Statistical Analysis Plan

Study Title:	Placebo-Controlled, Triple-Blind, Randomized Crossover Multi-Site Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)
Study Number:	MJP-1
Protocol Version and Date:	Amendment 5 Version 1, June 28, 2016
Phase of Development:	Phase 2
Sponsor:	Multidisciplinary Association for Psychedelic Studies (MAPS)
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Statistical Analysis Plan for MJP-1

1.0 List of Abbreviations and Definitions of Terms

Definitions of Terms

Categorical data: refers to discrete (indivisible) variables, such as gender or ethnicity; data will be presented as total numbers of each category as needed to describe the sample

Crossover set: all participants who completed Stage 2 in addition to completing Stage 1

Descriptive data: includes mean, median, standard deviation, minimum and maximum of numerical data used as needed to describe the sample

Difference scores: consist of scores computed by subtracting one value from another, as subtracting baseline from End of Stage 1 score, used to test for differences between and within groups to determine change as a function of experimental treatment over time

Efficacy: type of analysis used to assess therapeutic effects or benefits

Exploratory analyses: inferential or descriptive analysis of the data to determine trends that might lead to hypotheses for further study

Extension set: all participants who completed Stage 3 in addition to completing Stage 2

Frequency listing: tabular listing of numbers and/or percentages of events used as needed to describe the sample or data characteristics

Modified Intent-to-treat (mITT): sample including all participants who signed informed consent, were eligible for enrollment, and who were randomized and received study drug during introductory session 1 or afterwards

Outcome measures: primary and secondary study measures that are used to test the study hypotheses

Per protocol set (PP): all completer participants who finished Stage 1, with valid CAPS-5 scores at the primary endpoint assessment and did not experience major protocol deviations.

Process measures: study measures or qualitative observations collected during the study that may increase depth of understanding and that are not necessarily related to safety or efficacy

Protocol deviation: event that represents significant divergence from the intended study design as described in the protocol

Safety set: all participants who receive any study treatment.

Safety measures: study measures that assess safety, such as pulse monitoring, risks, adverse

events, and reactions that are used to assess safety of the study drug

Spontaneously reported reactions, reactions: specific expected reactions gathered from the literature on marijuana

Study design: all elements of a research project that define the study question, experimental methods, study procedures including blinding and randomization, measurement techniques, flow sheet of data, and statistical analysis

Tabular listing: list of each variable or item for each individual subject either in total or by concentration in a table format

List of Abbreviations

ACT = Actigraphy
AE = Adverse Event
ANOVA = Analysis of Variance
ANCOVA = Analysis of covariance
BT = body temperature
CAPS-5 = Clinician Administered PTSD Scale
CBD = cannabidiol
CRP= C-Reactive Protein
C-SSRS = Columbia Suicide Severity Rating Scale
CUDIT-R = Cannabis Use Disorders Identification Test-Revised
DEQ = Drug Effect Questionnaire
DBP = diastolic blood pressure
ES = Effect size
FDA= Food and Drug Administration
GLMM = Generalized Linear Mixed Model
GWB = General Well-being
HR = Heart Rate
IDAS = Inventory of Depression and Anxiety
IL-6 = Interleukin-6
IL-1β = Interleukin-1beta
IPF = Inventory of Psychosocial Functioning
IR = Independent Rater
ISI= Insomnia Severity Index
LTFU= Long Term Follow Up
MAPS = Multidisciplinary Association for Psychedelic Studies
mITT= Modified Intent to Treat
MWC = Marijuana Withdrawal Checklist
PCL-5 = PTSD Checklist
PP = Per Protocol
PTSD = Posttraumatic Stress Disorder
RCT = randomized controlled trial
SAE= Serious Adverse Event
SBP = systolic blood pressure
SE = sleep efficiency
SOL = sleep onset latency
SpO = blood oxygen levels
TEAE = Treatment Emergent Adverse Events

THC = Δ9-tetrahydrocannabinol
TLFB = Time-line Follow-back
TST = total sleep time
WASO = wake after sleep onset
WBR= Weekly Behavior Report

2.0 Introduction

This document contains a Statistical Analysis Plan for the study, "Placebo-Controlled, Triple-Blind, Randomized Crossover Multi-Site Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)."

The Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)3 non-profit, is collaborating with the University of Colorado, University of Pennsylvania, Johns Hopkins University, and Dr. Sisley on a pilot Phase 2 outpatient randomized, placebo- controlled, triple-blind, crossover, multi-site study that will gather preliminary evidence of the safety and efficacy of four concentrations of smoked marijuana to manage chronic, treatment- resistant PTSD symptoms among 76 US veterans. This study is the first randomized controlled trial (RCT) to test the therapeutic potential of smoked marijuana as a treatment for PTSD. This study is essential for understanding potential risks and therapeutic benefits of marijuana for PTSD patients. Results will provide physicians, patients, scientists and regulators with critical knowledge regarding whether marijuana benefits individuals with PTSD, whether adverse consequences occur, and the impact of marijuana type on outcomes.

After initial screening, including two weeks of biochemically verified abstinence, smoked marijuana containing different ratios of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) will be tested. In Stage 1, participants will be randomized to one of four marijuana concentrations differing by cannabinoid concentrations. Stage 1 will last for three weeks, during which time participants will self-administer up to 1.8 g of marijuana daily. Following a 2-week washout period during screening, participants will be randomized to one of the two remaining "active" marijuana concentrations for Stage 2, depending on Stage 1 concentration assignment. Stage 2 will last for three weeks, during which time participants will self-administer up to 1.8 g of marijuana daily. Drug assignment options for Stage 2 will be different than Stage 1 concentration assignment and will also exclude placebo. Stage 2 will permit a within-subjects comparison of symptom change as a function of marijuana concentration, including differences in personal marijuana type preference. To discourage diversion of unused marijuana and encourage participant use in a naturalistic *ad- libitum* fashion, the amount of unused marijuana from Stage 1 or Stage 2 will be offered from a fresh supply to participants in an optional Stage 3 extension that may last up to two months. Study duration for each participant will be eight and a half months, inclusive of the 6-month follow-up period. Marijuana will be obtained from the NIDA drug supply program and will be stored in compliance with DEA regulations.

Clinical and statistical significance will be determined by prospective analysis of study data, comparing independent effects of three active concentrations of smoked marijuana and placebo on PTSD symptom severity, measured by changes in objective observer-blind Clinician Administered PTSD Scale (CAPS-5) total score after 3-weeks of *ad-libitum* self-administration from Baseline to end of Stage 1 (Primary Aim). With 19 participants randomized to each group (N=76) who complete the specified treatment period, the study will have 82% power to detect an effect size of 0.4 on the primary outcome measure (change in CAPS-5 total score) in the Per Protocol sample. Adverse effects will be ascertained at least weekly throughout the active treatment and cessation phases of the study based on clinician assessment and participant self-reports. Biomarkers of inflammation in blood will be measured for potential predictive power and/or correlation with treatment outcomes, and quantitative blood/urine cannabinoid analysis

will be used to confirm qualitative urine drug tests positive for THC during required periods of abstinence from marijuana. Study results will provide novel and heretofore-unknown information regarding the safety and effect size of various marijuana concentrations compared to placebo among veterans suffering from chronic, treatment-resistant PTSD.

3.0 Study Objectives

The objectives of this study are to evaluate whether i) smoking whole plant marijuana attenuates PTSD symptoms, ii) to compare the efficacy of varying ratios of THC and CBD to placebo using standard clinical measures, and to iii) collect safety data.

3.1 Primary Objective

1. To compare independent effects of three active concentrations of smoked marijuana and placebo on PTSD symptom severity measured by changes in CAPS-5 total scores during 3-weeks of *ad-libitum* self-administration during Stage 1 of the study protocol.

3.2 Secondary Objectives

The following exploratory secondary objectives will be used to support the results of the primary objective:

1. Assess independent effects of three active concentrations of marijuana and placebo on self-reported symptoms of PTSD with the PCL-5, anxiety and depression with the IDAS, and psychosocial functioning with the IPF and WBR (self-report and observer) among veterans during Stage 1.

2. Assess independent effects of three active concentrations of marijuana and placebo on self-reported symptoms of PTSD with PCL-5, anxiety and depression with IDAS, and psychosocial functioning with the IPF and WBR (self-report and observer) among veterans during Stage 2.

3. Assess comparative efficacy between placebo and each active dose of marijuana based on a within-subjects analysis of PTSD symptoms as measured by the CAPS-5 in crossover participants at Baseline, End of Stage 1, Stage 2 Baseline, and End of Stage 2.

4. Assess whether Stage 2 crossover participants' preferences for marijuana concentrations in Stage 1 and Stage 2 correlate with changes in PTSD symptoms as measured by the CAPS-5 total score.

5. Assess whether participants experience clinically significant changes in PTSD symptoms based on CAPS-5 and PCL-5 total scores during the washout period between Stage 1 and Stage 2 compared with measures assessed at Baseline and during Stage 1.

6. Explore correlation of treatment outcomes measured by CAPS-5 score with objective changes in sleep via Actigraphy throughout the study and self-reported changes in sleep quality using the ISI on a weekly basis.

7. Explore correlation of Daily Diary items related to sleep with objective changes in sleep via Actigraphy and self-reported changes in sleep quality using the ISI on a weekly

basis.

8. Explore correlation of treatment effects measured by CAPS-5 total score with amount of marijuana used based on Daily Diary across Stage 1 and Stage 2.

9. Explore treatment outcomes measured by CAPS-5 total score by marijuana concentration, with concomitant substance and medication use as a covariate throughout the treatment period.

10. Explore durability of treatment outcomes measured by CAPS-5 total score, with any PTSD treatments based on the LTFU questionnaire treated as a covariate, six months after completing Stage 2.

11. Evaluate whether markers of inflammation CRP, IL-1β, and IL-6 levels in blood predict PTSD severity at baseline and treatment outcome as a function of marijuana concentration.

3.3 Safety Objectives

The safety of participants will be measured throughout the study by assessing physiological and subjective drug effects, psychological distress, adverse events (AEs), and suicidality, repeatedly as described in the following steps. Summaries of safety data by study stage will be provided to the Medical Monitors for review during the study.

1. Explore correlations of subjective effects with the DEQ and cardiovascular effects with heart rate of each active dose of marijuana and placebo during introductory sessions.

2. Explore independent effects of each active dose of marijuana and placebo on blood pressure and body temperature during introductory sessions.

3. Assess independent effects of each active dose of marijuana and placebo on marijuana withdrawal symptoms during screening and Cessation 1 and 2.

4. Assess independent effects of each active dose of marijuana and placebo on problems associated with marijuana use during the study, including follow-up, with the CUDIT-R.

5. Evaluate the subjective effects of each active dose of marijuana and placebo in both controlled laboratory and outpatient settings, including ratings of unpleasant drug effects, using the DEQ and Daily Diary entries.

6. Assess independent effects of each active dose of marijuana and placebo on suicidality with the CSSRS on a weekly basis throughout the treatment period, and more frequently if needed.

7. Assess independent effects of each active dose of marijuana and placebo on whether and for how many days participants were incarcerated throughout the study.

8. Assess independent effects of each active dose of marijuana and placebo on whether and

for how many days participants were hospitalized throughout the study.

9. Assess metabolites of alcohol use through urine testing at face-to-face visits.

10. Collect, review, and report Serious Adverse Events (SAEs) and AEs in accordance with FDA regulations and Section 8.0 of the protocol.

3.4 Process Objectives

The following objectives will include exploratory analyses intended to inform future studies:

1. Evaluate protocol compliance based on comparison of Daily Diary entries, including information on amount, time and frequency of marijuana use, and the weight of any unused marijuana across each study stage.

2. Evaluate protocol compliance using quantitative blood and/or urine cannabinoid levels. Assess the ability of site staff and participants to accurately guess concentration assignment in Stage 1 and Stage 2.

4.0 Study Design

This Phase 2 randomized, placebo-controlled, triple-blind, crossover, multi-site study will assess the efficacy and safety of four types of smoked marijuana to manage chronic, treatment-resistant PTSD symptoms among 76 veterans in an outpatient setting. The study will consist of a baseline period and three distinct study stages, which are described in detail below.

After completion of informed consent procedures, an initial 2-week screening period will be conducted to determine study eligibility based on a two-week screening period of verified marijuana abstinence prior to randomization, to obtain baseline measures of PTSD and substance use, to conduct study training, and ensure participants are willing and able to attend scheduled appointments and complete the study procedures.

Following randomization, participants will complete Stage 1, a three-week period of *ad- libitum* marijuana self-administration followed by a two-week period of marijuana abstinence (Cessation 1). This will be immediately followed by Stage 2, another three-week period of marijuana self-administration and two-week period of abstinence (Cessation 2). Stage 1 and Stage 2 will consist of identical procedures and measures, but the marijuana available to individual participants will vary.

During Stage 1, participants will be randomized to receive High THC, High CBD, THC/CBD, or Placebo marijuana to self-administer (up to 1.8 g/day) for the 3-week marijuana use period. As described in Section 4.2 of the protocol, randomization will be balanced across drug concentrations (N=19 per marijuana type; total N=76). During Stage 2, the Placebo marijuana concentration will be removed and all participants will be re-randomized to receive a different type of marijuana than they were assigned in Stage 1. Thus, Stage 2 will permit a within-subjects comparison of changes in CAPS-5 total score as a function of marijuana concentration, including differences in preferences for a specific marijuana concentration by self-report, and the removal of placebo as a possibility ensures that all study participants receive active marijuana at some point during the study.

Following completion of Stage 2, participants will be invited to participate in an optional Stage 3. During Stage 3, participants can choose to receive the amount equivalent to the unused and returned marijuana from Stage 1 or Stage 2 from a new supply. This design feature discourages diversion of unused marijuana and encourages participant use of marijuana in a naturalistic manner during Stages 1 and 2. Marijuana will be dispensed during Stage 3 based on the average daily rate of use during Stages 1 and 2 and will not last more than two months.

There will be a long-term follow-up assessment conducted six months after the end of Stage 2. Participants will complete the long-term follow-up questionnaire concerning their mental health, substance use, and changes in PTSD therapies and medications. A blinded Independent Rater (IR) will administer the CAPS-5. Participants will complete self-report measures and one week of Actigraphy (ACT) monitoring, followed by study termination.

Table 4.0-1: Overall Study Design

Treatment Concentration	Min. Participants Baseline (N)	Min. Participants End of Stage 1 (N)	Min. Participants End of Stage 2 (N)
High THC	19	19	25
High CBD	19	19	25
THC/CBD	19	19	26
Placebo	19	19	

For further details please refer to the protocol Section 6.2.1 Doses.

4.1 Time and Events Table

Table 4.1-1: Time and Events (Administrative Procedures)

				Stage 1			Cessation 1		Stage 2			Cessation 2		Stage 3	
	Screen	**Baseline**		**Introductory Sessions**	**Self-administration**	**Primary Endpoint**	**Cessation 1**	**Stage 2 Baseline**	**Introductory Sessions**	**Self-administration**	**Secondary Endpoint**	**Cessation 2**	**LTFU Baseline**	**Stage 3 (optional)**	**LTFU**
Visit #	Prescreen & Screen 1	Screen 2	Enrollment	V1 & V2	V3 & V4	V5	V6	V7	V8 & V9	V10 & V11	V12	V13	V14	V15-V23 (as needed)	LTFU
Type of Visit	Telemed Visit & Site Visit	Telemed Visit & Site Visit	Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Weekly Site Visits (as needed)	Telemed Visit and/or Site Visit
Visit Timing	Prescreen calls up to 2 months prior, in-person and Telemed procedures at least 2 weeks prior to Enrollment	2 weeks after Screen 1	2 weeks after Screen 1, once cannabinoid results are obtained (Day 0 begins at Enrollment)	Occur on 2 consecutive days (Week 1 begins following Introductory Session 2)	Between start of Week 2 & start of Week 3	Between end of Week 3 & start of Week 4	Within 2 days of Primary Endpoint	Between end of Week 5 & start of Week 6	Post cannabinoid results Occur on consecutive days (Week 6 begins after IntroductorySession 4)	Between start of Week 7 & start of Week 8	Between end of Week 8 & start of Week 9	Within 2 days of Secondary Endpoint	Between end of Week 10 & start of Week 11	Post cannabinoid results Week 11-18	6 months after V12 (may take place over more than one day)
Phone Screen	✓[A]														
ICF	✓														
Brief Medical & Psych History	✓														
Directed Physical	✓														
Collect Therapy & Medications	✓		✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
Enrollment & Randomization			✓												
Training on Self-Administration				✓					✓						
Video Data Review					Weekly					Weekly				Weekly	
Dispense Drug				Post V2	Weekly				Post V9	Weekly				Weekly	
Weigh Unused Marijuana					Weekly		✓			Weekly		✓		Weekly	
Phone Calls					Weekly[B]		Weekly[C]			Weekly[B]		Weekly[C]		Weekly[D]	
Collect AEs			✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓

A= Initial phone screen with coordinator, secondary phone screen to be performed by CI/Qualified designee or Clinician. B= Participants will have 3 days of phone contact after each second introductory session in Stage 1 and Stage 2. (more contact may occur as needed) Participants will have a mid-week phone contact during Stage 1 and Stage 2 self-administration weeks 2 and 3. C= Participants will be contacted one week after the beginning of Cessation. D= Participants will have a mid-week phone contact.

Table 4.1-2: Time and Events (Laboratory Procedures)

				Stage 1			Cessation 1		Stage 2			Cessation 2		Stage 3	
	Screen	**Baseline**		**Introductory Sessions**	**Self-administration**	**Primary Endpoint**	**Cessation 1**	**Stage 2 Baseline**	**Introductory Sessions**	**Self-administration**	**Secondary Endpoint**	**Cessation 2**	**LTFU Baseline**	**Stage 3 (optional)**	**LTFU**
Visit #	Prescreen & Screen 1	Screen 2	Enrollment	V1 & V2	V3 & V4	V5	V6	V7	V8 & V9	V10 & V11	V12	V13	V14	V15-V23 (as needed)	LTFU
Type of Visit	Telemed Visit & Site Visit	Telemed Visit & Site Visit	Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Weekly Site Visits (as needed)	Telemed Visit and/or Site Visit
Visit Timing	Prescreen calls up to 2 months prior, in-person and Telemed procedures at least 2 weeks prior to Enrollment	2 weeks after Screen 1	2 weeks after Screen 1, once cannabinoid results are obtained (Day 0 begins at Enrollment)	Occur on 2 consecutive days (Week 1 begins following Introductory Session 2)	Between start of Week 2 & start of Week 3	Between end of Week 3 & start of Week 4	Within 2 days of Primary Endpoint	Between end of Week 5 & start of Week 6	Post cannabinoid results Occur on 2 consecutive days (Week 6 begins after Introductory Session 4)	Between start of Week 7 & start of Week 8	Between end of Week 8 & start of Week 9	Within 2 days of Secondary Endpoint	Between end of Week 10 & start of Week 11	Post cannabinoid results Week 11-18	6 months after V12 (may take place over more than one day)
Blood Cannabinoid	✓[A]	✓[A]					✓[A]	✓[A]				✓[A]	✓[A]		
Biomarker		✓					✓	✓				✓	✓		
Qualitative Urinary Drug	✓	✓		✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
Quantitative Urinary Drug	✓[A]	✓[A]					✓[A]	✓[A]				✓[A]	✓[A]		
Urinary EtG	✓	✓	✓	✓	✓		✓		✓	✓		✓	✓	✓	
Urinary Pregnancy	✓	✓		✓	✓		✓	✓	✓	✓		✓	✓	✓	
Clinical Labs	✓														
ECG	✓														
BP & BT	✓			✓[C]	Weekly		✓		✓[C]	Weekly		✓	✓	Weekly	
Pulse Oximetry	✓			✓[B]					✓[B]						

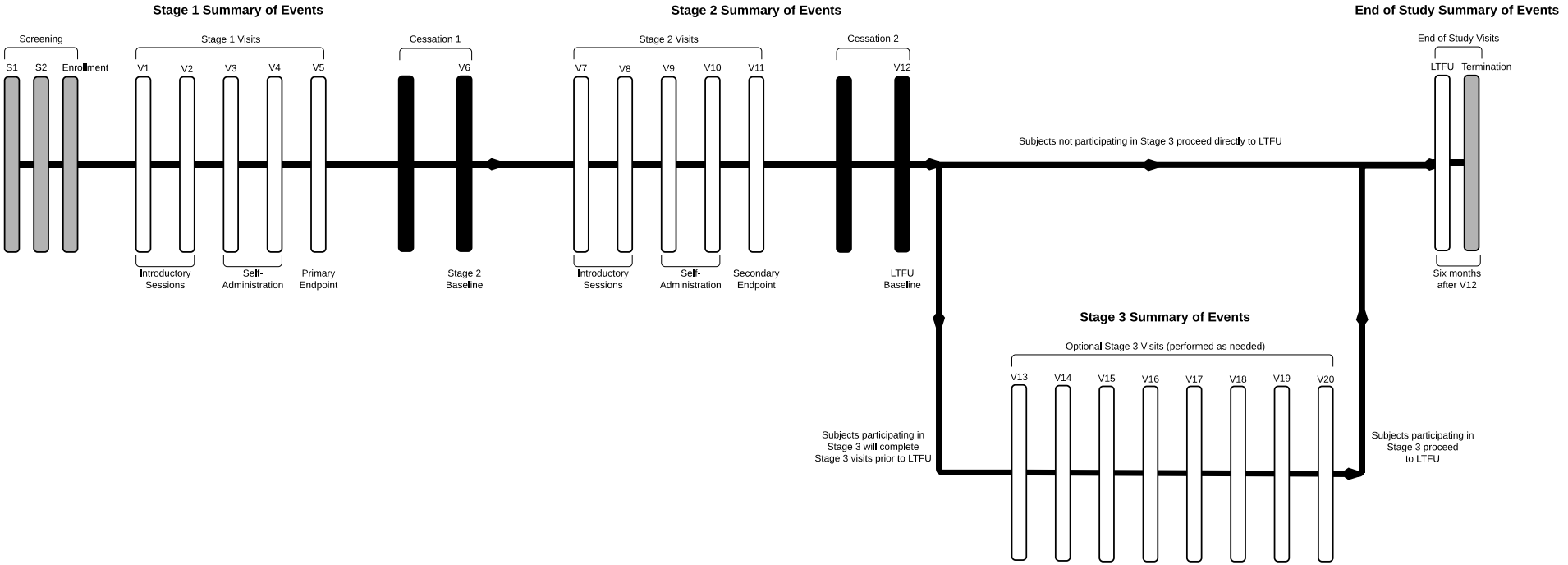
A = Quantitative THC testing to be conducted in THC positive participants only. Blood and urine will be obtained and stored regardless of THC results. B = Completed before & immediately after self-administration and every 30 minutes thereafter until end of the visit. C= BP and BT will be obtained prior to self-administration, 30 minutes after starting self-administration and again at the end of each session, approximately four hours after starting self-administration.

Table 4.1-3: Time and Events (Study Measures)

				Stage 1			Cessation 1		Stage 2			Cessation 2		Stage 3	
	Screen	**Baseline**		**Introductory Sessions**	**Self-administration**	**Primary Endpoint**	**Cessation 1**	**Stage 2 Baseline**	**Introductory Sessions**	**Self-administration**	**Secondary Endpoint**	**Cessation 2**	**LTFU Baseline**	**Stage 3 (optional)**	**LTFU**
Visit #	Prescreen & Screen 1	Screen 2	Enrollment	V1 & V2	V3 & V4	V5	V6	V7	V8 & V9	V10 & V11	V12	V13	V14	V15-V23 (as needed)	LTFU
Type of Visit	Telemed Visit & Site Visit	Telemed Visit & Site Visit	Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Site Visit	Weekly Site Visits	Telemed Visit	Site Visit	Telemed Visit & Site Visit	Weekly Site Visits (as needed)	Telemed Visit and/or Site Visit
SCID	✓														
CAPS-5		✓				✓		✓[F]			✓		✓[F]		✓
BDI-II	✓														
IDAS			✓		✓		✓	✓		✓		✓	✓		✓
ISI			✓		✓		✓	✓		✓		✓	✓		✓
IPF[G]			✓				✓	✓				✓	✓		✓
PCL-5[E]	✓		✓		✓		✓	✓		✓		✓	✓		✓
ACT		✓[C]		✓	✓		✓	✓	✓	✓		✓	✓		✓[D]
MWC[H]	✓		✓				✓	✓				✓	✓		✓
CUDIT-R	✓												✓		✓
DEQ				✓[A]	✓[B]				✓[A]	✓[B]				✓[B]	
Daily Diary			✓	✓[B]	✓[B]	✓	✓	✓	✓[B]	✓[B]	✓	✓	✓	✓[B]	
CSSRS & GWB	✓		✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
WBR		✓			✓		✓	✓		✓		✓	✓	✓	✓
STOP-Bang	✓														
Belief of Condition							✓					✓			
LTFU Questionnaire															✓
TLFB	✓														✓

A = Completed before & immediately after self-administration and every 30 minutes thereafter until end of session. B = Completed immediately after each self-administration C = Actigraphy use must begin one week prior to the first Introductory Session. D = Final week only. E= Will measure past week. LEC plus Criterion A to be assessed at baseline only. F= CAPS-5 assessments at these timepoints will measure the last week.G= Visit 6 will be based on past 3 weeks, Visit 7 will be based on the past 2 weeks, Visit 13 will be based on the past 3 weeks, Visit 14 will be based on the past 2 weeks, LTFU will be based on the last month. H= Will measure the past2 weeks.

Figure 4.1-1: Summary of Events



5.0 Randomization and Blinding

To achieve sufficient statistical power and account for dropouts, about 116 participants will be stratified by site and randomized in a 1:1:1:1 ratio across the four treatment groups (High THC, High CBD, THC/CBD, or Placebo) based on a sequential order of enrollment into the study. Participants will be assigned a randomization code that will correspond to a blinded concentration assignment. Randomization and enrollment will halt when 76 participants complete Stage 1 (at least N=19 per group). In order to maintain the blind for participants, site staff, IRs, and sponsor staff, a central electronic database will be utilized for randomization based on validated computer-generated lists. The Stage 1 randomization list will utilize blocks to balance treatment assignments. Stage 2 randomization will utilize multiple validated randomization lists that re-randomize participants in a blinded manner to one of two new treatment assignments in a 1:1 ratio, excluding the previously assigned Stage 1 dose and the placebo concentration as possibilities. Participants who received placebo in Stage 1 will only be permitted two options for Stage 2 randomization, as described in the protocol Section 6.2.1.

The blind may be broken for an individual participant if there is an AE or other emergency requiring knowledge of the participant's marijuana concentration assignment. This emergency unblinding would be evaluated on a case by case basis and require approval from the site CI and Coordinating Investigator. For this purpose, the Randomization Monitor will provide dose assignment through the electronic randomization system. In all other cases, the blind will be maintained until all participants have completed the study and the database is locked. The Coordinating Investigator, Co-investigators, Sub-Investigators, Independent Raters, and participants will be blind to concentration assignment.

For further details, refer to Section 6.0 Investigational Product of the protocol.

6.0 Sample Size and Power Considerations

The proposed study is a pilot investigation intended to gather preliminary data on the effect size and safety of marijuana in people with chronic, treatment-resistant PTSD. Because of their exploratory nature, pilot studies are often not powered for detecting the desired effect. This study will be the first to examine the effects of marijuana on PTSD.

This pilot RCT is the first study of its kind intended to gather estimates of effect size of marijuana for PTSD. In this study, the marijuana concentration effect of interest is among subjects who comply with the treatment. Thus in the proposed study, with 19 participants randomized to each group (N=76) who complete the specified treatment period, the study will have 82% power to detect an effect size of 0.4 on the primary outcome measure (change in CAPS-5 total score) in the Per Protocol sample. A meta-analysis of pharmacotherapies for combat-related PTSD in veterans found that the effect size of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) was equivalent to an F-test effect size of 0.3 [1]. Additional enrollment beyond N=76 to compensate for anticipated dropouts may increase the statistical power in the primary mITT analysis. However, the effect size may reduce among non-completers and when they are included in the mITT analysis the overall effect size may be reduced. The table

below provides power estimates for possible effect sizes in the Per Protocol Population and the mITT population(s), depending upon how many subjects are required to obtain 19 completers in each concentration group. Based on a meta-analysis of PTSD studies which found an average of 18% of participants dropped out without completing the investigational treatment, the expected dropout rate is 24% to 34% [2].

Table 6.0: Power Estimates for a One-Way ANOVA design, Overall mITT Test

F-Test Effect Size	N=76 Per Protocol/ Completers	Est. N=100 mITT Dropouts: 24%	Est. N=116 mITT Dropouts: 34%
0.3	55%	70%	77%
0.4	82%	92%	96%
0.5	96%	99%	99%

7.0 Measures

7.1 Screening Measures

Screening measures will not be formally analyzed as outcomes and will only be used to establish eligibility for the study at Baseline

Beck Depression Inventory –II (BDI-II): total score

STOP-Bang: total score

Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV)

SCID for Personality Disorders (SCID-PD)

7.2 Outcome Measures

Primary Outcome Measure:

Clinician-Administered PTSD Scale (CAPS-5): Total Severity Score, Criterion A Traumatic Event, Criterion E Duration of PTSD, Dissociative Subtype, Diagnostic criteria Met

Secondary Outcome Measures:

PCL-5: Total score

Insomnia Severity Index (ISI): Total score

Inventory of Depression and Anxiety (IDAS): General depression, dysphoria, lassitude, insomnia, suicidality, appetite loss, appetite gain, ill temper, well-being, social anxiety, panic, traumatic intrusions

Inventory of Psychosocial Functioning (IPF): Total score

Weekly Behavior Report (WBR) for Community Observer: Item-level data on relationship with partner or spouse, family, work, education, social, self-care, non-medical substance use, general mood and functioning

WBR for Participant: Item-level data on relationship with partner or spouse, family, work, education, social, self-care, non-medical substance use

Actigraphy (ACT): Weekly total sleep time (TST), wake after sleep onset (WASO), sleep onset latency (SOL), sleep efficiency (SE)

Plasma analysis of inflammation markers (CRP, IL-1β, and IL-6)

7.3 Safety Measures

Time-line Follow-back (TLFB):

a. Nicotine (cigarettes): Use present, Total Cigarettes, # of Days Using Cigarettes in Assessment Period, % of Days Using Cigarettes, Average Cigarettes Per Substance Use Day, Average Cigarettes Per Day, # of Abstinent ("0") days, Estimated Cigarettes Per Year, Greatest # of Cigarettes in 1 Day, Cigarettes Per Week
b. Marijuana (smoked cannabis flower): Use present, Total amount in weight, # of Days Using Marijuana in Assessment Period, % of Days Using Marijuana, Average amount in weight Per Substance Use Day, Average amount in weight Per Day, # of Abstinent ("0") days, Estimated Marijuana Use Per Year, Greatest Amount of Marijuana Use in Weight in 1 Day, Marijuana use in amount in weight Per Week

c. Drinking: Use present, Total Drinks, # of Days Drinking (Out of Assessment Period), % of Days Drinking, Average Drinks Per Drinking Day, Average Drinks Per Day, # of Abstinent ("0") days, Heavy Drinking Days (Heavy Drinking is defined as 5 or more drinks per day for a man and 4 or more drinks per day for a woman.), # of Drinks in 30 Days, Greatest # of Drinks in 1 Day, Drinks Per Week

d. Other drugs (specify): Use present, # of Days Using in Assessment Period, % of Days Using, # of Abstinent ("0") days, Percentage of Abstinent Days, Estimated Use Days Per Year, Average Use Days Per Week

Cannabis Use Disorders Identification Test-Revised (CUDIT-R): Total score

Marijuana Withdrawal Checklist (MWC): Total score

STOP-Bang: Total score

Columbia Suicide Severity Rating Scale (CSSR-S): Suicidal ideation, intensity of ideation, and suicidal behavior scores

General Well-being (GWB): Not formally analyzed

Drug Effect Questionnaire (DEQ): Drug effect, unpleasant drug effect, pleasant drug effect, sick, heart racing, anxious or nervous, relaxed, paranoid, sleepy or tired, alert, irritable, vigorous or motivated, restless, hungry or munchies, mouth dry, eyes dry, trouble with memory, throat irritated, difficulty performing routine tasks

Vital signs: Systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature (BT)

Pulse Oximetry: Pulse (HR) and blood oxygen levels (SpO)

Adverse events, including spontaneously reported reactions

Concomitant Medications and Therapies

7.4 Process Measures

Daily Diary: Daily use of study marijuana, daily use of other substances and medications, amount of study marijuana used, amount of other substance used, times of day study marijuana is used, times of day other substance is used, frequency of use of study marijuana per day, reason for self-administration of marijuana per self-administration, daily self-reported sleep data collection (time to sleep, time to wake, time out of bed, sleep onset latency, wake after sleep onset, sleep quality) will be summarized by descriptive statistics for analysis of continuous variables, e.g. weekly N, min, max, mean, SD, and for analysis of dichotomous variables by weekly frequency and percentages

Belief of Condition Assignment: Stage 1 concentration guess, Stage 2 concentration guess, participant and blinded site staff

Long-term Follow-up questionnaire: Item-level data

Quantitative blood and/or urine analysis of cannabinoids (THC, CBD)

8.0 Analyses

In general, nominal variables will be described in terms of frequencies and percentages and analyzed using chi square analysis. Ordinal and non-normal continuous data will be described using sample median and range, and analyzed by non-parametric statistical tests. Data that approximates a Gaussian distribution will be described using sample mean and standard deviations and analyzed by parametric statistical tests. Appropriate tests for comparative group homogeneity would be conducted and any significant lack of homogeneity will be appropriately addressed. No Type 1 error adjustments will be made for multiplicity.

8.1 Study Population

See protocol section 4.3 Recruitment and Participant Population. All participants must have a diagnosis of PTSD arising from their combat-related service in the U.S. military lasting at least six months, meet DSM-5 criteria for PTSD, have CAPS-5 Total Severity scores of 25 or greater upon enrollment, have undergone psychotherapy or pharmacotherapy of adequate dose and duration for PTSD (est. 12 weeks, as evaluated by the Investigator), and report no current hazardous marijuana use.

8.2 Handling of Dropouts, Missing Data

Participants who discontinue treatment prior to the End of Stage 1 or End of Stage 2 outcome assessment will be asked to complete an outcome assessment whenever possible prior to continuing to the long-term follow-up. Data from dropouts and at least one-follow-up assessment will be retrieved with last observation carried forward (LOCF).

For measures analyzed with linear modeling, data points that are missing due to subject attrition will be handled assuming that data are missing at random (MAR) conditional on observed information, which is less restrictive than missing completely at random assumed in fixed effects analyses such as ANCOVA. In this procedure, all available cases including the ones with missing information will be included in the analyses which increases power.

Early termination visit data for mITT and Safety analyses will be analyzed at the closest scheduled outcome visit after self-administration. If the closest visit has valid data, the early termination data will be assigned to the next available visit. If a participant discontinues and does not participate in an early termination visit, data from the last available visit will be used to replace the missing early termination visit data.

Partial or Missing Dates:

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then:

i) If the year matches the first dose date year, then impute the month and day of the first dose date.

ii) Otherwise, assign 'January.'

3) If the day is unknown, then:

i) If the month and year match the first dose date month and year, then impute the day of the first dose date.

ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then assign 'December.'

3) If the day is unknown, then assign the last day of the month.

8.3 Protocol Deviations

All protocol deviations will be included as a categorized listing. Participants with minor deviations will be included in all analyses. Analyses will be performed with and without deviations to examine the effects of including them in an analysis, via the mITT and PP populations. Participants with major deviations will be excluded from the PP analysis and included in the mITT analysis. Safety analyses will include all enrolled participants who took study drug with all available data, regardless of any deviations. The number of participants in each protocol deviation category listed below will be summarized by treatment group, and individual participants will be listed in the appendix.

Possible protocol deviations include the following five categories:

- Subject randomized in study did not meet entry criteria
- Subject developed withdrawal criteria during the study but were not withdrawn
- Subject received wrong treatment or incorrect dose
- Subject took excluded concomitant treatment
- Study procedures missed or performed out of window

8.4 Participant Demographics and Background

Population: mITT, PP, crossover, extension

Categorical data includes: gender (demographics), ethnicity/race (demographics), trauma etiology (CAPS-5), medical history (Medical History eCRF), presence of pre-study marijuana use (TLFB), presence of pre-study alcohol use (TLFB), presence of pre-study other drug use (TLFB), presence of pre-study cigarette use (TLFB), presence of pre-study prescribed opiate medications (Concomitant medications eCRF), presence of secondary traumatic events (demographics).

Descriptive data includes: age (demographics), number of years with PTSD (CAPS-5), number and duration of past therapy for PTSD (Healthcare utilization eCRF), number and duration of past medications for PTSD (Concomitant medications eCRF), number and duration of past medications for pain if present (Concomitant medications eCRF), amount of pre-study marijuana use (TLFB), amount of pre-study alcohol use (TLFB), amount of pre-study other drug use (TLFB), amount of pre-study cigarette use (TLFB), amount of baseline alcohol if present (Daily Diary), amount of baseline caffeine if present (Daily Diary), amount of baseline amphetamines if present (Daily Diary), amount of baseline benzodiazepines if present (Daily Diary), amount of baseline cocaine if present (Daily Diary), amount of baseline heroin if present (Daily Diary), amount of baseline non-medical opioids if present (Daily Diary), amount of baseline MDMA if present (Daily Diary), dose of pre-study prescribed opiate medications (Concomitant medications eCRF),

Format of presentation: summary tables including frequency listings in total and by concentration for categorical data, or mean, standard deviations, median, and range for descriptive data

Treatment group differences in baseline characteristics and PTSD severity, as measured by CAPS-5 total score, will be evaluated by ANOVA.

8.5 Subject Disposition and Dosing Summary

All participants enrolled in the study (i.e. who sign informed consent and meet inclusion/exclusion criteria) will be included in the summary of subject disposition and accountability. No inferential statistical tests will be performed. The tabulation of number of participants in each treatment group and overall will be displayed for all participants in the Safety Population, mITT Population, Crossover Population, Extension Population, and PP Population. The number and percent of participants who completed or discontinued the study will be displayed for each treatment group and overall together with reasons for early termination, where the percent is with respect to the total number of randomized participants in that treatment group.

8.6 Prior and Concomitant Medications and Therapies

The number and percent of subjects who took medications or received therapy prior to and after signing informed consent will be summarized descriptively for each treatment group. The tabulation of number of participants in each treatment group and overall will be displayed for all participants in the Safety Population, mITT Population, Crossover Population, Extension Population, and PP Population. Concomitant medications and therapies will be summarized similarly. Prior and concomitant medications and therapies will be summarized for the Safety Population. Psychiatric medications will be coded to common drug classes and terms.

8.7 Efficacy Analyses

Efficacy analyses intended to examine differences between groups in order to estimate effect size will be executed on the mITT population, the PP population, and the Crossover population, when appropriate. For all primary, secondary and exploratory endpoints descriptive statistics (N, mean, standard deviation, median, range, effect size (for measures of interest), or counts and percentages where appropriate will be provided by treatment group. All statistical tests will be executed at a type I error rate of 5%. No adjustments for multiplicity will be made. Effect size will be estimated based on all outcome measures using Cohen's techniques.

8.7.1 Primary Efficacy Analyses for Stage 1

The primary Stage 1 efficacy evaluation is an mITT LOCF analysis of the change from baseline to the primary outcome timepoint (visit 5) in the CAPS-5 Total Severity score of PTSD (difference score). The primary efficacy comparison will be made with ANOVA at an alpha level of 0.05 [3]. If the primary null hypothesis is rejected, pairwise comparisons among the treatment groups will be made with Student's t-tests. Previous studies have shown that the CAPS-4 difference scores followed a Gaussian distribution, and it is expected to be the same for the CAPS-5 scores. However, prior to hypothesis testing of the primary endpoint, the distributional properties of the CAPS-5 difference scores for the entire sample will be examined. If departure from a Gaussian distribution is detected, appropriate nonparametric methods will be used to test the primary null hypothesis.

8.7.2 Secondary Efficacy Analyses

Objective #1, 2, 3: PCL-5, ISI, ACT, IPF, and IDAS scores during Stage 1 and Stage 2 will be analyzed with Generalized Linear Mixed Effect Modelling (GLMM) with participant as a random effect, visit and concentration as fixed effects to fully utilize repeatedly measured outcome data. Maximum likelihood estimation will be implemented. Overall differences in treatment concentrations will be compared with a linear contrast. Concentration differences will be examined with pairwise contrasts. Data points that are missing due to subject attrition will be handled assuming that data are MAR. In GLMM, the change in the outcomes (PCL-5, ISI, ACT, IDAS) will be modeled as the Dependent Variable predicted by treatment group. The results of these longitudinal analyses can be easily converted to examine the treatment effect at each assessment point and within each group. Baseline characteristics, such as age, ethnicity/race, trauma etiology, medical history, psychiatric history, etc., will be explored as potential predictors/confounders.

Objective #4: Self-reported preference for marijuana assignment in Stage 1 or Stage 2 will be examined as an independent predictor for changes in PTSD symptom severity of PTSD measured with CAPS-5 during Stage 2 analyzed with ANCOVA.

Objective #5: Washout effects will be examined from the GLMM analysis of CAPS-5 total score and PCL-5 total score. To assess clinically significant washout effects, defined as an 8-point increase in the CAPS-5 total score from end of self-administration in Stage 1 or Stage 2, will be summarized by descriptive statistics.

Objective #6: GLMM will be conducted examining weekly assessments of self-reported (via the ISI) and objective (via Actigraphy) measures of sleep. For objective sleep (via Actigraphy) repeated measures of weekly TST, WASO, SOL, and SE will be analyzed longitudinally. Measures throughout Stage 1 and Stage 2 will be used. If the linear contrast of the effect of marijuana concentration is observed, then pairwise contrasts will be conducted to detect differences between each marijuana concentration. Missing data will be handled as described above for GLMM analyses.

Objective #7: Spearman's correlation will be used to assess the relationship between Daily Diary items related to sleep with objective changes in sleep via Actigraphy and self-reported changes in insomnia symptoms using the ISI. STOP-Bang scores will be used as a covariate in a regression analysis to determine if participants at high risk of breathing disorders is a predictor of sleep continuity outcomes.

Objective #8: Amount of marijuana used by each participant during Stage 1 and Stage 2 based on Daily Diary will be summed and used as a predictor in the GLMM analysis with CAPS-5 as the outcome variable.

Objective #9: The effects of marijuana concentration as measured by CAPS-5 in Stage 1 and Stage 2 will be analyzed in a GLMM analysis with concomitant medications evaluated in the model as potential predictors or confounders of the treatment effect.
Objective #10: The LTFU Questionnaire nominal variables will be described in terms of frequencies and percentages, while ordinal and non-normal continuous variables will be

described using sample mean, standard deviations, and range. Changes in CAPS-5 total score from end of treatment at either the end of Stage 1 (V5) or end of Stage 2 (V12) to the LTFU visit in participants who receive at least one type of active marijuana will be explored with ANCOVA. In the Extension set, the amount of Stage 3 marijuana and duration of Stage 3 will be collected and entered as covariates in analysis of long-term follow-up CAPS-5 total score.

8.7.3 Additional Exploratory Analyses

Additional exploratory analyses will be executed on the mITT population, the PP population, the Crossover population, and Extension population, when appropriate.

Process Objective #2: In order to compare the blinded site staff and participant's belief of condition assignment to actual marijuana concentration received, the number and frequency of correct guesses will be calculated and depicted by dose group and study role (subject and site staff).

Objective #11: Independent prognostic value of CRP, IL-1β and Il-6 will be examined using GLMM, with biomarker values gathered at Baseline, primary endpoint CAPS-5 total score, and biomarker values collected after two weeks of Cessation and the End of Stage 2. Baseline characteristics, such as age, ethnicity/race, trauma etiology, medical history, psychiatric history, etc., will be explored as potential predictors/confounders.

Process Objective #1: Quantitative levels of THC, CBD and their metabolites will be assessed in order to ascertain whether participants comply with only using the marijuana assigned to them during the study. If there is sufficient data, correlational analyses may also be conducted between quantitative THC and CDB levels in urine and blood and clinical outcomes as measured by CAPS-5 Total Severity score to determine whether there is a dose-response effect between THC and CBD exposure and clinical response.

Daily Diary, WBR for Participant and Observer data will be used to support protocol compliance with take-home dosing. Item-level data will be summarized for analysis of dichotomous variables by weekly frequency and percentages, while ordinal and non-normal continuous variables will be described using sample mean, standard deviations, and range.

8.8 Safety Analysis

Safety analyses will be executed on the mITT population, the PP population, the Crossover population, and Extension population, when appropriate.

Objective #10: The primary measure of safety will be the reporting of adverse events. The adverse events (AEs) considered are Treatment Emergent Adverse Events (TEAE) defined as those AE's that occurred after dosing and existing medical history diagnoses that worsened during the study. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary. For incidence reporting if a subject has more than one AE mapped to the same preferred term, that AE will be reported only once using the highest severity and closest relationship to study drug. Subject incidence of AEs will be displayed by concentration, by stage, and by system organ class. AEs will also be summarized by severity and relationship to study drug. Subject incidence of SAEs by concentration and by stage will also be displayed. In addition to the listing of all AEs, a listing of SAEs and a listing of AEs leading to discontinuation will be included.

Objective #1, 2, 5: GLMM will be used to examine DEQ, pulse, blood pressure, and body temperature during introductory sessions, with participant as a random effect, visit and concentration as fixed effects to fully utilize repeatedly measured safety data. Maximum likelihood estimation will be implemented. Overall differences in treatment concentrations will be compared with a linear contrast. Concentration differences will be examined with pairwise contrasts. Missing data will be handled as described above for secondary efficacy analyses.

Objective #3: Symptoms of marijuana withdrawal will be displayed by incidence, percentages and by concentration and crossover group for screening, Cessation 1 and Cessation 2. The MWC total score will be analyzed by GLMM to assess differences by concentration and crossover group. If a main effect of marijuana concentration or crossover group is observed, then pairwise contrasts will be used to detect differences between each marijuana concentration.

Objective #4: The CUDIT-R total score will be analyzed by GLMM to assess differences by concentration and crossover group. If a main effect of marijuana concentration or crossover group is observed, then pairwise contrasts will be used to detect differences between each marijuana concentration.

Objective #6: Suicidal ideation and behavior will be summarized according to suggestions made in the Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide [4]. A positive response for suicidal ideation is counted when a subject answers "yes" to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS, i.e. a score > 0 for suicidal ideation score. Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a subject answers "yes" to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS, i.e. a score > 0 for suicidal behavior score. The number and percent of positive responses of Positive Ideation, Serious Ideation, and Positive Behavior will be tabulated by Stage I concentration and crossover group. Analyses will compare lifetime serious suicidal ideation and positive behavior frequencies to cumulative frequencies anytime during the study until end of the last stage of self-administration completed.

Objective #7, 8: Incidence and percentages of hospitalizations and incarcerations will be displayed by stage and by concentration.

8.8.1 Additional Safety Analysis

Timeline follow-back (TLFB) will be used to support severity assessment of substance use disorder diagnoses made during screening via SCID-5-RV. Exploratory comparisons of substance use descriptives pre and post-treatment will be made with ANOVA at an alpha level of 0.05.

Incidence and percentages of concomitant medications and therapies will be displayed by concentration and by stage.

9.0 Interim Analyses

No interim analyses are planned for this study.

10.0 Timing of Analyses

The study will remain blinded until final database lock, at which point the randomization file will be merged by the unblinded Randomization Monitor with the clinical study database. The primary efficacy analysis will be conducted after database lock. Changes to protocol will not occur after primary analysis.

11.0 Statistical Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

12.0 References

References

1. Puetz, T.W., S.D. Youngstedt, and M.P. Herring, *Effects of Pharmacotherapy on Combat-Related PTSD, Anxiety, and Depression: A Systematic Review and Meta-Regression Analysis.* PLoS One, 2015. **10**(5): p. e0126529.

2. Imel, Z.E., et al., *Meta-analysis of dropout in treatments for posttraumatic stress disorder.* J Consult Clin Psychol, 2013. **81**(3): p. 394-404.
3. Senn, S.S., *Statistical issues in drug development*. Vol. 69. 2008, Chichester, England: John Wiley & Sons.
4. Nilsson, M.E., et al., *Columbia Suicide Severity Rating Scale Scoring and Data Analysis Guide*, in *CSSRS Scoring Version 2.0*. 2013: http://www.cssrs.columbia.edu/documents/ScoringandDataAnalysisGuide_Feb2013.pdf. p. 1-13.