (ex. participants who have completed the Introductory Session 1 without safety issues but whose Introductory Session 2 is delayed by the COVID-19 pandemic may be provided with the study cannabis and start self-administration at home, as clinically indicated.)
- Delaying visits
  (ex. for Baseline)
- Conducting visits at the participants' home
  (ex. Study Cannabis Resupply Visit)
- Delaying IR assessments for participants who cannot complete them remotely off-site

For any participant with COVID-19 related illness, continued trial participation after full recovery of the disease may be appropriate after discussion between the site physicians and Medical Monitors on a case-by-case basis.

4.3 Discontinuation and Completion Criteria

4.3.1 Complete or Evaluable Participants

A participant is considered 'Evaluable' and eligible for the mITT analysis if they have completed at least one Introductory Session and one CAPS-5 or one PCL-5 assessment post Baseline.

A participant is considered 'Evaluable and Completed Per Protocol' if they have completed all Introductory Sessions and CAPS-5 assessments as planned. These participants will be included in the mITT analysis set and the Per Protocol analysis set.

A participant is considered 'Evaluable and Early Termination' if they have completed at least one Introductory Session and one CAPS-5 assessment post Baseline but terminated early. These participants will be included in the mITT analysis.

4.3.2 Participant Withdrawal of Consent

Participants can withdraw consent at any time without prejudice. The CI can discontinue a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with the experimental procedures and related visits that are critical for safety, and this will be recorded in the participant's source records and CRF. If the CI discontinues a participant from treatment, the CI will explain the reason to the participant, and may refer him/her to standard clinical care for PTSD, as needed. Participants who are discontinued will not be denied care within or outside of the VA or participating institutions. Participants will be clinically monitored after withdrawal by the CI. Whenever possible, the evaluations listed for the termination visit will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable. All participants who sign informed consents, meet study eligibility criteria, and who receive the initial dose of study cannabis will be included in intent-to-treat (ITT) analyses (including withdrawal of consent data, from time of consent through study withdrawal).

Participants who discontinue treatment during the study will not be replaced. Recruitment and enrollment will continue until 360 participants have been enrolled and exposed to IMP. The sample size may be modified if recommended by the iDMC.

4.3.3 Screen Failures

'Screen Failures' are defined as participants who pass phone screening but are deemed ineligible to participate in the study. Screen failures may fail to meet all Inclusion Criteria and may meet one or more Exclusion Criteria or withdraw consent prior to Enrollment. All potential participants who begin Screening will be tracked on a Screening Log, and reasons for Screen Failure will be recorded. Screen Failures are not considered evaluable.

At any time during Screening, if a potential participant is deemed to be ineligible, classify as a Screen Failure, notify the potential participant that they are unfortunately not eligible for the study, and do not schedule additional Screening assessments. Participants who fail Screening may be rescreened at a later date if deemed appropriate by the investigator but should sign a new copy of the Informed Consent Form (ICF). Participants with a positive THC urine analysis test will not be eligible for participation in the study but will be allowed to rescreen (maximum twice) after a 1-month cessation of cannabis use off study.

4.3.2**Error! Reference source not found.**

4.3.4 Early Terminations

Participants who are removed from the study after they are randomized and receive study cannabis but do not complete the study will be considered Post-Randomization Early Termination. If a participant has received study cannabis in at least one Introductory Session and completed one CAPS-5 or PCL-5 assessment following randomization, they will be considered evaluable. All participants who receive study cannabis in at least one Introductory Session will be included in all safety analyses.

Participants can withdraw from treatment or withdraw consent at any time for any reason without judgment. The site team can withdraw a participant if, in their clinical judgment, it is in the best interest of the participant or if the participant cannot comply with elements of the protocol that are critical for safety or for the scientific integrity of the study. If the site team makes the decision to terminate the participant from treatment or the study, they will explain the reason for withdrawal and document in the participant's source records and Electronic Case Report Form (eCRF). If a participant develops any Exclusion Criteria that, in the opinion of the Medical Monitor or Site, affects the safety of the participant, including psychiatric diagnosis, medical diagnosis, pregnancy, or requiring use of prohibited medications, the participant will discontinue treatment. Any time a participant terminates from the study early, the site team will attempt to schedule the participant for an EoT Visit (in person or via telemedicine; see Section 7.3.3) or, if not to available, to obtain information about AE outcomes by telephone, if appropriate, as determined by the site physician and Medical Monitor.

Post-Randomization Early Termination: Participants who discontinue study treatment but continue to participate in IR primary and secondary outcome assessments. Data collection by IRs will continue on the same schedule as planned through Study Termination visit procedures.

4.3.5 Lost to follow-up

A participant will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the site staff. If the participant has completed at least one Introductory Session and one CAPS-5 assessment following randomization, they will be considered evaluable. All participants who receive at least one dose of study cannabis will be included in the safety analysis.

If a participant does not attend a scheduled visit, the site must attempt to contact the participant to reschedule the visit as soon as possible and emphasize the importance of complying with the protocol specified visit schedule. The staff should determine if the participant is willing to comply with future visits.

If a participant does not respond to this initial contact, the site staff must make multiple efforts to contact the study participant and document each attempt in the source record. At least three attempts should be made via telephone, over the course of approximately 7 days, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. The emergency contact the participant provided should be contacted and asked to attempt to contact the participant. Lastly, a certified letter (or equivalent) should be sent to the participant's last known mailing address. If the participant fails to respond to all of these contacts, he/she will be considered to have withdrawn from the study and lost to follow-up.

4.3.6 End of Study Definition and Premature Discontinuation

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the trial.

The sponsor has the right to discontinue this study at any time. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All study cannabis will be returned to the sponsor and will be treated in accordance with federal and state regulations.

5.0 Participant and Staff Training

5.1 ePRO Training

Many self-report measures used in this study are performed using an electronic Participant Reported Outcome (ePRO) platform. Participants will create a password and enter their self-report questionnaire data using the ePROs directly into Medrio. At Screening, participants will be provided with a quick training on how to log in and use the ePROs.

5.2 Mobile Device App Training

At the Baseline Visit, participants will be provided with a Mobile Device App to record the daily dose (number of puffs) and method of cannabis self-administration (smoke/vape). The Mobile Device App will provide study reminders for daily self-administration or discontinuation of study cannabis use at the EoT. The Mobile Device App will also allow participants to alert the clinical site in case of an emergency.

At the Baseline Visit, participants will be trained on how to record information in the Mobile Device App. This training will be performed on site with qualified study staff. The participant will be provided with their own device at the visit during Introductory Session 1.

5.3 Accurate Symptom Reporting Training

Placebo responses can significantly reduce assay sensitivity in clinical trials, causing randomized controlled drug trials (RCTs) that should be efficacious to fail. In the pilot study MJP1, participants receiving placebo cannabis showed improvements in PTSD symptoms on the CAPS-5 that were not statistically significantly different from those receiving High THC cannabis, indicating a possible placebo response. Patients' expectations of benefit are considered one of the primary reason placebo responses occur, and this phenomenon is especially important in RCTs which rely on patient-reported outcome measures as primary endpoints. To reduce the potential placebo response in the present study, two measures will be implemented:

1. Accurate Symptom Reporting Training (ASRT): At Baseline, before completing the baseline measures, participants will be trained to accurately complete the various self-report measures by improving their interoceptive awareness of symptoms.
2. Placebo Response Reduction Training Program (PRRTP): At Baseline, before completing the baseline measures, participants will be trained for reduction of the placebo response using the PRRTP [45]. The PRRTP has been implemented in multiple clinical trials, and most recently in a completed trial in patients with lumbosacral radiculopathy. Results show that the study using the PRRTP had a smaller placebo response than two comparable studies in lumbosacral radiculopathy, and smaller than the placebo response in all other included studies in lower back pain [45].

5.4 Coping Skills Training

During Introductory Sessions 1 and 2, the clinical staff will train participants on how to inhale cannabis using the devices and will teach participants 'coping techniques' (adaptive stress coping including deep slow breathing techniques, relaxation, meditation, grounding techniques, etc.) to cope with potential side effects of cannabis inhalation. This training will cover common short-term effects such as strong psychoactive effects, drowsiness, and cardiovascular effects, as well as longer-term effects such as paranoia and mood alteration.

6.0 Measures

The following eligibility, outcome, exploratory, and safety measures will be used in the study.

6.1 Primary Outcome Measure: CAPS-5 (Clinician-Administered PTSD Scale for DSM-5)

The CAPS-5 [5] is the gold standard for PTSD assessment and has been used to obtain FDA approval for PTSD medications. CAPS-5 is a 30-item semi-structured interview administered by a blinded independent rater that can be used to provides diagnostic status (presence versus absence) of PTSD as well as quantitate PTSD symptom severity. The CAPS-5 is used to assess the index history of DSM-5-defined traumatic event exposure [46], including the most distressing event, time since exposure, and total number of exposures, as well as the frequency and severity of posttraumatic stress symptoms, as evidenced by CAPS-5 total score.

A recall period of 1 month (which is the standard for CAPS-5) will be used at each visit. The CAPS-5 will be administered by trained independent raters (under supervision by qualified personnel). The change in mean CAPS-5 total severity score will be used as the primary outcome measure and will be the primary determinant of effect size between treatment groups for this study.

6.2 Secondary Measure: SDS (Sheehan Disability Scale)

The SDS [47] is a brief, 5-item clinician-collected tool that assesses functional impairment in the domains of work/school, social life, and family life with response options of not at all, mildly, moderately, markedly, or extremely. Which are scored from 0 (= "*Not at all*") to 10 (= "*Extremely*"). The SDS takes 1 to 2 minutes to complete.

6.3 Safety Measures

6.3.1 C-SSRS (Columbia Suicide Severity Rating Scale)

The C-SSRS [48] will be used to assess and monitor suicidality in this trial. The "Baseline/Screening" and "Since Last Visit" versions of the scale will be used for the study. The "Baseline/Screening" version, which assesses the experience of the participant with suicidal ideation and behavior over their lifetime and within 6 months prior to entry into the trial, will be completed for all potential participants at screening to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at the Baseline visit prior to the first administration to assure that participant continue to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at all post-baseline visits. The C-SSRS consists of a series of questions and can be administered during a face-to-face interview or over the telephone. The C-SSRS Intensity scale for Lifetime obtained a Cronbach's alpha of 0.93 and 0.94 for the Since Last Visit form, and

Last Visit C-SSRS severity scores were positively correlated with the Beck Depression Inventory "suicide thoughts" item [49].

6.3.2 MWC (Marijuana Withdrawal Checklist)

The MWC [50, 51] will be used to assess the presence of cannabis withdrawal symptoms during periods of abstinence. The MWC will be labeled as 'Behavior Checklist' to minimize expectation effects. It lists 32 symptoms for which participants indicate severity on a four-point scale (0 = "*Not at all,"* 1 = *"Mild,"* 2 = *"Moderate,"* 3 = *"Severe"*). The symptom list comprises the valid items found in prior cannabis withdrawal studies and additional non-specific items to minimize response bias. At screening, participants will be instructed to indicate whether and to what degree they experienced each symptom during past periods of cannabis abstinence lasting at least 48 hours, if they are past or current cannabis users. During study visits, participants will be asked to rate how they have felt in the last week. Administered in this way, the MWC has been used effectively to detect reliable cannabis withdrawal effects in several prior studies [50-55]. A total withdrawal discomfort score (WDS) will be computed from the Checklist and will be the outcome variable for this measure. This summary score will include the symptoms reliably observed in prior cannabis withdrawal studies[56].

6.4 Screening Measures

6.4.1 MINI (Mini-International Neuropsychiatric Interview)

This version of the MINI (7.0.2), a structured interview that was first developed in 1998 to be compatible with DSM and International Classification of Disease criteria for psychiatric illnesses [57], is now compatible with DSM-5 and will be administered by a member of the Independent Rater Pool to screen for psychiatric conditions per DSM-5. Each module of the MINI consists of two or three questions where the answer is either "Yes" or "No," and decision-tree logic is used to determine whether to ask additional questions [58]. The MINI takes between 15 and 20 minutes to perform and addresses major psychiatric disorders. MINI items were highly reliable (interrater reliability between kappa of 0.8 and 0.99; test-retest reliability between 0.6 and 0.9 for all scales save "current mania), and diagnosis via MINI was comparable to that made with the Composite Diagnostic Interview and the SCID [58, 59] Testing on nonpsychiatric samples did not create false positives [57]. The IR pool will not assess the PTSD or Antisocial Personality Disorder modules.

6.4.2 SCID-5-PD (Structured Clinical Interview for DSM-5 for Personality Disorders)

The SCID-5-PD will be administered by a blinded IR via telemedicine [60]. Prior to the SCID-5-PD clinical interview, participants will complete a brief self-report questionnaire called the SCID-5 Self-report Personality Questionnaire (SCID-5-SPQ) as a self-report screening tool. IRs will receive training on administering these measures from a research reliable trainer. Interviews may be recorded in as many instances as necessary to establish reliability of a random selection of interviews for accuracy.

6.4.3 PCL-5 (PTSD Checklist)

The PCL-5 is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the symptoms of PTSD per DSM-5 [61]. Participants indicate how much distress they have experienced due to symptoms such as "Repeated, disturbing memories, thoughts, or images of a stressful experience from the past," "Trouble remembering important parts of a stressful experience from the past," and "Feeling irritable or having angry outbursts" on a five-point Likert-type scale (1=Not at all to 5=Extremely).

6.5 Exploratory Measures

6.5.1 IDAS (Inventory of Depression and Anxiety)

The IDAS [62] is a 64-item self-report measure of depression and anxiety symptoms. Factor analytic research indicates that the IDAS has strong convergent and discriminate validity, as well as criterion validity[63]. Additionally, factor analytic research indicates that the general depression and anxiety subscales of the IDAS differentiate anxiety from depression[62, 63]. A subset of the IDAS comprising the General Depression scale (20 items) and Anxiety Symptoms (Panic, Social Anxiety, and Traumatic Intrusions domains) will be administered in this study.

6.5.2 DVPRS (Defense and Veterans Pain Rating Scale)

The DVPRS is a numeric rating scale (NRS) to provide patients, clinicians, and researchers with a standard pain screening and assessment tool. The DVPRS consists of a NRS (0 to 10) enhanced with functional word descriptor anchors at each pain level and "traffic light" color coded bars to delineate levels of pain; mild (1 to 4, green), moderate (5 to 6, yellow), and severe (7 to 10, red) pain [64, 65]. This "traffic light" designation is applied in quality improvement and patient safety initiatives and is incorporated into clinical decision support systems (CDSS) to alert clinicians to outcomes requiring actions. Facial expressions are also part of the DVPRS pain intensity item coinciding with pain levels to provide additional visual cues. To screen for co-existing problems, four supplemental questions are included to quantify levels of pain interference with usual activity and sleep and the effects of pain on mood and stress.

6.5.3 Pain Medication Use

The use of cannabis may lower pain intensity and/or reduce the use of opioid pain medications in this population, which would be important to reduce the opioid abuse epidemic in the US. Pain medication use and dose will be tracked on a daily basis by participants. The quantity of opioid pain medication used will be collected from participants' entry and will be calculated in morphine equivalent.

6.5.4 ISI (Insomnia Severity Index)

The ISI is a brief self-report measure of insomnia [66, 67]. It consists of 7 questions, with responses made on a 5-point Likert scale. Three items address difficulty at sleep onset, maintaining sleep and early waking, and 4 questions address perceived quality of sleep and effects of sleep difficulties on daily function. Questions are summed into a total score that ranges from 0 to 28 and can be interpreted as ranging from no signs of insomnia to severe insomnia. The ISI exhibits adequate to very good validity when compared with other self-report measures of sleep quality, statements concerning sleep quality and polysomnography, and is sensitive to changes in sleep quality[67-69].

6.5.5 ASEX (Arizona Sexual Experiences Scale)

The ASEX [70] is a self- or clinician-administered 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm during the past week. Each item is scored on a Likert scale from 1 to 6, and possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The ASEX has demonstrated good internal consistency, test–retest reliability, and convergent and discriminant validity[70]. In this study, the ASEX will be self-administered.

6.5.6 Patient General Impression of Change (PGIC)

The Patient General Impression of Change (PGIC) is a patient reported outcome measure that evaluates participants' overall health status in a 7-point single-item scale ranging from 1 = "*Very much worse*," to 4 = "*No change*," to 7 = "*Very much improved*."

6.5.7 EQ-5D-5L (EuroQol Five Dimensions-Five Levels Questionnaire)

The EQ-5D-5L is a two-part self-report questionnaire assessing health status. It consists of five dimensions; mobility, self-care, usual activities, pain-discomfort and anxiety-depression, and one visual analog scale (VAS). Responses are made on each dimension by checking one of five statement that best reflects their health on the day of measure completion, from the healthiest or fewest problems (e.g., "I have no trouble walking about") to the most trouble (e.g., "I am unable to walk about") [71, 72]. In the second part of the EQ-5D-5L, current degree of health ("your health today") is indicated by marking a 20 cm line marked from one to 100, with 100 considered "the best health you can imagine" and one "the worst health you can imagine." The EQ-5D-5L does not sum responses but treats each response on a dimension as a scale score, and the VAS is the location of the mark in centimeters. The scale can permit comparison across groups on health profiles, and an index can be derived from matching the five-dimension scores and the VAS response with nation-specific datasets and calculator software or statistical software syntax designed for the measure. The EQ-5D-5L began as part of the EuroQoL measure, published in 1990 [73]. The instrument has been validated in populations from eight countries. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation. EQ-5D-5L index scores and VAS scores assessed in people with stroke varied with degree of recovery assessed via long-term observation [74]. The EQ-5D-5L takes about 3 minutes to complete.

7.0 Study Procedures

All assessments must be performed by qualified study staff delegated these duties on the Site Responsibilities Log. The Clinical Research Associate (CRA) should be notified of any delays or deviations to study procedures and Medical Monitor consulted if necessary. If scheduled visits are delayed for more than 7 days from the scheduled date, the site should assess the need for additional telephone contact with the participant to ensure safety.

Note: all in-person visit should be in a quiet and safe setting with minimal staff interaction (preferably with one person).

7.1 Screening Period

7.1.1 Pre-Screening and Informed Consent

Prospective participants will be pre-screened by telephone according to an IRB-approved script to ascertain if they meet basic eligibility criteria. All individuals who are pre-screened should be assigned a Screening Number and recorded on the Screening Log. Data from potential participants who do not pass telephone pre-screening will not be entered in the eCRF, but the reason for ineligibility will be documented on the Screening Log.

If deemed potentially eligible, the prospective participant will receive a copy of the ICF for review and be invited to begin screening. Relevant medical records are required for the site physician to obtain a well-characterized medical history and assess eligibility.

Site staff will explain and obtain written (or electronic) informed consent using the IRB-approved ICF. ICF discussion will include the potential risks of using cannabis (see Section 8.7.3). Written consent must be obtained prior to performing any tests or evaluations for the study. The signature may be obtained using an electronic 21 CFR Part 11 compliant system due to COVID-19. Discussion about the ICF may take place over a telemedicine visit or at the Screening in-person visit. If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

Screening will take place at the Screening Visit and will be completed in-person (although some procedures may be completed via telemedicine). All procedures must be completed but there can be some flexibility in timing and order of individual assessments. The sponsor suggests the following order of assessments to minimize in-person screening in light of COVID-19:

- Initial Eligibility, including measures, in-person discussions, and review of medical records.
- Medical Assessments, including labs, electrocardiogram (ECG), and physical exam.
- IR screening measures, on-site visit occurring after CI in-person (+2 days) allowing for IR assessment review period.

7.1.2 Initial Eligibility Assessment

Qualified site staff will complete the following assessments in-person or via telemedicine:

- Collect demographics information
- Support the participant during completion of the PCL-5 to confirm PTSD diagnosis and severity. Support is needed to ensure proper identification of the index trauma on the PCL-5. Symptom severity is assessed in relation to the index trauma.
- Administer the Lifetime C-SSRS.
- Show participant how to use the ePRO platform and direct participant to complete the self-reported SCID-5-SPQ ePRO.
- Review results of all measures and discussions against eligibility criteria to assess initial eligibility. If deemed initially eligible, continue collection of information on source records and schedule a meeting with a site physician.

7.1.3 In-person Screening

In advance of meeting with the participant, the CI or designee will review medical and psychiatric history through provided medical records from the participant. If no records were provided or those provided are not sufficient, additional records should be requested.

A site physician will meet with the participant in-person to perform the following:

- Review medical history and concomitant medications with the participant via interview, confirming information collected in medical records.
- Review past and current medications and adherence to prescriptions.
- Assess ability to become pregnant and discuss requirement for commitment to adequate birth control for the duration of the study.
- Conduct the following medical assessments:
  - Measure blood pressure, pulse, pulse oximetry, and body temperature.
  - Measure height and weight, which will be used to calculate body mass index (BMI).
  - Perform a physical examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities.

- Perform a brief neurological exam (cranial nerves 2 to 12, sensory, motor, reflexes, and cerebellar function).
- Perform an ECG and 1-minute rhythm strip.
- Perform urine pregnancy test for participants who are of childbearing potential.
- Perform a urine drug test and a urine EtG test.
- Review central lab records for clinical laboratory assessments, per Section 9.3. The clinical laboratory values will not be captured in the eCRF but will be used to establish eligibility and will be kept with the participant's source record. Clinically significant abnormal values will be captured as medical history.

Some findings may trigger additional testing:

Additional medical considerations should be taken for potential participants with conditions such as controlled hypertension or diabetes mellitus (Type 2). The participant's history, physical exam, or ECG will be carefully examined to determine if there is evidence of significant vascular or other cardiac disease. If, upon examination, there are questions raised about possible medical problems, the site physician may request additional tests, assessments, or measures as indicated. The site physician may also contact outside providers with participant permission as needed.

7.1.4 Independent Rater Screening

If the participant is deemed initially eligible based on data already collected, an IR will perform the IR screening. IR visits may occur 1-2 days following study visit to allow for IR assessment review time. The first IR screening assessment will be done at the study site so the clinical staff can provide technical and emotional support before the assessment, if needed. The site staff will instruct the participant on how to access the telemedicine platform going forward. For all future IR assessments, participants may be approved to do assessments at home, as determined by the Senior Independent Raters, considering information obtained by site staff and IRs. In addition, participants will be required to have adequate internet access, be in a quiet private space where they are comfortable talking about personal matters when conducting the IR assessment, and meet other requirements as defined by the sponsor.

- The IR will complete the MINI interview.
- Using the results of the SCID-5-SPQ provided to guide the interview, the IR will perform the SCID-5-PD. Only appropriate modules will be completed.
- The IR will then complete the C-SSRS.

The results from the MINI, SCID-5-PD, and C-SSRS will be provided to the investigator at the site to review along with all other screening information to determine eligibility.

After the baseline visit, the IRs will be blinded to visit number, treatment assignment, number of treatments received, and any study data for the participant. IR visits will be assigned based on availability.

7.1.5 Enrollment

The site team will review medical records, medical history, concomitant medications, medical assessment results, ePRO measure results, IR assessments, notes, and discussions against eligibility criteria to determine the potential participant's eligibility.

At study onset at each site, if a potential participant is eligible, the study team will contact the Medical Monitor and send a summary of the medical history for approval to enroll the potential participant. After the Medical Monitor establishes confidence in the enrollment procedures at

each site, the Medical Monitor will inform the site that for future participants they need only contact the Medical Monitor if they have questions about further participants' eligibility. Once enrolled, AE collection requirements begin (refer to Section 9.0).

If a participant is approved by the sponsor, the staff will reach the participant by telephone to:

- Notify the participant of enrollment and confirm that the participant wishes to be enrolled in the study.
- Review contraception requirements with the participant. Remind the participant that the study site should be contacted immediately if the participant becomes pregnant at any time during the study. Remind participant of lifestyle modifications, including refraining from using non-approved medications.
- Schedule the Baseline Visit after IR Screening is completed.

7.2 Treatment Period

7.2.1 Baseline Visit

The Baseline Visit will occur in person. Some procedures may be performed via telemedicine.

7.2.1.1 *Training*

The following training will occur at Baseline, before any procedure is performed (see Section 5.0 for details):

- Accurate Symptom Reporting Training: Participants will be trained to accurately complete the various self-report measures by improving their interoceptive awareness of symptoms.
- PRRTP: Participants will be trained for reduction of the placebo response using the PRRTP[45].
- Mobile Device App: Participants will be trained to use the Mobile Device App to record **in real-time** the amount (number of puffs) and method of cannabis self-administration (smoke/vape). This training will be performed on a site device – the participant will be provided with his/her own device at the end of the visit, after the Introductory Session.
- Participants will be trained on the use of a log to track changes in health and concomitant medications used (including dose and date of use).

These training sessions will be performed by a qualified clinical staff member and can be done via telemedicine or by using an interactive platform to assess participants' understanding of the trainings.

7.2.1.2 *Confirmation of Eligibility, Randomization, and Baseline Measures*

Procedures to confirm eligibility will be performed by the clinical staff in the following order:

- Review any changes in participant medical history.
- Perform urine pregnancy test for participants who are of childbearing potential.
- Perform urine drug test.
- Perform urine EtG test.
- Administer Since Last Visit C-SSRS.
- Collect concomitant medications and therapy information.
- Collect vital signs and pulse oximetry.

The site team will confirm eligibility by reassessing eligibility criteria in light of the above test results and ensure that the participant continues to agree to all study procedures. If so, enrollment will be confirmed. If any of these eligibility requirements is not met, the participant will be considered a Pre-randomization Early Termination (see Section 4.4.4).

Eligible participants will be randomized to treatment (High THC or Placebo) in a double-blind manner via IWRS (see Section 8.4). This can be accomplished while the participant is completing the ePROs (see below).

Eligible participants will complete Baseline self-reported measures via ePRO (with minimal input from the clinical staff to avoid bias. PCL-5 requires staff support for proper index trauma identification, as symptom severity is assessed in relation to the index trauma):

- PCL-5
- IDAS
- ISI
- DVPRS
- ASEX
- EQ-5D-5L
- PGIC

7.2.1.3 *Introductory Inhalation Session 1*

After randomization to treatment, participants will be prepared for inhalation of study cannabis by the clinical staff before the Introductory Session. The clinical staff will:

- Remind the participant of the possible effects of inhaling cannabis, including:
  - Potential short term side effects
  - Potential long term side effects
- Ensure that the participant has arranged a ride home or arrange a ride.
- Provide coping techniques to the participant to cope from the possible undesirable effects of inhaling cannabis.
- Provide inhalation devices and training on how to use the inhalation devices (mock).
- Explain to the participant that they will be monitored for 3 hours post inhaling to ensure safety. Remind the participant to notify the investigator of any unpleasant effect when inhaling.
- Ask the participant if he/she has any question/concern before inhalation of study cannabis and answer the questions/concerns.
- Have the participant go to the bathroom and eat a snack if hungry before the Introductory Session to decrease potential interruption during the 3 hours.

The clinical staff will continue the visit with Introductory Session 1. For this, the participant will be seated comfortably (provide water and a snack); the participant should attempt to remain seated whenever possible for the duration of the session):

- Measure participant's pre-inhalation blood pressure and pulse oximetry (leave the equipment in place for ease of post-inhalation measurements)
- Provide the participant with the study cannabis according to the randomization scheme.
- Have the participant prepare the inhalation device (participant's choice) under supervision/coaching.

- Have the participant smoke or vape study cannabis under supervision/coaching.
- Have the participant relax in the chair. Observe the participant quietly for any sign of adverse effect. Monitor pulse oximetry, pulse, and blood pressure measurement at 10, 30, 60 minutes, and every 30 minutes afterwards up to 3 hours. Assure all blood pressure measurements are performed in the same position (Monitoring may be continued longer if the participant experiences strong cardiovascular effects)
- If the participant experiences undesirable effects, assist the participant in coping with these effects.
- If the participant experiences any AEs, record them. A participant experiencing a drug related SAE should be discontinued from the study and the sponsor should be notified within 24 hours.

When the participant has completed the session, the participant may leave in their pre-arranged ride.

- Remind the participant to call the 24-hour number provided in case of an emergency.
- Remind the participant of lifestyle modifications, including refraining from using non-approved medications.
- Schedule Introductory Inhalation Session 2.
- Provide the participant with the Mobile Device App and remind the participant on how to use it.
- Provide the participant with an "wallet card" stating that they may test positive for drugs of abuse as a result of being a research participant, listing the number of a 24-hour hotline, and containing contact information for the CI, identifying the sponsor and the relevant IRB, and the study NCT number. The CI will remind participants that they may still be cited or face penalties for erratic driving and the card will not mitigate this.
- Ensure that the participant is not driving and that a ride is arranged.

7.2.2 Introductory Inhalation Session 2

The clinical staff will:

- Collect AEs that may have occurred since last visit using a non-leading question.
- Collect concomitant medications and therapy information since last visit.
- Conduct a qualitative urine drug test (excluding THC).
- Remind the participant the possible effects of inhaling cannabis, including impairment in driving.
- Ensure that the participant has arranged a ride home or arrange a ride for them.
- Remind the participant of the coping techniques used to cope for the possible undesirable effects of inhaling cannabis.
- Remind the participant on how to use the inhalation devices (mock). Concentrate on the device not used at Baseline.
- Remind the participant that they will be monitored for 3 hours post inhaling to ensure safety. Remind the participant to notify the investigator of any unpleasant effect when inhaling.
- Ask the participant if they have any question/concern before inhaling study cannabis and answer the questions/concerns.
- Have the participant go to the bathroom and eat a snack if hungry before the inhalation session to decrease potential interruptions during the 3 hours.

The clinical staff will continue with the training portion of Introductory Session 2. For this, the participant will be seated in a comfortable chair (provide water and a snack); the participant should attempt to remain seated whenever possible for the duration of the session):

- Measure participant's pre-inhalation blood pressure and pulse oximetry (leave the equipment in place for ease of post-inhalation measurements)
- Provide the participant with the study cannabis according to the randomization scheme.
- Have the participant prepare the inhalation device (not used in Introductory Session 1) under supervision/coaching.
- Have the participant inhale study cannabis under supervision/coaching.
- Have the participant relax in the chair. Observe the participant quietly for any sign of adverse effect. Monitor pulse oximetry, pulse, and blood pressure measurement at 10, 30, 60 minutes, and every 30 minutes afterwards up to 3 hours. (Monitoring may be continued longer if the participant experiences strong cardiovascular effects)
- If the participant experiences undesirable effects, assist the participant in coping with these effects.
- If the participant experiences an AE, record it. A participant experiencing a drug related SAE should be discontinued from further study drug administration and the sponsor should be notified within 24 hours.

When the participant has completed the session:

- Remind the participant to call the 24-hour number provided in case of an emergency.
- Provide the participant with an inhalation device.
- Dispense study cannabis supply to the participant according to the participant's randomization group. Remind the participant of safety precautions when using study cannabis:
    - To refrain from driving until 3 hours after inhalation
    - To lock the study cannabis and inhalation devices in the lock box after use.
    - Not to share study cannabis with ANYONE.
- Provide the participant with a lock box.
- Remind the participant to record **in real-time** in the Mobile Device App:
    - The amount (number of puffs) and method of cannabis self-administration (smoke/vape)
- Remind the participant to log on a daily basis:
    - Any changes in health
    - Any concomitant medications used (including dose and date of use)
- Remind the participant of lifestyle modifications, including refraining from using non-approved medications.
- Schedule Study Cannabis Resupply Visit.
- Remind the participant to stop study cannabis at bedtime the evening before the Study Cannabis Resupply Visit. (An automated call scheduled for the day prior will remind the participant).
- Remind the participant to bring all unused study cannabis at the Study Cannabis Resupply Visit.
- Ensure that the participant is not driving and that a ride is arranged.

7.2.3 Study Cannabis Resupply Visit

This visit will need to occur in person; some procedures can be done via telemedicine.

- Verify that the participant stopped study cannabis at bedtime the evening before the visit and that the participant is not intoxicated.
- Collect unused study cannabis and weight it.
- Perform urine pregnancy test for participants who are of childbearing potential.
- Have the participant complete the ePRO PCL-5.
- Check changes in health reported since last visit. Discuss any AE with the participant and record in the subject source worksheet.
- Collect concomitant medications and therapy information since last visit.
- Conduct a qualitative urine drug test (excluding THC).
- Dispense study cannabis (enough supply to last until EoT visit + 2 days) to the participant according to the participant's randomization group. Remind the participant of safety precautions when using study cannabis:
    - To refrain from driving until 3 hours after inhalation.
    - To lock the study cannabis and inhalation devices in the lock box after use.
    - Not to share study cannabis with ANYONE.
- Remind the participant to record **in real-time** in the Mobile Device App:
    - The amount (number of puffs) and method of cannabis self-administration (smoke/vape).
- Remind the participant to stop study cannabis at bedtime the evening before EoT Visit.
- Remind the participant to bring all unused study cannabis at the EoT Visit.

7.2.4 EoT Visit

This visit will need to occur in-person but some procedures can be done via telemedicine. Procedures may be completed on more than one day. The following order of procedures is recommended:

- Conduct a qualitative urine drug test (excluding THC)
- Perform urine pregnancy test for participants who are of childbearing potential.
- Verify that the participant stopped study cannabis use at bedtime the evening before the visit and that the participant is not intoxicated.
- Collect unused study cannabis and weigh it.
- Have the participant complete the following ePROs:
    - PCL-5
    - MWC
    - DVPRS
    - IDAS
    - ISI
    - ASEX
    - EQ-5D-5L
    - PGIC
- Administer the C-SSRS
- Check changes in health reported since last visit. Discuss any AE with the participant and record in the subject source worksheet.
- Collect concomitant medications and therapy information since last visit.
- Refer participant for clinical laboratory assessments if clinically indicated to follow-up on safety.
- Schedule EoS Visit.
- Remind the participant to record on a daily basis:
    - Any changes in health
    - Any concomitant medications used, including dose and date of use

7.3 Follow-up Period and End-of-Study Visit

7.3.1 Follow-up Period

After the EoT Visit, participants will enter a Follow-up Period during which they will not use study cannabis.

7.3.2 EoS/ET Visit

The EoS/ET Visit will occur after the EoT. The EoS/ET Visit will occur in person or via telemedicine. The following order of procedures is recommended:

- Have the participant complete the following ePROs:
  - PCL-5
  - MWC
  - DVPRS
  - IDAS
  - ISI
  - ASEX
  - EQ-5D-5L
  - PGIC
- Administer the C-SSRS.
- Check changes in health reported since last visit. Discuss any AE with the participant. If any AE is still ongoing, follow the AE until resolution via phone contact after this visit and add to the source worksheet.
- Collect concomitant medications and therapy information since last visit.

Any of the following additional procedures may be conducted if deemed necessary by the CI (e.g., for following up on an AE, suspicion of pregnancy, suspicion of substance abuse, etc.) (these assessments will necessitate an in-person visit):

- Blood pressure, pulse, pulse oximetry, and body temperature.
- Physical examination.
- ECG and 1-minute rhythm strip.
- Urine pregnancy test for participants who are of childbearing potential.
- Urine drug test and a urine EtG test.
- Clinical laboratory assessments.

After all measures and assessments are completed, the participant is considered terminated from the study. The participant can resume normal everyday life.

7.3.3 Early Termination Procedures

For participants who discontinue the study early, the clinical staff should attempt to schedule the participant for an ET Visit in person or via telemedicine. The ET Visit should include the same procedures as in the EoS Visit plus any procedure deemed necessary by the CI (see Section 7.3.2).

8.0 Investigational Medicinal Product

8.1 Description of Active and Inactive Compounds

Study cannabis will consist of the dried flower of the *Cannabis sativa* or *indica* plant (supply dependent on an approved Drug Master File for cannabis) containing specific amounts of THC and CBD, as described in Table 3. The study cannabis will be of high quality (i.e., equivalent to cannabis product that can be found in dispensaries). 'Placebo cannabis' will be prepared from the study cannabis as described by the producer in the Drug Master File.

Study cannabis will be manufactured and packaged according to applicable Good Manufacturing Practices for botanical products. All required Chemistry Manufacturing and Control data will be cross referenced to an active Drug Master File with an appropriate Letter of Authorization.

8.1.1 Route of Administration, Dose, and Regimen

Ad libitum daily self-administration of inhaled cannabis with high THC content will be used in this study to provide a naturalistic setting that is generalizable to what many Veterans are currently using to manage PTSD symptoms in states with legalized medical cannabis.

At Baseline, participants will be randomized to either High THC cannabis or Placebo cannabis *ad libitum* daily at up to 3 g/day during the Treatment Period. First, after baseline assessments, participants will undergo two introductory inhalation sessions under clinical staff supervision during which they will inhale a very small amount of study cannabis (1- 4 puffs within 30 min of intro session). The purpose of the Introductory Sessions is to train participants on how to inhale cannabis using the devices and to teach participants coping techniques to cope with potential side effects of cannabis inhalation. Participants will be observed for 3 hours after the inhalation session to monitor AEs and vital signs. After the second Introductory Session, participants will be provided with a supply of study cannabis to self- administer at home and to be stored in their study provided lock box. Participants will return to the clinic after ~2 weeks for a resupply of study cannabis. Participants will be reminded to stop study cannabis at bedtime on the day before the EoT Visit.

Table 1: Study Cannabis

Type of Cannabis	THC Content[a]	CBD Content[a]	Dose[b]
High THC	15-25%	<1%	Up to 3 g/day
Placebo	<1%	<1%	Up to 3 g/day

a. THC and CBD contents of the study cannabis will be determined by analytical testing prior to the study.
b. Participants will be provided with 3 g of study cannabis per day but will choose their daily dose.

Participants will have the choice of either smoke or vape the study cannabis. Participants may change between smoking and vaping at any time. Although there are some pharmacokinetic differences between smoking and vaping cannabis, the rationale for allowing both modalities is to allow participants to find their preferred inhalation modality (i.e., 'what works best for them) and self-titrate.

8.1.2 Dose Adjustments

Participants will only smoke a small amount of study cannabis (<0.25 g) during the Introductory Sessions. These amounts are intended to be used on-site and will not be dispensed.

Participants will be able to inhale up to 3 g of study cannabis daily. Participants will be allowed to adjust the amount (up to 3 g/day) and regimen (time and frequency) of inhaled cannabis at any time to suit their needs for PTSD symptom relief.

8.2 Rationale for Dose Selection

Pilot study MJP1 evaluated the efficacy of three types of active cannabis harboring different concentrations of THC and CBD: (i) High THC/Low CBD, (ii) THC+CBD, and (iii) High CBD/Low THC. The results of the study showed that, of the three types of active cannabis evaluated, High THC/Low CBD cannabis was the most effective at relieving PTSD symptoms, reducing anxiety and depression, and improving sleep. Therefore, High THC cannabis was selected as active PTSD treatment for the present study. The other two active cannabis (THC+CBD and High CBD/Low THC) were abandoned to simplify the study design to one active group and one placebo group (at a 2:1 ratio). This was implemented to (i) reduce the placebo response (participants will have a 67% chance to get High THC cannabis), (ii) increase the sample size in each group (to increase the power of the study), and (iii) increase the effect size (detect greater differences between active and placebo groups).

8.3 Handling

8.3.1 Accountability

Forms will be provided to track study cannabis accountability and administration throughout the study. Blinded study cannabis accountability and administration logs will be reviewed during routine monitoring visits or through central monitoring. Cannabis will be handled in accordance with all local, state, and federal regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the appropriate controlled substance license holder or delegate.

Each primary container label will contain a unique container number for the study cannabis assigned to a single participant. The container numbers will be used to track study cannabis administration in the Source Record and the study cannabis administration log. The web-based randomization system will enable tracking of blinded primary containers for accountability purposes.

8.3.2 Storage

Cannabis is a controlled substance and will be stored and handled in compliance with all relevant federal and state regulations. In accordance with these requirements, the appropriate license holder or designee will be responsible for handling, storing, dispensing, and administering study cannabis. It will be stored securely in accordance with federal, state, and local regulations.

8.3.3 Dispensing

Study cannabis will only be removed from storage for the Baseline/ Introductory Sessions, participant initial supply, and participant resupply.

- At Introductory Sessions 1 and 2, a small amount of study cannabis (up to 0.25 g) will be used. These amounts are intended to be used on-site and will not be dispensed.
- At Introductory Session 2, an initial supply will be provided to the participant for inhalation.
- At the Study Cannabis Resupply Visit, participants will return any unused study cannabis and receive a new supply for inhalation through the End of Treatment Visit.

All doses administered during the Introductory Sessions and dispensed to participants will be recorded on the appropriate accountability and administration logs. A person at the site authorized to manage and administer controlled substances will dispense the appropriate container during the Treatment Period. If a dose is not administered, the unused study cannabis will be kept for accountability. Records pertaining to the use of scheduled, regulated compounds will be maintained in accordance with relevant federal and state regulations.

8.3.4 Treatment Compliance

Compliance to protocol required doses will be overseen by the person licensed to manage and administer controlled substances at each site. All doses administered during the two Introductory Sessions and dispensed to the participants will be recorded for study cannabis accountability. At the Study Cannabis Resupply and EoT Visits, participants will return all unused study cannabis in their original packaging, which will be weighed to determine the average daily amount of study cannabis consumed by each participant. The unused cannabis weight will be recorded for study cannabis accountability. These data will be compared with participants' record of daily inhaled study cannabis entered in the Mobile Device App.

8.4 Randomization and Participant Numbering

Every potential participant who is prescreened by telephone according to the IRB-approved script will be assigned a seven-character alphanumeric Screening Number and recorded on the Screening Log. This number will begin with 'S4' to identify that it is a Screening Number. The next two digits represent the site number (e.g., '11'), followed by a three-digit screening identifier starting with '401'. The screening identifier will be assigned to each prescreened participant at a site sequentially. For example, the first Screening Number at Site 11 will be S411401 and first Screening Number at Site 12 will be S412401.

Each participant who passes Screening and is enrolled in the trial will be assigned a seven-digit Participant Number. The first two digits will be '22'. The next two digits represent the site number (e.g., '11'), followed by a three-digit participant identifier starting with '001'. The Participant Number will be assigned to each enrolled participant at a site sequentially. For example, the first Participant Number at Site 12 will be 2212001. This unique Participant Number will be entered in the database for use in data analysis.

Participants will be randomized in 2:1 allocation in a blinded fashion to the High THC group and the placebo group, stratified by clinical site. Randomization will be managed via an Interactive Web Randomization System (IWRS) based on a centralized randomization schedule developed by an independent third-party vendor to maintain blinding.

8.5 Blinding and Bias Minimization

Eligibility will be determined by review of screening by the CI, site team and as needed by the sponsor Medical Monitor prior to randomization. Participants, site staff, and the sponsor will remain blinded to participant group assignment until after the database is locked.

8.5.1 Blinded Primary and Key Secondary Outcome Measurements:

To minimize bias in measuring efficacy, the sponsor will use an observer-blind, centralized, reliable IR pool to administer the primary outcome (CAPS-5) and key secondary outcome (SDS) measures via live video interviews. The IR Pool will be blinded to full study design, visit number, treatment assignment, and any pre- or post-Baseline data. IRs will be assigned to participants

based on availability. The IR Pool will have no knowledge of AEs. Participants will be instructed to withhold their opinion on treatment group assignment from IRs. The participants, sponsor, and site staff will not see the CAPS-5 and SDS results until the end of the study. Timing of CAPS-5 and SDS assessments are pre-specified in the study protocol within visit windows. Changes in study management and analysis, if any, will be made by sponsor personnel who are blinded to group assignment and CAPS-5 and SDS data.

To minimize bias, protect the study's double-blind and to ensure data quality, the sponsor will use a second Electronic Data Capture (EDC) database that is dedicated to the collection of critical primary and key secondary outcome measures, including the Total Severity Score on the CAPS-5 and item scores on the SDS, administered by the centralized blinded IR Pool through telemedicine. This second database, termed the Independent Rater Database (IRDB), will be separate from the blinded, clinical EDC database in order to ensure that site and sponsor staff engaged in study conduct are masked from study outcomes. The IRDB will only be accessible by: (1) qualified, observer-blind individuals who are in the established IR Pool, (2) the Senior IR responsible for oversight and data quality of the IR Pool, and (3) the IR Coordinator(s) responsible for data entry.

In case of an emergency requiring knowledge of a participant's treatment assignment, the blind may be broken for an individual participant through the IWRS by the CI or designee. Upon database lock, the study will be unblinded and participants will be notified of treatment assignment.

8.5.2 Unblinded Data Monitoring Committee (DMC):

The DMC will act in an advisory capacity to the sponsor to monitor participant safety, data quality, and review outcomes to ensure the trial is conducted safely, ethically, and meets endpoint objectives. The DMC will be the only group reviewing unblinded data. The DMC will conduct any unblinded interim analyses specified in the study protocol.

8.6 Prior and Concomitant Medications

8.6.1 Prohibited Medications

There is pre-clinical evidence of drug interactions between THC, CBD and certain medications. However clinical studies reported that these medications were well tolerated, and many of the observed adverse effects were those typically associated with psychotropic effects of cannabis and cannabinoids (please refer to the IB for a comprehensive review of the proposed interactions and outcomes from pre-clinical and clinical studies). Therefore, all herbal supplements, prescription medications, and non-prescription medications will be reviewed and approved for use in the study by the CI and Medical Monitor.

The following medications will be prohibited during the entire study:

- Cannabis (other than study cannabis) in all its forms
- THC and CBD in all its forms

8.6.2 Allowed Concomitant Medications

The use of all concomitant medications will be tracked by the participant. Participants will be allowed to use pain relievers PRN, including NSAIDs, acetaminophen, naproxen sodium.

8.7 Risk Assessment

8.7.1 Non-drug Related Risks

Blood draws and a full physical examination are required to establish eligibility for the study. Temporary discomfort, inflammation or infection could arise as a result of blood sampling at the punctured vein. Measures of blood pressure, body temperature, and heart rate will be taken to assess drug effects and participant safety. Participants may experience mild discomfort from having blood pressure assessed. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol.

Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The clinical investigator (CI) has experience working with people with PTSD, and he/she will seek to reduce anxiety and distress during these interviews.

There are potential risks associated with the use of telemedicine. In rare cases, information transmitted may not be sufficient (e.g., poor resolution or choppy video connection) to allow for appropriate medical decision making by site staff. Delays in medical evaluation and treatment could occur due to deficiencies or failures of the equipment or internet service. Though the telemedicine system that will be used is secure, in very rare instances, security protocols could fail, causing a breach of privacy of personal medical information.

Participants will be provided with a Mobile Device App to enter data. A screen passcode will be used, and encryption will be used to minimize the likelihood that anyone without the passcode could access stored files on the cloud. Breach of confidentiality can occur even with these measures; another individual may be able to view records of a participant's cannabis use should they obtain the participant's Mobile Device App. If this happens, it is possible that such records could be uploaded to a computer or displayed on a social media website. Participants will be trained at the Introductory Session and reminded throughout the duration of the study on confidentiality best practices for protecting their Mobile Device App information.

A breach may also happen through mishandling of participant records. This risk is mitigated by the use of standard research procedures for the secure storage and management of research health information (RHI) described in more detail in Section 12.1.2.

8.7.2 PTSD-Associated Risks

During Screening and during assessment of study measures, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about these events. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress and exacerbate suicidal ideation during and immediately after assessments.

8.7.3 Risks of Receiving Cannabis

There is an extensive literature on the risks of habitual cannabis use in humans, and a sizeable but considerably smaller literature on the acute effects of cannabis in the context of PTSD, including AEs. 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.

Participants who will receive placebo cannabis are exposed to combustion products without receiving either THC or CBD. They will also be less likely to experience the adverse effects associated with THC described above, such as anxiety or impaired performance on tests of cognitive function. Participants will be permitted to remain on medications and therapies to allow for continued symptom management throughout the study.

8.7.3.1 *Alteration of Mood and Psychological State*

Cannabis can alter mood, affect, and perception, enhancing positive and negative mood states (such as euphoria and anxiety), and intensifying sensory experiences, such as music seeming more intense [75].

Cannabis may provoke psychotic symptoms or psychosis in vulnerable individuals, though cannabis use alone is not a "cause" of psychosis [76, 77]. The literature is inconclusive but indicates an association between regular cannabis use and psychosis or exacerbated psychotic symptoms.

Cannabis use may be associated with increased occurrence of panic attacks. A prospective (longitudinal) study in adolescents reported that cannabis use or dependence was associated with a greater likelihood of experiencing panic attacks[78], and people with cannabis dependence were more likely to report experiencing panic attacks [79].

Van Ours and colleagues (2013) examined the predictive value of cannabis use onset and monthly use upon self-reported suicidal ideation through examining data from a longitudinal study of a cohort born in 1972, concluding that onset of cannabis use preceded likelihood of reporting suicidal ideation in males, but not females [80]. The authors did not find that suicidal ideation preceded cannabis use, though it is notable that questions concerning suicidal ideation were not posed until respondents were 15 years old. Previous research has addressed suicidal ideation in cannabis users, largely in samples of adolescents.

8.7.3.2 *Alteration of Cognitive and Motor Functions*

Regular, heavy use of cannabis is associated with impairments in cognitive function, especially in the area of short-term memory and executive functioning, with impairment retained up to a week after abstaining from use, but no longer detectable after 28 days of abstinence [81-83].

Cannabis can impair attention, memory, and visual tracking, and slow psychomotor performance. In a review of the literature, subjective effects were more strongly associated with cannabis than other effects [84]. One study found impaired visual tracking in male occasional cannabis users approximately 1 hour after administration [85]. The combination of alcohol and cannabis impaired simulated driving, particularly night-time driving, with regular cannabis users making a greater number of errors than occasional users [86], and the same team of researchers reported that alcohol and cannabis affected performance on a field sobriety test more than either substance alone [87].

Visual tracking and divided attention was impaired in heavy daily cannabis users compared with ecstasy-user controls [88], but tracking and attention improved with three weeks of abstinence from cannabis. Since cannabis interferes with attention, alters mood and may generate shifts in sensory attention and perception, it is not surprising that regular use may be taxing on cognitive task performance. The degree of potential impairment experienced after a month of daily use

cannot be estimated from these findings. It is likely that if impaired cognitive function is present, it will not remain after prolonged abstinence [89].

Though a review of studies found that cannabis impairs most skills used in driving motor vehicles, driving and simulation studies fail to find strong effects of cannabis upon driving [90]. Researchers conducting controlled studies of people driving under the influence of cannabis reported that effects, while present, were relatively small and comparable to other medicines or alcohol [91]. This may be the result of people under the influence of cannabis overestimating their level of impairment, and thus driving more conservatively [90, 92]. Nonetheless, epidemiological studies of road accidents have found a relation between use of cannabis, including blood THC levels, and road accidents [93-96], with higher levels of THC associated with greater impairment in driving. A meta-analysis evaluating the likelihood of a road traffic accident in illicit psychoactive drug users reported that cannabis was associated with minor not significant increased odds of traffic accidents, lower than the rate associated with benzodiazepines [94]. A review of the literature suggested that there was inter-individual variability in the impairment experienced by drivers after cannabis use, with less impairment in experienced users [90]. The authors recommend that people not drive or use heavy machinery for up to 3 hours after cannabis use, and that people using cannabis seek a designated driver. These recommendations are supported by other analyses [97, 98].

8.7.3.3 *Substance Abuse*

Like many substances that produce increased positive mood and relaxation, cannabis can lead to abuse or dependence in some people, with approximately 1.6% of the general population experiencing dependence upon cannabis [99]. The rate at which people who try cannabis become dependent is estimated as either slightly lower than or similar to that for alcohol, and higher than rates of dependence for hallucinogenic (psychedelic) compounds [100].

8.7.3.4 *Cardiovascular Effects*

Acutely, cannabis increases heart rate, increases supine blood pressure, and, after higher doses, produces orthostatic hypotension; it increases cardiac output, decreases peripheral vascular resistance, and dose-dependently decreases maximum exercise performance. Changes in cardiovascular function may occur with prolonged use. These include: hypotension when lying down, an increase in blood volume, slowed heart rate and diminished circulatory response to exercise [101]. These findings are in line with findings in animals of enhanced parasympathetic activity. A review of the literature showed that the cardiovascular effects of cannabis posed little risk to young, healthy adults, while increased cardiac work, increased hypotension, and increased catecholamines might pose greater risk for older adults [101].

A case report detailed an instance of a type of heart attack [ST-segment elevation myocardial infarction] in a 37-year old man who reported smoking cannabis prior to arrival at the emergency department [102], possibly as a result of having an inadequate myocardial oxygen supply from smoking cannabis. Cardiac events associated with cannabis have been reported since 1979 [103], and a previous ST-segment elevation myocardial infarction was reported in 2010 [104]. Researchers presented a case series addressing cannabis use and stroke [105]. The existence and nature of the relationship between cannabis use and stroke remains controversial [106].

8.7.3.5 *Respiratory Function*

Regular and heavy cannabis use is associated with increased symptoms of chronic bronchitis, coughing, production of sputum, and wheezing [107, 108]. Regular cannabis use may impair function of alveolar macrophages, a type of immune cell found in the lung [108, 109]. Reduced

alveolar macrophages could place individuals at increased risk of lung infection. One of three studies of lung function in people reporting regular, and often heavy, use of inhaled cannabis failed to find a reduction in lung function, and another found reduced lung function but concluded that this was related to confounding factors [107, 110, 111]. A review of the literature addressing cannabis use and lung injury concluded that findings were often inconsistent [112]. Cannabis use does not appear to be associated with lung cancer [112-114]. Rather, the positive association between extended periods of cannabis use and lung cancer may be related to other confounding factors, such as co-occurring tobacco use. Of note, the duration of use in the studies reviewed by Hashibe et al. is considerably longer than the 5-week treatment period planned in this study [114].

8.7.3.6 *Reproductive and Developmental Risks*

Regular use of cannabis throughout pregnancy may have effects on birth weight, as well as specific tasks involving visual analysis or processing. However, to date, there are no reports of teratological effects from cannabis use [75, 115-118]. THC can pass into breast milk [118]. Participants of childbearing potential enrolled in this study will be required to use an effective method of birth control, and the study will exclude participants who are pregnant or lactating.

8.7.3.7 *Other Risks*

There are several reports of cannabis-associated hyperemesis syndrome in regular cannabis users, marked by excessive, cyclical vomiting and abdominal pain that is relieved by taking a hot bath or shower [119-121].

The immunological effects of cannabis and cannabinoids are complex and largely appear to arise from effects on CB2 receptors rather than central CB1 receptors. Some of the benefits of cannabis, such as for multiple sclerosis, may relate in part to anti-inflammatory and immunosuppressive effects [122, 123]. However, cannabis and cannabinoids failed to affect immune function in HIV-positive individuals [124, 125]. Regular cannabis users have greater numbers of a cannabinoid receptor implicated in regulating immune function, the CB2 receptor, which is generally considered to have immunosuppressive and anti-inflammatory effects [126], and in vitro studies suggest that THC and cannabis may reduce immunosupportive Th1 cytokines and increase immunosuppressive Th2 cytokines [122, 127]. It is possible that cannabis may increase the risk of opportunistic infections. However, in studies of HIV-positive individuals using either cannabis or oral THC (as dronabinol) at similar use levels to this study failed to find any changes in T-cell (CD4 or CD8) profiles, findings that do not support this form of immunosuppression [124, 128].

Published reports of events associated with cannabis use include seizures upon cessation of use, pancreatitis, and gingival (gum) enlargement. Two cases were described in which seizures increased after cessation of cannabis use and upon entry into an epilepsy unit [129]. Two case reports describe acute pancreatitis in cannabis users, with one report acknowledging the difficulty of linking previous cannabis use with subsequent pancreatitis [130, 131]. Only six cases of pancreatitis associated with cannabis have been reported in the literature [131]. A recent case report describes gingival enlargement in two extensive cannabis users [132].

Beyond these risks, there are only a few reports of adverse effects occurring outside the organs and systems listed above. There are no known effects on the liver (and only a few case reports of effects on the kidneys [75]).

Using the study drug poses a social risk of actual or perceived stigmatization. Cannabis use is a socially stigmatized activity [133, 134]. Participants may be ostracized or experience social

stigma from relatives, friends or community members who view or hear about their cannabis use, or they may be aware of and internalize these prejudices relating to cannabis use.

Participants may test positive after urinary assay for drugs of abuse, as those used for workplace drug testing, or as a result of police response to a traffic violation. Even participants who are not using their cannabis on a daily basis may test positive for cannabis for up to three weeks after study participation. Testing positive for cannabis could pose risk of arrest or job termination.

8.7.4 Risk Mitigation

The CI will minimize risks by carefully screening participants for the presence of any contraindicating factors and carefully preparing participants for the expected effects of cannabis. Prior to receiving supplies of cannabis, study participants will be prepared for the effects of the substance during two supervised Introductory Sessions described in Section 7.2.1.3. They will be informed of what to expect and will have an opportunity to inhale the cannabis that they have been randomly assigned to receive in a standardized manner. A site staff member will observe the participant for 3 hours after each session to monitor AEs and vital signs. A site physician will be on-call during Introductory Sessions by telephone or in-person.

8.7.4.1 *Cardiovascular Risk Mitigation*

Potential participants who have a current diagnosis or evidence of significant or uncontrolled disease will be excluded from study participation. These conditions will be identified via medical history, vital sign measurements, physical examination, and ECG and 1 minute rhythm strip.

If the potential participant has a condition such as controlled hypertension or diabetes mellitus (Type 2), additional testing may be conducted and the participant's history, physical exam, or ECG and 1 minute rhythm strip will be carefully examined to determine if the participant has evidence of significant vascular or other cardiac disease. The investigator will record and review medications used to control hypertension prior to enrollment.

8.7.4.2 *Psychological, Cognitive, and Motor Risks Mitigation*

Untoward psychological reactions to cannabis will be dealt with by preparing participants for the subjective effects of the substance, and through first inhalation cannabis in the presence of site staff during two Introductory Sessions. During this time, site staff will be able to help address any anxiety or paranoid feelings that may arise. A site physician will be on-call during Introductory Sessions by phone or in-person.

Participants will be informed of the effects that cannabis might have on driving and they will be advised to avoid driving immediately after use by seeking a designated driver and by waiting a minimum of three hours after use prior to driving a motor vehicle. Participants will arrange rides home after each Introductory Session, and if they are unable to do so, the CI will assist them in locating a ride from the study site. All study participants will be issued a study participant identification card (e.g. "wallet card") stating that they may test positive for drugs of abuse as a result of being a research participant, listing the number of a 24-hour hotline, and containing contact information for the CI, identifying the sponsor and the relevant Institutional Review Board (IRB), and the study National Clinical Trial Registry (NCT) number. Site staff will remind participants that they may still be cited or face penalties for erratic driving and the card will not mitigate this.

8.7.4.3 *Suicide Risk Mitigation*

During Screening through Baseline, and during assessments of study measures, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material.

The CI will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants will be enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician and Medical Monitor.

Qualified site staff will administer the C-SSRS according to Section 7.0, and as needed depending on clinical presentation of the participants, to monitor for development and intensity of suicidal ideation and/or behavior. The administrator will implement the following plan to assess elevated or imminent suicide risk.

If the Since Last Visit C-SSRS reveals current serious Suicidal Ideation, indicating risk at the time of the assessment, or positive Suicidal Behavior, the participant will be referred for further management.

Treatment would be continued when deemed appropriate by the investigator and Medical Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.

8.7.4.4 *Stigma, Abuse Liability, Withdrawal, and Diversion Risk Mitigation*

The CI will discuss with participants the perceived stigma ascribed to cannabis use and to consider the degree to which friends, family, or other people within the community might respond if they observe or learn about the participant's cannabis use.

In the MJP1 study, there were no AEs indicative of drug dependence, intentional drug misuse, or substance abuse, and a low rate (<2%) of secondary terms, AE terms defined as not directly indicative of abuse potential that reflect acute intoxication in PTSD patients. 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 ($\Delta = 12.6$, SD = 11.41, $p = 0.0004$). Total cannabis withdrawal symptoms were in the mild to moderate range by the end of treatment in Stage 1, despite having 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 treatment to one-week follow-up.

In this RCT of whole plant cannabis, the overall rates of AEs were low and generally reversible upon discontinuation. In addition, there was a low rate of AEs supporting abuse liability and acute intoxication in PTSD patients. 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, however as with any drug this treatment is not without risks.

To monitor the abuse potential of study cannabis in this study, AEs involving the terms of "behavioral addiction," "drug abuser," "substance abuser," "dependence," "intentional product misuse," "overdose" (accidental, intentional, or prescribed), or "drug diversion" that are related to study cannabis will be collected and coded as AESIs in the eCRF.

Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs.

Qualitative urine drug test data (excluding THC following intro session) will be collected at each visit to assess compliance with ongoing eligibility criteria and for presence of AESIs.

This study involves take-home doses of study cannabis. To mitigate the risk of diversion of unused cannabis, participants will be required to return all unused cannabis. The unused cannabis will be weighed, and the amount used will be compared to the participant's daily entry of inhaled study cannabis in the Mobile Device App. Participants will be questioned is discrepancies are found.

Withdrawal is a common symptom that may occur after cessation of cannabis use. Withdrawal will be measured at each visit (except Day 2 and 14) to determine whether participants experience withdrawal. Withdrawal will be recorded as an AESI.

8.7.4.5 *Reproductive and Developmental Risk Mitigation*

Potential reproductive risks will be mitigated by restricting enrollment to persons who are not pregnant or lactating, and by requiring that participants of childbearing potential use an effective form of birth control.

8.7.4.6 *Common Adverse Reaction Mitigation*

In the MJP1 study, the most common AEs reported were cough (12.3%), followed by throat irritation (11.7%), and anxiety (10.4%). Although AESIs were not tracked in MJP1, AESIs will be tracked in MJP2 study and will be defined as a subset of AEs involving abuse liability (cannabis use disorder) and cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, and non-postural syncope. Withdrawal will be recorded as an AESI. Tracking these AEs will allow CI to provide treatment when necessary and follow the participant until the AE is resolved.

8.7.4.7 *Confidentiality Breach Risk Mitigation*

If a Mobile Device is lost or stolen, the study team will notify local police in the case of theft and make every attempt to recover the unit. All devices will be password-protected and encrypted to minimize the likelihood that misplaced units will result in breach of confidentiality. Given the safeguards in place, breach of confidentiality from the device is unlikely as long as participants follow instructions for use and storage.

All participant PHI will be stored in locked files at the site or on secure computer servers and managed in accordance with patient confidentiality procedures pertaining to electronic systems.

9.0 Safety

9.1 Adverse Events

9.1.1 AE Definition and Monitoring

In accordance with the FDA Safety Reporting Requirements for INDs, an AE is defined as any untoward medical occurrence in a participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected AE is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

Events related to planned treatments or physician visits for Baseline conditions collected in the medical history will not be collected, unless there is an exacerbation of the condition, in which case they will be actively followed until resolution.

The site physician will be responsible for reviewing and confirming all AEs, AESI, and SAEs collected during the study. The CI will collect AEs during study visits from Screening through EoS. Participants will be asked directly regarding any changes in their health. Participants will be instructed to report any emergency or hospitalization while on study as soon as possible. The clinical staff will assess AEs as soon as possible and contact the participant by telephone to follow up, if deemed necessary. Completed measures may create suspicion that an AE occurred; in this case, the site staff should follow-up with the participant.

All AEs will be monitored by the CI until resolution or if an AE is unresolved when a participant terminates the study, a clinical assessment will be made by the site physician, investigator, and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the Adverse Events eCRF will be determined by the site physician as:

- **Mild**: No limitation in normal daily activity
- **Moderate**: Some limitation in normal daily activity
- **Severe**: Unable to perform normal daily activity

The relationship of each AE to the study cannabis will be collected in the opinion of the investigator as related/not related.

9.1.2 Adverse Events of Special Interest

The sponsor will pay special attention to a subset of AEs involving abuse liability (cannabis use disorder) and cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, including Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, and non-postural syncope. Withdrawal will be recorded as an AESI.

The subset of AEs involving suicide risk under the following terms are also of special interest:

- suicides
- suicide attempts
- self-injurious behavior associated with suicidal ideation
- suicidal ideation assessed on the C-SSRS
- suicidal ideation judged to be serious or severe in the opinion of the investigator.

These AEs will be marked in the eCRF with the denotation "AESIs" whether serious or non-serious.

In order to assess signals of abuse potential for the study cannabis in the intended patient population:

- AESIs involving the terms of Behavioral addiction or Drug diversion in cases that are related to THC will be collected and coded as AESIs in the eCRF.
- Cases of noncompliance, protocol violations, participants lost to follow-up, and any other reasons why participants dropped out of the study will be assessed for presence of AESIs.
- Qualitative urine drug test data (excluding THC following first intro session) will be collected prior to each study visit. Any positive findings that cannot be attributed to pre-approved concomitant medications or diet will be reviewed by the Medical Monitor to assess compliance with ongoing eligibility criteria and for presence of AESIs.

If an AESI is a SAE or if it involves suicide risk, it should be reported to the sponsor with a narrative via the eCRF within 24 hours of the site's awareness of the event.

9.1.3 Serious Adverse Events

In accordance with FDA, an SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the event causes substantial disruption of a person's ability to conduct normal life functions).
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent permanent impairment or damage.
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe AE is not necessarily serious in nature and that an SAE is not necessarily, by definition, severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as a study-related SAE, unless, in the view of the site physician, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-

existing condition. This is because the onset of the event (the reason for the procedure) occurred before the participant was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis, or elective abortion does not result in an SAE report, unless, in the view of the site physician, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

All SAEs will be collected from Screening through EoS visit. All SAEs which occur during the course of the trial, whether considered to be associated with study cannabis or not, must be reported to the sponsor within 24 hours of the site staff's awareness of occurrence. Reporting procedures will be provided to the site. All SAEs will be assessed for relationship, expectedness, and any required actions to address safety at the time of reporting of the event. SAEs will be evaluated by the site physician and Medical Monitor to determine if it is appropriate for the participant to continue treatment or enter follow-up.

SAEs will be reported to the Medical Monitor.

9.1.4 Other Significant Events

Significant life events that may occur during the course of the study, including death of a loved one, loss of employment, or other hardship, may have an impact on treatment outcome. Such events will be entered as Comments in the eCRF and if appropriate, described in the Case Study Report for data outliers, if any.

9.2 Pregnancy

9.2.1 Definition of Childbearing Potential

A participant is considered of childbearing potential if they were assigned female at birth and are post-menarche. A participant is considered not of childbearing potential if they are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), permanently sterile by medical device such as Essure, postmenopausal, or assigned male at birth.

9.2.2 Pregnancy Contraception Guidelines

Study participants who were assigned male at birth with partners of childbearing potential will not be required to practice birth control. Adequate birth control methods are required for participants of childbearing potential and include:

- Intrauterine device
- Intrauterine hormone-releasing system
- Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal
- Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide)
- Double barrier method (at least two of the following: condom, diaphragm, and spermicide)
- Vasectomized sole partner
- Abstinence from penile-vaginal intercourse. The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the participant in case they decide to engage in penile-vaginal intercourse during the course of the study.

For questions about acceptable birth control methods, contact the Medical Monitor.

9.2.3 Pregnancy Testing and Follow-up Requirements

A urine-dip pregnancy test for participants of childbearing potential will be performed at Screening, Baseline, Study Cannabis Resupply and EoT Visits, as specified in Section 7.0.

Participants who become pregnant at any time from Screening to 14 days post EoS Visit should contact the site immediately. Pregnancies should be reported to the sponsor via telephone or email within 24 hours of site staff awareness.

In the event of a pregnancy, the participant will discontinue using study cannabis. At a minimum, prior to withdrawal from the study, efforts should be made to complete a CAPS-5 assessment and Early Termination procedures. The participant will be emergency unblinded if the participant wishes as described in Section 8.5, after the CAPS-5 assessment.

The investigator will collect follow-up information on the participant and neonate and forward to the sponsor until the outcome of the pregnancy, which will be reported on an optional Pregnancy eCRF. Any termination of pregnancy, elective or spontaneous, will be reported. Abnormal pregnancy outcomes, such as spontaneous abortion, fetal death, stillbirth, congenital abnormalities, or ectopic pregnancy will be reported as SAEs.

9.3 Clinical Laboratory Assessments

The site physician will confirm laboratory assessments gathered at Screening for assessing eligibility. The site physician will use a list of normal ranges to conclude whether participants are eligible for the protocol and will indicate justification for admitting participants with abnormal values after consultation with the Medical Monitor.

The following laboratory assessments will be performed as a part of Screening:

- Serum electrolytes and metabolic profile
  - Alanine aminotransferase (ALT)
  - Albumin:globulin ratio
  - Albumin, serum
  - Alkaline phosphatase, serum
  - Aspartate aminotransferase (AST)
  - Bilirubin, total
  - Blood urea nitrogen (BUN): creatinine ratio
  - Calcium, serum
  - Carbon dioxide
  - Chloride, serum
  - Creatinine, serum
  - Globulin, total
  - Glucose, serum
  - Potassium, serum
  - Protein, total, serum
  - Sodium, serum
- Complete Blood Count
  - Hematocrit
  - Hemoglobin
  - Mean corpuscular volume
  - Mean corpuscular hemoglobin
  - Mean corpuscular hemoglobin concentration
  - Red cell distribution width

  - Percentage and absolute differential counts
  - Red blood cell count
  - White blood cell count
- Urinalysis
  - Color
  - Appearance
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Occult blood
  - Leukocyte esterase
  - Nitrite
  - Bilirubin
  - Urobilinogen
- %Carbohydrate deficient transferrin to detect heavy alcohol use

Laboratory assessments, with the exception of urine pregnancy and drug tests, will be performed at the nearest clinical laboratory to the site. Clinical laboratories for each site will be specified in a separate document. Certificates and normal ranges will be stored in the site's Investigator Site File (ISF).

9.4 Vital Signs

Participants vital signs, including blood pressure (systolic/diastolic), heart rate, and body temperature, will be measured as specified in Section 7.0. In addition, vital signs and pulse oximetry will be measured at Screening and before, during, and after the Introductory Sessions.

9.5 ECG

A 12-lead ECG and 1-minute rhythm strip will be performed at Screening.

9.6 Concomitant Medications and Therapies

The use of concomitant medications and therapies will be recorded throughout the study and collected from participants at the Study Cannabis Resupply, EoT, and EoS Visits.

9.7 Mobile Device App

Participants will be provided with a Mobile Device App to record the daily dose (number of puffs) and method of cannabis self-administration (smoke/vape). The Mobile Device App will also allow participants to alert the clinical site in case of an emergency and receive study reminders. The Mobile Device App will be password protected. Data will be stored in the cloud, and accessible by the clinical staff in real time.

10.0 Statistical Considerations

Key personnel, MAPS PBC and the biostatistician will agree on a detailed Statistical Analysis Plan (SAP) prior to starting the study. Analyses will be conducted using the SAS Version 9.4 software or higher (Cary, NC: SAS Institute). Statistical significance will be set at $p<0.05$ for all tests unless specified otherwise.

10.1 Power and Sample Size Determination

In the absence of published effect sizes of cannabis for PTSD, possible effect sizes are estimated to be 0.3(small to medium effect) for a between-group comparison to ensure an adequately powered study size, based on a recent meta-analysis conducted with the National Center for PTSD[6]. Thus, in the proposed study, N = 360 with 240 participants randomized to the MDMA group and 120 to the Placebo group will have 80% power to detect these or greater differences between groups on the primary outcome measure (change in mean CAPS-5 total severity score from Baseline to Week 5) with an alpha level of 0.0499. Similar calculations apply for secondary outcomes.

10.2 Analysis Sets

Safety Set: Participants who receive at least one dose (inhaled) of study cannabis. Participants will be analyzed according to the treatment actually received. All safety analyses will use the Safety Population.

Intent-to-treat (ITT) Set: The ITT Population will include all randomized participants. Participants will be analyzed according to their randomized treatment assignment. The primary efficacy analyses will be carried out with the ITT Population.

Per Protocol (PP) Set: The PP Population will include all randomized participants who receive study drug for 4 weeks, provide one follow-up CAPS-5 assessment, and do not experience significant protocol deviations.

10.3 Statistical Analyses

Summary statistics will be performed using chi-square or *t* tests to compare demographics and baseline characteristics between high THC vs. placebo groups on the ITT population.

10.3.1 Efficacy Analyses

10.3.1.1 *Primary Outcome*

The primary endpoint will be the ***change in mean CAPS-5 total severity scores***. Analysis of the primary endpoint will be conducted using a an ANCOVA model with change from initial score as the outcome with treatment group and initial CAPS-5 score as independent variables. Adjustment for additional potential covariates, will be explored. The effect size between high THC and placebo groups will be estimated using Cohen's techniques. Additional details will be provided in the SAP.

10.3.1.2 *Secondary and Exploratory Outcomes*

The key secondary endpoint is the change in mean SDS score.

The exploratory endpoints are:

- The mean changes in:
  - PCL-5 score
  - DVPRS score
  - IDAS Depression score
  - IDAS Anxiety score
  - ISI score

  - EQ-5D-5L score
  - ASEX score
  - PGIC score (categorized as: 1-3 worsened; 4 no change; 5-7 improved)
- Average use of opioid medications during the Treatment Period (in morphine equivalents)
- Dropout rate for lack of efficacy during the Treatment Period

Analysis of the secondary and exploratory outcomes will be conducted in the same manner as the primary efficacy analysis. Adjustment for potential covariates will be explored.

10.3.2 Safety Analyses

AEs: AEs will be mapped to preferred term and system organ class using the most up to date Medical Dictionary for Regulatory Activities. AEs that begin after the first administration of study drug or existing AEs that worsen after the first dose of study medication are considered TEAEs. The number and percentage of participants reporting TEAEs will be summarized for each treatment group by system organ class and preferred term, by severity, and by relationship to study drug. The number and percentage of participants with SAEs, and the number and percentage of participants with AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term. Clinically significant changes in physical examination, laboratory parameters, vital signs, ECG, psychiatric health, withdrawal, and suicidality will be reported as AEs.

Concomitant medications: Concomitant medications will be coded using WHO Drug Dictionary and will be classified by Anatomical Therapeutic Chemical classification level 4 and preferred term for the Safety Analysis Set. Frequencies and percentages of participants using each concomitant medication will be presented by treatment group. All medication use will be listed regardless of the timing of the start of the medication.

Vital signs: Vital signs will be summarized using descriptive statistics of actual values and changes from baseline over time. The incidence of clinically notable vital signs will be summarized by treatment group. Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time in each treatment group. These data will also be categorized as low, normal, or high based on the reference ranges of the central laboratory. Shift tables from baseline to each post baseline time point will be presented.

Suicidality: For each subject, C-SSRS data will be categorized into (1) suicidal ideation (nonspecific, method but no intent or plan, method and intent but no plan and method, intent and plan) and (2) suicidal behavior (suicide attempt, interrupted attempt, aborted attempt and preparatory acts and non-suicidal self-injurious behavior) at each visit. An increase in suicidality (i.e., passive suicidal ideation defined as an onset of suicidal ideation or behavior, or active suicidal behavior defined as an escalation from suicidal ideation to suicidal behavior) in a subject will be reported as an AE. The percentage of participants with passive suicidal ideation and active suicidal behavior will be presented by visit and by treatment group.

Withdrawal: WDS scores will be calculated using the MWC and analyzed by visit and by treatment group. Clinically significant withdrawal symptoms will be reported as an AE.

10.4 Interim Analysis

When primary outcome data are clean and available from 60% (n=216) of the participants, an interim analysis for futility will be performed for the Data Monitoring Committee (DMC). The DMC will communicate whether the study has crossed the futility boundary and should be stopped or continue as planned. The sponsor will be blinded to the actual results of the interim analysis, which will be performed by an independent statistician. Conditional Power less than 20% will be the boundary used for stopping for futility. The efficacy analysis will proceed first followed by the futility analysis, as the futility analysis will not be necessary in the presence of efficacy. If neither the efficacy nor the futility boundary is crossed the DMC will determine if the sample size should be increased to restore power to 80%. For example, if an effect size of 0.2 is determined at the interim analysis the DMC may recommend adding additional Further details will be provided in the SAP and the DMC Charter.

10.5 Data Monitoring Committee

The sponsor will appoint a DMC with appropriate expertise in the conduct of clinical trials to independently monitor participant safety information during this study, conduct the sample size re-estimation analysis, and make associated recommendations for all reviews. The DMC is an independent expert advisory group commissioned and charged with the responsibility of periodically evaluating cumulative safety and other clinical trial data for evidence of safety concern and recommending Study continuation, discontinuation, or modification. The composition of the DMC will include clinician experts and at least one biostatistician.

The objective of the DMC Charter is to outline the specific purposes and functions of the DMC. In addition, it describes the procedures for data abstraction and data delivery conventions to and from the DMC members for review purposes. Access to the DMC charter will be restricted to the DMC and only limited specified sponsor staff who were involved in the trial design.

The DMC will periodically receive blinded safety reports and may receive aggregate data on the key secondary outcome measure, the SDS, to assess suitability of continuation of the study based on the risk/benefit profile and make recommendations as necessary. The objective of the DMC safety review is to monitor the safety of the participants enrolled and to be enrolled in the study. The DMC may also make recommendations on updating the adaptive design elements to the study protocol, interim analysis, and/or data analysis of the MJP2 study.

A single representative within MAPS will be designated to receive written communication of recommendations following DMC review of the trial. The sponsor representative within MAPS and DMC members will sign a written confidentiality agreement in the case that additional participants must be enrolled to ensure this is not disclosed to the outside community.

11.0 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the ICF must be reviewed and approved by a properly constituted institutional review board (IRB) or ethics committee and FDA before study start. Signed and dated documentation of approvals must be provided to the sponsor. Prior to study start, the investigator

is required to sign a signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol, and to give access to all relevant data and records to the sponsor.

11.1 Financial Disclosure

Investigators will adequately and accurately disclose financial interests to the sponsor prior to study start, during the study if financial interests change, and 1 year after study completion. The sponsor will submit necessary disclosures to the appropriate regulatory bodies.

12.0 Supporting Documentation and Operation Considerations

12.1 Regulatory and Study Oversight Considerations

12.1.1 Informed Consent

The investigator and clinical team are responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the participant into the trial. Potential participants may be sent the ICF to review after the initial phone screen. Preferably, informed consent will be obtained by the CI that will treat the participant. Information about the study must be given orally and in an understandable written ICF. The informed consent discussion must be conducted by a person who is qualified according to federal, state, or local regulations. The participant should have the opportunity to inquire about details of the study and to consider participation.

The CI may meet with the potential participant via telemedicine for ICF review and signing prior to in person screening if necessary, for scheduling of screening activities. If this is completed by telemedicine visit, the pair will ensure that the ICF is thoroughly explained and reviewed just as it would be at an in-person visit. If the potential participant is still interested after review, he/she will sign the consent during that telemedicine visit. The participant will then bring his/her signed copy of the ICF to the next in-person visit where study staff will then countersign the ICF, copy the ICF for the participant, and file the original at the site. The signature may instead be obtained using an electronic 21 CFR Part 11 compliant system due to COVID-19.

In addition to the explanation of study visits, the information should include that access to original medical records and processing of coded personal information must be authorized. A written release is needed to give permission to site staff to request and view the participant's medical records to assess protocol eligibility, if needed. Information necessary for study participation includes past medical history, psychiatric interview, physical examination, urine drug test, and clinical laboratory tests.

Eligible participants may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol beyond phone screening). The process of obtaining informed consent should be documented in the participant's source records. The study staff will provide a copy of the signed ICF to the participant and will maintain the original in the ISF.

The written ICF and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised ICF and written information should receive approval from an IRB before use. The participant should be informed in a timely manner if new information becomes available that may affect the decision to take part or continue in the study. The communication of this information should be documented. Participants can withdraw consent at

any time without prejudice. If a participant withdraws consent but does not revoke the HIPAA authorization, the study team will have full access to his/her medical records, including termination visit information. If a participant revokes only the HIPAA authorization, the study team will have full access to all medical records prior to the date and time of revocation.

If a participant fails Screening and is rescreened at a later date, a new ICF form should be signed.

12.1.2 Confidentiality

Every effort will be made to strictly safeguard the confidentiality of participants. Despite this, privacy cannot be guaranteed. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data. Except for the Screening Log, the Informed Consent, previous medical records, emails with the participant, and a Contact Information Sheet that will be stored separately from other documents, all source data will be identified only by the participant's initials and number (SUBJID). If past medical records are needed, participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. In accordance with the guidance for a specific study site location and FDA E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), all assessment records will be kept in a locked file drawer or cabinet in a locked office, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators who are directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data. The sponsor will utilize confidentiality procedures to assure participant privacy. Audiovisual recordings are necessary for sponsor oversight of therapy processes. Any requests for use of audiovisual recordings outside of research and training requests will result in participants receiving information on the request. Participants will have control over any presentation of audiovisual recordings beyond viewing by authorized researchers, sponsor staff, or regulatory agencies. The sponsor uses encrypted, secure technology to transfer and store recordings, but there is always a risk of a security breach. The sponsor is committed to taking preventative measures to avoid such an event. In the case of a security breach, the participant will be notified, and all efforts will be made to minimize the dissemination of recorded content.

Clinical trial data other than audiovisual recordings will be hosted on an EDC system that is FDA-compliant. All data entered into this system will be de-identified. Participants will only be referred to by numbers and a secondary identifier code. Source Records and identifying information will be retained at clinical sites per GCP. The sponsor will train the study staff on EDC procedures. Each study staff member with access to the data will be given an individual password.

The sponsor has developed a feature that will allow participants to create a password and enter their self-report questionnaire data directly into Medrio using the electronic Participant Reported Outcome (ePRO) feature.

12.2 Costs to Participants

There will be no costs to the study participants for participation. The sponsor will cover all direct costs of study procedures required for participation, including any assessments or tests performed solely for the purpose of establishing eligibility for participation. Charges for treatment of a participant's condition that is unrelated to the research study or any unrelated procedures will not be covered by the sponsor. Participants who previously received treatment from a site physician

prior to the study, and who will continue to receive ongoing treatment outside of the study from that physician, are responsible for those non-study related costs. Participants may be reimbursed for reasonable expenses incurred for study participation, such as local travel to the treatment site; this will be specified in each site's informed consent.

12.3 Treatment and Compensation for Study Related Injury

Participants will be compensated $50 for each completed visit (Screening, Baseline/Introductory Session 1, Introductory Session 2, Study Cannabis Resupply, EoT, and EoS/ET) for a maximum compensation of $300.

If a participant becomes sick or injured during the study, he/she should call the site physician. Some study-related injuries or sickness can be treated by the site physicians. If the site physicians cannot treat a study-related emergency, emergency services should be contacted. There are contingency plans for the transport of participants to the nearest hospital.

Treatment of a study-related injury, sickness, or emergency would first be billed to a participant's health insurance provider, if the participant has health insurance. If the participant's private or employer health insurance plan does not cover clinical trial-related claims that occurred during the course of the study, or the participant does not have health insurance, the sponsor will cover any treatment costs directly related to the study. To cover these costs, the sponsor carries third-party insurance.

The sponsor will not cover costs of ongoing treatment unrelated to the study due to pre-existing conditions, or the cost of the participant's time spent obtaining treatment for pre-existing conditions before receiving treatment in the study.

12.4 Key roles and Study Governance

The sponsor, MAPS, holds the IND for Cannabis and is responsible for funding the clinical development program. The sponsor has delegated the primary responsibility of trial organization to MAPS PBC, including designing, initiating, managing, coordinating, continuing, and concluding the clinical trials within the clinical development program. MPBC is tasked with maintaining the quality of study conduct through ongoing monitoring of data and participating in writing study publications. MAPS PBC contracts with independent entities who represent clinical sites to accomplish these goals. Collectively, MAPS and MAPS PBC are referred to as sponsor throughout this document.

12.4.1 Study Monitoring, Auditing, and Documentation

12.4.1.1 *Study Monitoring*

Investigators and all study staff will be trained prior study start for each site. Study sites will be monitored by site visits and telephone calls by representatives of the sponsor. In addition, critical data and systemic issues will be subject to centralized monitoring via the EDC system to develop and evaluate strategies for correction across sites. Sites will be monitored as appropriate for the rate of enrollment to comply with GCP guidelines and to ensure the validity of study data. During each monitoring visit, source data verification will be performed to ensure compliance, including accurate and complete recording of data on eCRFs, source records, and study cannabis accountability records. An eCRF collation will be completed for each participant enrolled within the EDC system.

CAPS-5 results will not be sent to site staff until the end of the study and will be sent to the IR Coordinator for filing during the study. The IR Coordinator will be responsible for review and data entry of the CAPS-5 source records into CAPS-5 eCRFs which will be blinded to sponsor and site personnel during the study.

During or after the study, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, eCRFs, and other protocol documentation for on-site audit or inspection. Monitoring and auditing procedures will be supplied in a separate document.

12.4.1.2 *Source Documents*

Source documents contain all primary evidence of existence of the participant and document all study procedures. Source documents include but are not limited to medical records, measures, checklists, notes, emails, and laboratory reports. All data reported in the eCRF will be transcribed from primary source documents and must be consistent. These documents are maintained at the study site securely. Source records of CAPS-5 assessments will be stored in dedicated limited access files during the study.

12.4.2 Record Retention

Investigators must retain all study records required by the sponsor and applicable ICH-GCP, FDA regulations in a secure and safe facility. The investigator must consult a representative of the sponsor before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents will be filed according to ICH-GCP regulations in the ISF. It is the responsibility of the sponsor to inform the investigator or institution when these documents no longer need to be retained.

12.4.3 Publication and Data Sharing Policy

The sponsor recognizes the importance of communicating medical research and scientific data and their obligations to participants enrolled in a study and therefore, encourage publication of such material in reputable scientific journals and at professional and/or academic seminars or conferences. For multicenter studies, it is intended that the first publication of the study’s primary clinical data be coauthored by designated participating centers and the sponsor or designated representatives. Inclusion of CIs in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. All publications will follow ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, unless other guidelines are required by the journal. It is understood by the CIs that the information generated in this study will be used by the sponsor in connection with the development of the study cannabis and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigators are obliged to provide the sponsor with complete test results, all study data, and access to all study records. It is mandatory that all data analyses are performed using the official monitored sponsor database and that the analysis plan is agreed upon with the sponsor statistician.

Any results of medical investigations with the sponsor and/or publication/lecture/manuscripts based thereon shall be exchanged and discussed by the investigator and sponsor prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating and maintaining submissions to health authorities, and coordinating with other ongoing studies in the

same field. The full details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Trial Agreement.

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