A PHASE I/II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF CANNABIDIOL AS A TREATMENT FOR ALCOHOL USE DISORDER COMORBID WITH POSTTRAUMATIC STRESS DISORDER

Principal Investigator:	Charles Marmar, MD NYU School of Medicine, Department of Psychiatry One Park Ave Charles.marmar@nyumc.org 646-754-4855
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Regulatory Sponsor:	Charles Marmar, MD NYU School of Medicine, Department of Psychiatry One Park Ave. Charles.marmar@nyumc.org 646-754-4855 Michael Bogenschutz, M.D. Professor of Psychiatry, NYU School of Medicine Bellevue Hospital Center 462 First Avenue A Building, 8th Floor, Rm. A832 New York, NY 10016 Phone No: (646) 501-4026 Email: Michael.Bogenschutz@nyumc.org
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Contents

List of Abbreviations

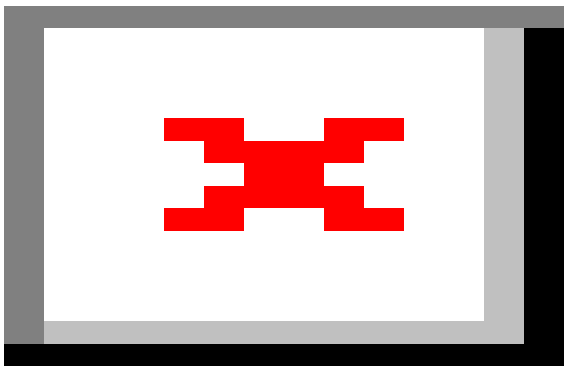
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
n	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
CBD	Cannabidiol
THC	Tetrahydrocannabinol
AUD	Alcohol Use Disorder
PTSD	Post-Traumatic Stress Disorder

Protocol Summary

Title	A Phase I/II Randomized, Double-Blind, Placebo-Controlled Trial of Cannabidiol for Alcohol Use Disorder comorbid with Post Traumatic Stress Disorder
Brief Summary	The proposed study is a double-blind, randomized proof-of-concept study designed to assess feasibility and contrast effects of CBD treatment to those of placebo on safety, drinking-related outcomes and PTSD related outcomes in patients with AUD+PTSD. We will evaluate the safety of an extended daily CBD treatment regimen in an AUD+PTSD population, measure resulting CBD, THC, and anandamide levels, and generate preliminary data on the impact of CBD on alcohol use, PTSD symptoms, and neuropsychological and neurophysiological domains implicated in AUD and PTSD. 150 participants will be enrolled to randomize 48 eligible participants who fully meet study criteria in a 5:3 ratio to receive either 600mg CBD/day (PO) or placebo respectively for 6 weeks (N=30 participants on CBD and N=18 participants on placebo). Clinical interviews or portions of the interview will be audio taped to ensure quality control. De-identified audio recordings of participants who consent to participate in the voice-markers analysis will be encrypted and sent via secure sites for analysis to a HIPAA compliant specialized labs.
Phase	Clinical study phase I/II
Objectives	To assess the safety and feasibility of administering CBD in an AUD+PTSD population; to generate preliminary data on the effect of CBD in reducing self-reported measures of alcohol use and PTSD symptoms and the impact of CBD upon neurophysiological and neuropsychological domains relevant to AUD+PTSD; to assess plasma for CBD, THC and anandamide levels.
Methodology	Double-blind, placebo-controlled
Endpoint	Primary endpoints: Adverse events and scores on psychomotor and cognitive tasks, number of drinks per day and PCL-5 total score. Secondary endpoints: circulating concentrations of CBD, THC and anandamide.
Study Duration	2 years
Participant Duration	9 weeks
Duration of IP administration	6 weeks
Population	n=48 (randomized) 18–70 year-old males and females with moderate to severe AUD, as well as a DSM diagnosis of either PTSD or subthreshold PTSD in the New York area.
Study Sites	New York University Grossman School of Medicine
Number of participants	150 participants expected to be enrolled, 48 participants expected to be randomized
Description of Study Agent/Procedure	Cannabidiol PO 600mg/day
Reference Therapy	Placebo with medication management
Key Procedures	Blood draws

Statistical Analysis	The primary outcome measure for AUD, the number of drinks per day, is the change from baseline to treatment end (week 6, T8), as analyzed with a Mixed Model Repeated Measures (MMRM) with within and between group comparisons. The primary outcome measure for PTSD, PCL-5 total score, and secondary outcomes for traumatic stress induced craving from the human laboratory task, and AUD and PTSD related domains will be analyzed in the same manner. For secondary outcomes of plasma levels within- and between-group comparisons of plasma CBD levels will be assessed at baseline (pre-CBD levels), following 45 minutes (T1- 45min post-CBD levels), 1 day (T2- 45min post-CBD levels), 1 week (T3- 45min post-CBD and pre-CBD levels), 2 weeks (T4- 45min post-CBD and pre-CBD levels), 4 weeks (T6- 45min post-CBD and pre-CBD levels),6 weeks (T8- 45min post-CBD and pre-CBD levels), and 7 weeks (T9- pre-CBD levels) after the first CBD vs. placebo dose. Effects of dose will be assessed and the interaction between group and time-points will be evaluated.

Schematic of Study Design



1 Key Roles

Charles Marmar, MD, Principal Investigator
NYU School of Medicine, Department of Psychiatry
One Park Ave. 8th Floor
(646) 754-4855
Charles.marmar@nyumc.org

Esther Blessing, MD, PhD, Co-Investigator
NYU School of Medicine, Department of Psychiatry
One Park Ave. 8th Floor
(646) 754-4808
Esther.Blessing@nyumc.org

Michael Bogenschutz, M.D, Co-Investigator.
Bellevue Hospital Center
462 First Avenue
A Building, 8th Floor, Rm. A832
New York, NY 10016
(646) 501-4026
Michael.Bogenschutz@nyumc.org

Gene Laska Ph.D, Co-Investigator.
New York University Langone School of Medicine
One Park Avenue. 8th Floor
New York, NY 10016
(646) 754-4828
Eugene.Laska@nyumc.org

John Rotrosen, MD, Co-Investigator
New York University School of Medicine
Department of Psychiatry
One Park Ave, 8th Fl
(646) 754-4763
John.Rotrosen@nyumc.org

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Need for improved treatments for AUD comorbid with PTSD

Alcohol use disorder (AUD) is one of the most common and debilitating psychiatric disorders. It has a lifetime prevalence of ~29.1% in the United States, and is a major cause of medical and social disability, preventable death and economic burden ($249 billion in 2010) [1, 2]. Several medications are available for treating AUD, however associated effect sizes treatment compliance rates remain low [3] [4, 5]. A major barrier to improving medical treatment of AUD is the high level of heterogeneity between individuals with this disorder: AUD comprises multiple clinical subtypes with distinct patterns of alcohol misuse and distinct psychological and neurobiological disturbances. This means that a given medication may only work for certain subtypes of AUD patients, leading to overall lower treatment effectiveness in the absence of more targeted approaches. Differing co-existing psychiatric disorders (present in a high proportion of individuals with AUD) make an important contribution to this heterogeneity in [6-8]. The National institute of Alcohol use disorder (NIAAA) has therefore emphasized ongoing drug development should address this heterogeneity by targeting potential treatments to specific AUD subpopulations including psychiatric comorbidities, particularly those that are common, that involve severe AUD, and have low treatment response [6-8].

Based on these criteria, the NIAAA recently mandated research to target medications to AUD comorbid with post-traumatic stress disorder (PTSD) [6-8]. PTSD is a condition that may develop following a traumatic event: it involves intrusive thoughts about the traumatic event, avoidance of event relevant stimuli, negative changes

in mood and cognition, heightened vigilance and physiological arousal. PTSD is present in 30–60% of individuals diagnosed with AUD and conversely 20–70% of individuals diagnosed with PTSD meet criteria for AUD, with higher rates in military veterans; there this comorbidity (AUD+PTSD) represents a significant proportion of all AUD [9-14]. Subthreshold PTSD criteria requires that at least six symptoms of PTSD are present, but do not meet full threshold criteria due to failure to meet criterion specifiers. Previous research has shown that subthreshold PTSD is a clinically relevant concept. For instance, it has been found that psychiatric outpatients with subthreshold PTSD had social and occupation morbidity levels comparable to those with fully-threshold PTSD [104]. Other research has also found high rates of psychiatric comorbidity and psychosocial impairment in a sizable epidemiologic study [105]. Similar outcomes have been shown in samples of veterans [103]. When examining the leading subthreshold definitions utilized by clinicians the Six-symptom definition was found to trend toward significance and perform the best of all four definitions tested [102]. In addition, AUD+PTSD/subthreshold PTSD is associated with more severe AUD, higher mortality and impairment and poorer response to treatment. Findings also suggest that this comorbidity involves a vicious cycle in which each disorder exacerbates and impedes treatment of the other [10, 12, 15-22]; therefore, coordinated treatment of both disorders should be more efficacious than treating each disorder in isolation. Various medications have been tested for AUD or efficacy in randomized clinical trials involving AUD+PTSD/subthreshold PTSD patients. However, no Phase III trials have been reported [23].

Stress induced craving and extended amygdala activation as a target for treating AUD+PTSD

Perhaps the most promising medication target for treating AUD+PTSD/subthreshold PTSD is the addiction domain of stress-induced alcohol craving, with the neurobiological substrate of increased activity in the extended amygdala. Clinical studies find that AUD+PTSD/subthreshold PTSD patients use alcohol as a coping mechanism to reduce stress associated with PTSD/subthreshold PTSD [10, 12, 15-22, 24-26]. Animal models show stress and alcohol craving are linked by common neurobiological circuits, namely the extended amygdala, and that pharmacological inhibition of stress or ethanol-withdrawal associated activity in this area simultaneously reduces both anxiety and ethanol-seeking behaviors [27-29]. Receptor actions implicated in this inhibitory effect include cannabindoid 1 (CB1) receptor stimulation and 5-HT1a receptor activation [27-29]. Clinical and human experimental studies support the idea that increased stress and amygdala activation increases alcohol craving and use. In AUD patients who report alcohol use to mitigate negative emotions, higher amygdala reactivity predicts future problem drinking [30]. In PTSD/subthreshold PTSD patients, PTSD symptoms predict alcohol craving and use [16, 31]; further, a hyper-reactive amygdala response to threat, and heightened sympathetic physiological arousal including skin conductance and heart rate, reliably distinguishes PTSD/subthreshold PTSD from controls and predicts PTSD symptoms [2, 32-34]. The well-validated human laboratory paradigm of guided trauma imagery-elicited alcohol craving shows that trauma re-experiencing elicits negative emotion, physiological arousal, and alcohol craving [35-39].

Potential for CBD to treat AUD+PTSD/subthreshold PTSD **by targeting stress induced extended amygdala activation** Cannabidiol (CBD), a pharmacologically broad spectrum anxiolytic and non-psychotomimetic phytocannabinoid contained in cannabis, is a promising drug candidate for reducing negative emotion-induced alcohol craving. In animal models, CBD produces anxiolytic, anti-compulsive, anti-fear-conditioning and pro-fear-extinction effects, by acting at serotonin 1A ($5\text{-}HT_{1a}$) and CB_1 receptors within extended amygdala areas (the central nucleus [40], bed nucleus of the stria terminalis [41-43] and nucleus accumbens shell [44]), and within functionally connected brain regions including the periaqueductal grey [45], prelimbic and infralimbic regions of the medial prefrontal cortex [46], and hippocampus [47], reviewed in [48]. CBD indirectly increases endocannabinoid agonism at the CB_1 receptor [49], an action that reduces extended amygdala output and alcohol seeking [50]. CBD also potently reduced ethanol seeking in animal models of relapse during 7-days of treatment, and drug seeking remained fully attenuated up to 5 months following treatment termination [51]. In human experimental studies, CBD at doses between 300–800 mg rapidly (within 2 hours) reduces subjective anxiety in both healthy and social anxiety disorder subjects, and reduces threat related amygdala activity and sympathetic arousal measured by skin conductance [52], reviewed in [48]. Importantly, skin conductance and amygdala activation were reduced by CBD in a closely correlated manner [53], suggesting threat related sympathetic arousal may serve as a proxy for amygdala activation [52]. These findings suggest that CBD will reduce extended amygdala activity and negative emotion associated with PTSD symptoms, and thereby, reduce alcohol craving and use. Further findings suggest that human laboratory measures of the subject and physiological effects of traumatic stress upon emotional state and alcohol craving may serve as a useful measure of drug target engagement.

a. Name and Description of the Investigational Agent

Cannabidiol (CBD) is a phytocannabinoid constituent of cannabis that lacks the psychotomimetic and rewarding effects of tetrahydrocannabinol (THC) [54], and has an excellent safety profile in the human experimental studies and clinical trials reported thus far [43, 55]. CBD is a schedule 1 drug, a class that includes compounds with high potential for abuse and no medical value. Contrary to this scheduling, CBD does not appear to possess a high abuse potential. Nonetheless, this formulation has not been FDA-approved for medical use. Therefore, this study will be performed under an Investigational New Drug Application (140108).

CBD has a broad spectrum of pharmacological effects. As distinct from THC, CBD is a very low-affinity cannabinoid 1 (CB_1) receptor ligand; nevertheless CBD appears to achieve an agonist effect at this receptor, potentially by inhibiting fatty acid amide hydroxylase (FAAH), which is the enzyme responsible for hydrolysis the endocannabinoid anandamide, which acts as CB_1 agonist [49]. In addition to its impact on the endocannabinoid system, CBD also acts as an agonist at the serotonin 1A ($5\text{-}HT_{1A}$) receptor [42, 56]; produces allosteric modulation of ligand-binding kinetics at μ and δ opioid receptors [57]; increases intracellular calcium through activation of transient receptor potential vanilloid type 1 (TRPV1) cation channels [58]; enhances adenosinergic neurotransmission via inhibition of the adenosine transporter [59]; CBD also regulates, directly or indirectly, the peroxisome proliferator-activated receptor-γ, the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, additional TRP channels, glycine receptors and GABA receptors [11, 12, 19, 21]. CBD may also have non-receptor based enzymatic and other effects. Only some of these actions (CB_1 and $5\text{-}HT_{1A}$ actions) have been related to animal model effects of CBD anxiolytic or anti-addictive effects [48].

2.2.1 ***Preclinical Data***

As discussed, extensive evidence in animal models shows that CBD reduces anxiety behaviors, compulsive behaviors, panic response and physiological stress responses by inhibiting extended amygdala activation and promoting response in the hippocampus and medial prefrontal cortex [48]. This suggests the potential to reduce stress-induced craving. Several other effects of CBD may also act improve PTSD symptoms and combat alcohol addiction. Cannabidiol modifies consolidation and reconsolidation, suggesting the ability to modify traumatic memories [48, 60]; CBD produces several pro-cognitive effects: including protecting against ethanol induced neurotoxicity [61], promoting hippocampal neurogenesis [47], and attenuating cognitive impairment in several animal models of neurodegenerative disease [62] [63].

Animal model studies also show that CBD reduces addictive behaviors: CBD reduces cue-induced heroin seeking, potentiates extinction of cocaine- and amphetamine-induced conditioned place preference [64], and normalizes heroin-seeking-induced changes in glutamatergic GluR1-containing amino-hydroxy- methyl-isoxazolepropionic (AMPA) receptors and CB1 receptor expression in the nucleus accumbens [65] induced by alcohol intoxication in a delay discounting task 6-15 days after the cessation of treatment.

2.2.2 ***Clinical Data to Date***

Clinical trials in PTSD or anxiety: No clinical trials of CBD for PTSD/subthreshold PTSD have been reported, nor for any anxiety related outcome – although some trials in anxiety may be currently in progress. In human experimental studies, CBD at doses between 300–800 mg rapidly (within 2 hours) reduces subjective anxiety in both healthy and social anxiety disorder subjects, and CBD reduces threat-related amygdala activity and sympathetic arousal measured by skin conductance [66] [43, 48, 52].

Clinical trials in AUD: No extended clinical trials of CBD's effects in alcohol use disorder or any addictive disorder have yet been reported. However, there are limited studies of CBD's acute effects on addiction- related behaviors. The only study to assess the impact of CBD on alcohol-related behaviors found no impact of 200mg of CBD on symptoms of intoxication in healthy volunteers [67]. CBD was also reported to reduce cigarette smoking in dependent humans [68], and a single case study reported that daily CBD prevented marijuana withdrawal symptoms [69].

Other clinical data: A considerable and rapidly growing number of human experimental studies and clinical trials of CBD's effects in other neuropsychiatric disorders (other than PTSD/subthreshold PTSD or AUD) have been conducted. Findings in general show CBD to have multiple therapeutic effects, including anxiolytic, anti-addictive, anticonvulsive, antipsychotic and analgesic [70], combined with an excellent safety profile and lack of adverse effects [43, 55]. GW pharmaceuticals is developing CBD (Epidiolex®) as a medication for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, and recently completed successful Phase 3 trials in 2016 [71, 72], and a successful Phase 2 trial in schizophrenia [73].

2.2.3 ***Dose Rationale (If applicable)***

The proposed dose of 600 mg (~8 mg/kg) daily is within the range of doses (300–800 mg) shown to be anxiolytic in humans, is expected to be safe and tolerable in humans and to yield steady state levels within a safe and therapeutic range.

Anxiolytic target dose. As discussed above, human experimental studies showed that acute oral CBD in the 300–800 mg range was anxiolytic in humans, suggesting daily dosing should have similar therapeutic effects. Potentially cautioning against much higher doses, preclinical studies suggest attrition of anxiolytic effects may occur at the highest doses [48] although no such data yet support this in humans.

Safety: CBD was found to be safe and well tolerated in all Phase I and Phase IIa clinical trials (>10) reported thus far, which included daily doses up to 1000 mg PO and treatment durations up to 6 weeks, whereas doses up to 1500 mg daily have been reported safe in case studies, reviewed in [43, 74]. We considered dose titration, but elected not to because acute doses of up to 1500 mg, and repeated daily doses of up to 1000 mg were previously safe and well tolerated [43, 74]. Regarding interactions with alcohol, a double-blind, randomized placebo controlled acute dosing trial showed that 200 mg PO CBD did not increase the psychomotor effects of alcohol (1gm/kg) or blood alcohol levels [67]. Relevant to the AUD population, CBD showed no risk for abuse liability in humans [75].

Potential for dose accumulation: Regarding repeated dosing pharmacokinetics, two studies in adults that assessed plasma levels over repeated dosing showed no progressive accumulation of CBD levels, including a 6-week trial of oral CBD at 700 mg daily [67, 76]. Preliminary data with transdermal CBD up to 30mg/kg/day in rodents shows no serum accumulation over 7 days of treatment (Weiss, unpublished data). Therefore, under the proposed dosing regimen we expect to achieve steady-state serum levels of CBD within a week.

2.3 Rationale

There is an urgent need for medications that are effective in treating AUD+PTSD/subthreshold PTSD comorbidity, and which are targeted to specific addiction domains and their neurobiological substrates. Pre-clinical and human experimental findings suggest the phytocannabinoid CBD is a promising candidate medication for reducing stress induced craving by inhibiting extended amygdala output, in addition to potential anti-addictive, traumatic and addictive memory modifying and pro-cognitive effects, thereby providing an integrated treatment for both AUD and PTSD/subthreshold PTSD. This promise is augmented by CBD's proven safety record, lack of intoxicating effects and low potential for abuse. Clinical trials of CBD in other disorders together with human experimental studies provide a strong basis for determining a suitable therapeutic dose for AUD+PTSD/subthreshold PTSD. There are few or no clinical trials reported of CBD for AUD, PTSD/subthreshold PTSD, or more generally for stress and addiction disorders, creating a mandate for the current trial.

The proposed study is a double-blind, randomized proof-of-concept study designed to assess feasibility and contrast effects of CBD treatment to those of placebo on safety, drinking-related outcomes and PTSD/subthreshold PTSD related outcomes in patients with AUD+PTSD/subthreshold PTSD. We will evaluate the safety of an extended daily CBD treatment regimen in an AUD+PTSD/subthreshold PTSD population and measure resulting CBD, THC, and anandamide levels. We will also generate preliminary data on the impact of CBD on alcohol use, PTSD symptoms, a human laboratory traumatic stress induced craving task, neuropsychological and neurophysiological domains implicated in AUD and PTSD/subthreshold PTSD, and cognitive ability. Cannabidiol levels will be obtained from CBD-treated participants to estimate the plasma levels corresponding with putative therapeutic effects and to determine whether dose accumulation occurs. THC levels will be obtained from CBD-treated participants to determine whether CBD metabolites are converted into THC, as has been suggested in the literature [77]. Anandamide levels will be obtained from all participants to test whether CBD elevates plasma anandamide, and to provide preliminary data for relating anandamide levels to putative therapeutic effects. Following screening and baseline assessments, 48 participants will be randomized in a 5:3 ratio to receive either 600mg CBD/day (PO) or placebo respectively for 6 weeks (N=30 participants on CBD and N=18 participants on placebo). Safety measures (adverse events, cognitive and motoric function), drinking related outcomes and PTSD symptoms will be assessed weekly throughout the study. Human laboratory tasks, neuropsychological domains implicated in AUD and PTSD/subthreshold PTSD and cognition will be assessed at baseline and at the end of treatment. Measurement of circulating levels of Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC will be obtained from CBD-treated participants only at baseline, 45 minutes, 1 day, 1 week, 2 weeks, 4 weeks, 6 weeks, and 7 weeks after treatment with the first dose of CBD vs. placebo. Anandamide levels will be obtained from both CBD- and placebo-treated participants at the aforementioned timepoints.

2.4 Potential Risks & Benefits

2.3.1 Known Potential Risks

The available evidence suggests that CBD is safe and well-tolerated in human participants. Numerous studies, including several blinded, placebo-controlled trials, have revealed few adverse effects of CBD orally in doses ranging from 10 mg to 1500 mg per day; there have been no reported effects on blood pressure, heart rate, or respiratory rate, no negative mood effects, and no psychomotor slowing. Commonly reported treatment-emergent adverse events in Phase 3 trials of CBD for Lennox-Gastaut or Dravet Syndrome included diarrhea, somnolence, pyrexia, decreased appetite, vomiting, fatigue, lethargy, convulsion, and elevated liver enzymes. All participants in these trials were on concomitant anti-seizure medications. CBD is not noticeably psychoactive.

2.3.2 Incidental Findings

In some cases, the safety blood draw results may indicate an abnormality with (or without) a clinical significance. Every blood draw performed in this study will be saved and handled under the standard PHI confidentiality restrictions and regulations employed for patients' information. The results are always reviewed by a licensed nurse practitioner or an MD, who may then detect an abnormality. If clinically useful information is uncovered, either the Principal Investigator or another clinician on the study will speak to the participant in person or on the telephone regarding the new information. A copy of the original report will also be provided to the participant who will then be advised to consult with their treating physician.

2.3.3 Known Potential Benefits

Participants may or may not experience clinical benefit from this study. Pre-existing clinical data suggest a possibility that the study drug could produce anxiolytic and anti-addictive effects. Aspects of study participation likely to be beneficial include free medical and psychiatric evaluations, and the attention and support of participating in a clinical trial.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective is to obtain a preliminary assessment of the safety, tolerability, efficacy, and effect size of CBD in reducing self-reported measures of alcohol use and PTSD symptoms in the AUD+PTSD/subthreshold PTSD population.

We predict that treatment with 600mg CBD daily will be well tolerated with no greater psychomotor or other motor side effects compared to treatment with placebo. We predict that CBD will be associated with a greater reduction in drinks per day and PTSD symptoms (total PCL-5 score) compared to placebo.

3.2 Secondary Objectives

Secondary objectives of this study are as follows.

1) To assess the effect of CBD upon plasma CBD and THC levels when administered to patients with AUD+PTSD/subthreshold PTSD. We predict that within-group plasma CBD levels will stabilize within one week, i.e. 45 minutes post-CBD dosing levels obtained after 1 week of treatment will not differ from those obtained after 4 weeks of treatment.
2) To contrast the effects of CBD to those of placebo on psychological and cognitive domains relevant to AUD and PTSD/subthreshold PTSD. Relative to placebo, we predict that CBD will improve self-report measures of craving, anxiety, mood, and self-efficacy, and improve cognitive function. We will also specifically target the domain of traumatic stress induced craving using a human laboratory task. We predict that relative to placebo, CBD will lead to a greater attenuation in subjective traumatic stress and alcohol cue-induced craving and accompanying physiological stress response.
3) To assess the effect of CBD on plasma anandamide levels. We will contrast levels of plasma anandamide between samples taken at baseline and after CBD treatment, and between samples taken at predicted pre- and 45 minutes post-dosing CBD levels. We predict that relative to placebo, CBD will lead to an increase in plasma anandamide between these time points.
4) To assess the temporal relationship between the onset in reduction of PTSD symptoms and the onset in reduction of AUD symptoms. We predict that a reduction in PTSD symptoms will precede a reduction in

AUD symptoms.

Exploratory Aim 1: To examine voicemarkers as a function of a patient's AUD and PTSD status and to develop assessment models that use lexical and prosodic features to classify a patient's AUD and PTSD status.

4 Study Design and Endpoints

4.1 Description of Study Design

The proposed study is a phase I/II, single-center, double-blind, randomized proof-of-concept study designed to assess safety and feasibility in the AUD+PTSD/subthreshold PTSD population and contrast effects of CBD treatment to those of placebo on drinking-related outcomes and PTSD symptoms. We will evaluate the safety of an extended daily CBD treatment regimen in an AUD+PTSD/subthreshold PTSD population, measure resulting plasma and CBD and THC levels, generate preliminary data on the impact of CBD on alcohol consumption and PTSD symptoms, assess the effect of CBD on a human laboratory measure of traumatic-stress induced craving and neuropsychological measures relevant to AUD and PTSD/subthreshold PTSD, and assess the effect of CBD dosing no plasma anandamide levels.

150 participants are expected to be enrolled in the study prior to screening and randomization. Following screening and baseline assessments, 48 participants who fully meet study criteria are expected to be randomized in a 5:3 ratio to receive either 600mg CBD/day (PO) or placebo respectively for 6 weeks (N=30 participants on CBD and N=18 participants on placebo). This dose was selected to optimize anxiolytic affects to target stress induced alcohol craving. Assessments of drinking and PTSD related outcomes will be completed at baseline and weekly over 6 weeks of treatment, with an assessment one week following the end of treatment. The human laboratory task and assessments of cognitive function will be completed at baseline and at the end of 6 weeks of treatment. Measurement of circulating levels of CBD, THC, and THC metabolites (Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC) will be obtained from CBD-treated participants at baseline, 45 minutes, 1 day, 1 week, 2 weeks, 4 weeks, 6 weeks, and 7 weeks after treatment with the first dose of CBD vs. placebo. Anandamide levels will be obtained from both CBD- and placebo-treated participants at the aforementioned time-points.

Outcomes will include drinking outcomes; PTSD symptoms; responses to personalized trauma and alcohol scripts designed to elicit stress- and cue-induced craving and anxiety; cognitive function; circulating levels of CBD, THC and anandamide and safety measures (adverse events, cognitive and motoric function), and psychological domains relevant to AUD+PTSD/subthreshold PTSD including self- reported craving, depression, and anxiety across 6 weeks of treatment and one week following the end of treatment.

Voice-markers: High-fidelity audio recordings from in-person or remote sessions of clinical interviews will be collected at screening. The audio recordings will be encrypted and transferred via secure transfer methods to a HIPAA compliant specialized entity for quality control and voice-makers analyses. If the participant gives their consent, the collected audio recordings will be used to examine voice-markers as a function of a patient's AUD and PTSD status and to develop assessment models that use lexical and prosodic features to classify a patient's AUD and PTSD status. All the recordings will be de-identified and labeled with a unique study code number for each participant in the study. Study personnel of the HIPAA compliant specialized entity receiving voice-marker data will not have access to link participants' study code to any identifying information collected throughout the study. These personnel will not be able to re-identify study participants associated with the respective data using the unique identifiers. If the recorded audio data has any identifying information embedded in the recordings, that information will be removed by study staff, who will review each audio file and delete any PHI before the file is sent to the specialized lab. Once the files are received, the specialized lab will double check the data for any PHI and if found, this will be removed prior to the data being used.

4.2 Study Endpoints

4.2.1 **Primary Study Endpoints**

The primary study endpoint for alcohol use will be number of drinks per day assessed by the Time Line Follow Back methodology [78]. The primary study endpoint for PTSD symptoms will be the PCL-5 total score. Safety will be assessed by collection of adverse events at all visits after treatment is initiated in addition to LFTs collected at screening, as well as weeks 2, 6, and 7 to assess the liver function during and after treatment

with study medication.

4.2.2 Secondary Study Endpoints Secondary Alcohol use endpoints

Secondary efficacy endpoints are the percent carbohydrate-deficient transferrin (CDT); the percentage of heavy drinking days (four or more drinks for women or five or more drinks for men per drinking day) averaged for each treatment week; weekly average severity of alcohol craving assessed by the Penn Alcohol Craving scale [79]; weekly percentage of very heavy drinking days (8+/10+ drinks per day for women and men respectively); weekly percentage of days abstinent; weekly percentage of subjects with no heavy drinking days, and weekly percentage of subjects that are 'present and clean', i.e. present to provide breath alcohol levels (BAC) and have a BAC of zero [80].

AUD-related measures

The Penn Alcohol Craving Scale (PACS) [79] will be used to assess craving. This scale has 5 Likert-scaled items with excellent internal consistency and evidence of predictive, construct, and discriminant validity. Self-efficacy will be assessed using the Alcohol Abstinence Self-Efficacy Scale (AASE) [81], a self-report questionnaire which has been used widely in the alcohol treatment research, both as a predictor of outcome and as a patient-treatment matching variable [82]. Craving, self-efficacy, and alcohol use will be assessed before treatment (baseline), week 1, week 4, week 6, and at one week following the completion of treatment. Mood and Anxiety will be measured with the Beck Anxiety Inventory (BAI) [99] and Beck Depression Inventory-II (BDI-II) [100] scales at baseline, treatment weeks 1, 4 and 6, and at one week following treatment completion.

Risk of suicidality will be assessed by a licensed study provider using the Columbia-Suicide Severity Rating Scale (C-SSRS) [98] as part of each study visit.

PTSD-related measures

The PCL-5 will be administered at baseline, weeks 2, 4, 6 and 7. In addition to the PCL-5 score (primary PTSD endpoint), childhood trauma (child abuse and neglect) will be assessed at baseline using the self-report Childhood Trauma Questionnaire (CTQ) (28 item).

Traumatic stress and cue response task

The Cue and Stress Response Task will be performed at the 4- week time-point using methodology developed in Rajita Sinha's lab, similar to those in used in past studies with alcohol dependent patients [84]. Dr. Sinha will provide consultation on the implementation of these methods. Briefly, imagery scripts will be developed at baseline. Traumatic stress imagery scripts will be based on a recent highly stressful traumatic situation the participant has experienced unrelated to alcohol use. Alcohol cue scripts will be derived from a recent event that included alcohol-related stimuli and led to alcohol use. Neutral or relaxing scripts will also be developed. All scripts will be developed by obtaining specific details of stimulus and response, including contextual details, cognitive and verbal content, affective experience, and bodily sensations. These details form the basis of a 5-minute imagery script, which will be developed for each of the three conditions. Imagery sessions will be structured with a 5-minute pre-imagery period, a 5-minute imagery period, and a 5-minute recovery period. Pulse, skin conductance, heart rate variability, and blood pressure will be monitored during each imagery session with an ADInstruments PowerLab 4/30 Galvanic Skin Response device and a Contec Patient Monitor. In Human laboratory studies with CBD, skin conductance and amygdala activation were reduced by CBD in a closely correlated manner [52], suggesting threat-related sympathetic arousal may serve as a proxy for amygdala activation [53].

Participants will complete Likert scale ratings of vividness, craving, anxiety, and the 30-item Differential Emotion Scale [84] following each of the three periods. After each condition, a progressive relaxation procedure will be implemented to facilitate return to baseline of vital signs, craving and anxiety, an approximate period of 10 minutes, as shown in previous research from the Sinha lab [84]. The entire imagery protocol will take 120 minutes. The order of the sessions will be randomized and counterbalanced among participants. The task will be completed at T6 (the end of 4 weeks of treatment with 600mg daily). At this point, we expect steady-state plasma CBD levels to have been reached.

Plasma CBD, THC and anandamide levels

Measurement of circulating levels of CBD, THC, Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC will be obtained from CBD-treated participants at baseline (pre-CBD levels), following 45 minutes (T1-

45min post-CBD levels), 1 day (T2- 45min post-CBD levels), 1 week (T3- 45min post-CBD and pre-CBD levels), 2 weeks (T4- 45min post-CBD and pre-CBD levels), 4 weeks (T6- 45min post-CBD and pre-CBD levels),6 weeks (T8- 45min post-CBD and pre-CBD levels), and 7 weeks (T9- pre-CBD levels) after the first CBD vs. placebo dose. Anandamide levels will be obtained from both CBD- and placebo-treated participants at the aforementioned timepoints. All three levels (CBD, THC and anandamide) will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) by the Nathan Kline Institute.

Psychomotor and subjective effects of CBD

Basic motoric and cognitive function will be evaluated throughout treatment with several established field sobriety tests, including a walk-and-turn task, one-leg stand, Romberg's test, finger-finger test, and counting backwards [85]. The Addiction Resource Center Inventory (ARCI), 49-item version [86], will be used as a measure of the intoxicating effects and abuse potential of CBD. Breath Alcohol Concentration (BAC) will also be measured to ensure participants are not under the influence of alcohol during administration of these tasks.

Cognitive Function

Several established neuropsychiatric and cognitive tasks will be administered to evaluate the impact of CBD vs. placebo treatment on cognitive domains potentially affected by CBD and/or THC. The Rey Auditory Verbal Learning Task (RAVLT) will be used to assess episodic memory [87], the Mental Rotation Task (MRT) will evaluate visuospatial ability [88, 89], a Time Reproduction Task (TRT) will measure encoding and retrieval of time intervals [67] and several WM Span tasks (OSpan, RSpan, SymSpan, RotSpan) will measure working memory capacity [90, 91]. Cognitive function will be measured at day 1 (T2) and at the end of treatment (T8).

3 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Males and females age 18-70
2. DSM-5 diagnosis of moderate or severe AUD
3. DSM-5 diagnosis of PTSD with Clinician Administered PTSD Scale (CAPS-5) OR subPTSD diagnosis (meeting criterion A, F, G, H and at least 6 symptoms across any criteria B-E) with Clinician Administered PTSD Scale (CAPS-5)
4. Able to provide voluntary informed consent
5. At least 4 heavy drinking days (4 or more drinks per day for a woman, 5 or more drinks per day for a man) in the 30 days prior to screen
6. If of childbearing potential (male or female), are willing to use approved form of contraception from screening for duration of the trial
7. Able to provide at least two locators
8. Endorse desire to cut down or stop drinking
9. Agrees to abstain from all other cannabinoid use for the duration of the study
10. Confirms they are reliably domiciled

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current alcohol withdrawal (CIWA-Ar score >7)
2. Exclusionary medical conditions (e.g. current severe alcohol withdrawal requiring medical hospitalization, significantly impaired liver function)
3. DSM-5 diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder I
4. High risk of adverse emotional or behavioral reaction, and/or an inability to understand study procedures or the informed consent process, based on investigator's clinical evaluation (e.g., evidence of serious personality disorder, antisocial behavior, serious current stressors, lack of meaningful social support)
5. Exposure to trauma in the last 30 days, including police duty or military service
6. Current significant suicidality (assessed using the C-SSRS), any significant suicidal behavior in the past 12 months, or any history of serious suicide attempts requiring hospitalization, or current significant homicidality
7. History of Severe Traumatic Brain Injury (TBI; as indicated by Loss of Consciousness > 24 hours)
8. DSM-5 diagnosis of current mild cannabis use disorder and/or moderate or severe substance use disorder for a substance other than alcohol or nicotine

9. Significant laboratory abnormalities, including significantly impaired liver function, serious abnormalities of complete blood count or metabolic panel
10. Active legal problems likely to result in incarceration within 12 weeks of treatment initiation
11. Pregnancy or lactation
12. Current use of exclusionary medications, including cannabinoids; treatments for addictions including alcohol; moderate to strong inhibitors of CYP3A4 or CYP2C19; medications metabolized primarily by CYP3A5 or CYP3A7; and medications with a narrow therapeutic index which are substrates of CYP3A4, UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19, CYP1A2, or CYP2B6.
13. Current treatment for AUD (with exceptions of: AA/12-step treatment and/or psychosocial treatment initiated more than 2 months prior to the screening visit)
14. Current treatment for methadone or opioid abuse
15. Psychotherapy for PTSD or other psychiatric condition, if initiated within 2 months of screening
16. Inpatient psychiatric treatment in the last 12 months, with the exception of detox and extended Emergency Department stays
17. A positive urine drug screen for opioids at screen, baseline, or any later visits. If a participant has a positive drug screen for THC or cocaine at screen, baseline or a later visit- their enrollment will be subject to the clinical judgement of the Principal Investigator. Please refer to the Medical and Psychiatric Safety SOP for further details.

5.3 Vulnerable populations

This study will not enroll any vulnerable populations. As per the exclusion criteria, all enrolled participants will have the capacity to consent. Capacity will be determined by MD or PhD qualified research staff as per the legally specified criteria for determination of decision making capacity, assessed by verbal responses from the participant.

5.4 Strategies for Recruitment and Retention

Subjects will be approximately 48 women and men, age 18-70, with moderate to severe AUD and PTSD or subthreshold PTSD, recruited from the public through local media advertisements. Participants will be recruited between approximately November 2018 and August 2021.

48 men and women with moderate to severe AUD and comorbid PTSD or subthreshold PTSD will be recruited from the community and from local clinical programs. We will initiate contact with subjects through multimodal outreach including contacts with treating clinicians in medical and psychiatric clinics at the Cohen Veteran Center (600 recruited annually) and Military Family Clinic at NYUMC (500 enrolled annually); Manhattan VA, Bronx, Manhattan and Brooklyn VA PTSD clinics and other VA medical centers within the greater New York City area (over 1300 with PTSD and comorbid AUD); Women's Mental Health Consortium of NY, Derner Institute at Adelphi University; addiction services sites, including the detox unit and Chemical Dependency Outpatient Program at Bellevue (11,400 visits annually, combined), Psychiatry Outpatient Clinic and Primary Care Clinic at Bellevue hospital, addiction services at the Manhattan and Brooklyn VA, and at the Federally Qualified Health Center (FQHC), an outpatient psychiatry clinic at NYU Lutheran Medical Center (115,000 visits annually). Additionally, patients will be recruited at the Nathan Kline Institute/Rockland Psychiatric Center and Gouverneur Health. Fliers and brochures will be distributed by clinicians to potentially interested participants.

Clinicians will be asked to only refer individuals who they believe are appropriate for the study, can safely delay treatment for 24 hours and who are capable of deciding to participate. At the time of referral, clinicians will provide study staff with names, contact information, and relevant clinical information for interested patients, who will sign an authorization form allowing the clinic to release their relevant information to study staff. Once referrals are given, the study team will access EPIC to determine the participant's initial eligibility. Dr. Marmar and the study coordinators will maintain relationships with clinicians at these institutions in order to generate referrals. Additionally, the study team will use NYU's DataCore service to gather information from EPIC for current NYU patients who may be eligible. Participants can be referred to the study by their physician, the clinic, or through DataCore reports. To gather the information from EPIC, DataCore will request a report. Data gathered will be used to identify subjects that did not opt out of being contacted for research, and who fit eligibility criteria for this study. The data gathered will include inclusionary and exclusionary criteria, including the following information:

Inclusion Criteria:
-18-70 years old
WITH diagnosis of PTSD (Post Traumatic Stress Disorder) OR Acute Stress Disorder OR Adjustment Disorder AND Alcoholism OR Alcohol Use Disorder OR Alcohol Abuse WITHOUT a diagnosis of Schizophrenia OR

DataCore will request this information from EPIC monthly. Once a patient has been deemed potentially eligible for the study, and is also noted in EPIC as having consented to be contacted for research, approved staff will e-mail potential participants' treating physicians following scheduling the patient for their assessment visit. Approved staff will contact potential participants identified through EPIC by either email, MyChart, or by phone. Due to sharing the same recruitment resources, the phone consent and screen will be identical to those used in Dr. Charles Marmar's study, s18-01405. Any recruitment information sent by email will use Send Safe email (or will be done through MyChart). Once contact is made, approved recruitment language will be used to communicate the reason for contact and potential participants will be asked if they are interested in participating in this specific study. If the potential participants agree, the study team will provide with information regarding the next steps for participation. If a participant requests information regarding opting out of further recruitment for all research, they will be directed to contact our team.

Active recruitment will also take place through social media sources, including Facebook, Twitter, Instagram, Reddit, Craigslist, clinical trial pre-screening services like StudyKik, Patient Wise, BuildClinical, and TrialFacts, online research recruitment sites such as ResearchMatch, VolunteerMatch ClinicalConnection, Antidote, and TrialSpark, online forums, local newspapers and other print media (i.e. Bushwick Daily, Queens Chronicle, New York Post, Schneps Media etc.), online periodicals such as Time Out Magazine, Military Times and Schneps media, radio advertisements within New York City, online targeted advertisement services from companies such as the Washington Post, email newsletters such as Division of Veteran Services, through academic email listservs (including Child and Adolescent Mental Health Studies [CAMS] listserv), at social service agencies, community mental health clinics, community organizations, local professional organizations, residential treatment facilities, consenting support and recovery centers, regional employee assistance programs, religious organizations, cultural centers, social clubs, local shops, and local universities. Fliers and brochures will be distributed by clinicians to potentially interested participants. Additionally, the study team will use NYU's DataCore service to gather information from EPIC for current NYU patients who may be eligible.

TrialFacts: TrialFacts is a referral service that targets advertisements to individuals who may be eligible for the study. Participants are provided with detailed information about the study and then complete a brief IRB-approved questionnaire. Participants who complete the questionnaire have consented to collection of their responses to the questionnaire, including their contact information, as well as TrialFacts' sharing their information with the study team. Trialfacts provides the study team with the respondents' questionnaire responses and contact information (name, phone number, email, state, zip code, gender, and DOB) if they meet minimum eligibility requirements via a restricted access spreadsheet. If not eligible, TrialFacts releases the questionnaire responses but not the respondents' contact information. The study team may request ineligible respondents' contact information from TrialFacts to double-check on responses on an as needed basis.

Eligible, participants are invited to book an appointment for the phone screen using the TrialFacts online platform. If they do not book an appointment, the study team reaches out to the participant to schedule. If the participant chooses to book online, they are sent a calendar invitation and a confirmation email.With an online booking, TrialFacts sends the participant email reminders 24 hours and 1 hour before their phone screen appointment, and text message reminders 1 hour and 10 minutes before the phone screen appointment.

After the study team completes the phone screen, the restricted access spreadsheet is updated with participant's enrollment status and/or reason for exclusion in order to help TrialFacts better target audiences. The study team only indicates whether the participants was enrolled or not enrolled and which of the exclusion criteria were met. The reasons for exclusion on the spreadsheet are limited to: not enough drinking days; current life stressors; exclusionary medication; exclusionary medical condition; exclusionary psychiatric disorder; exclusionary treatment; drug use; no PTSD; age; scheduling; new treatment; unwilling to use contraceptives; recent trauma; behavioral concerns; and legal issues. No identifiers or health information are added to the spreadsheet.

Potential participants can either call the study line directly to speak with research staff or they can follow the link to a study screening questionnaire located at the bottom of the flyers and ads. The link re-directs to a secure, RedCap survey. Potential participants will indicate that they consent to complete the survey electronically before completing the questionnaire. Staff will contact respondents who meet minimum eligibility criteria via phone, email, and/or text message. Respondents will indicate their preferred method of contact on the RedCap survey.

BuildClinical: BuildClinical is an advertising and referral service that targets advertisements to individuals

who may be eligible for the study. Study advertisements will be developed, IRB approved, and then optimally deployed across web platforms to target and engage the study population via the BuildClinical patient advertising network. Individuals who click on a BuildClinical ad will be redirected to a brief IRB approved REDCap questionnaire. BuildClinical provides the study team with the respondents' questionnaire responses and contact information (name, phone number, email, and state) if they meet minimum eligibility requirements via a HIPAA compliant internet portal. The internet portal is a one-way transfer of information from BuildClinical to the study team. The study team will not share any additional information with BuildClinical. All BuildClinical ads will be submitted to the IRB for approval prior to use.

All potential participants will be asked to complete a brief pre-screening interview either in person or by telephone, using an IRB approved, and scripted pre-screening form describing the basic facts of the study and inquiring about inclusion and exclusion criteria. (See request for waiver of authorization and waiver of documentation of consent). Study staff conducting the screening may ask follow-up questions or use the Timeline Followback tool to clarify responses and assess eligibility. An abridged version of the LEC (Life Events Checklist) will be completed during the pre-screening interview. Participants who pass the pre-screening interview (i.e., those who appear likely to qualify for the study and remain interested in participating) will be scheduled for a screening visit.

Individuals that do not pass the pre-screening or decline to enroll in the study will be asked whether they would like their information retained so they can be contacted for future research purposes. Participants may also opt-in to being re-contacted for the current study if their PTSD and/or AUD symptoms are near the inclusion threshold. If they decline, all information collected will be de-identified and all PHI information will be destroyed at the end of the study. The study team will have no linking information for those who fail the pre-screen or decline participation. If they assent to re-contact, PHI data collected on the initial screening form will be retained only for and shared with NYU-affiliated researchers strictly for the purpose of re-contacting for future research opportunities.

Participants in Dr. Marmar's clinical trial "Leveraging Biomarkers for Personalized Treatment of AUD Comorbid with PTSD" (IRB # s18-01405) who are determined to be ineligible will be evaluated for eligibility in this trial. Consenting participants' data will be linked to this study and procedures completed under the Biomarkers trial will not be duplicated for this trial except at PI or co-Investigator discretion.

Based on successful recruitment in current and past AUD and PTSD trials at NYULMC, we do not expect any significant barriers to recruitment. If recruitment lags, strategies would include altering staffing patterns and increasing advertisement and outreach to clinical programs. To maximize rates of completion of the follow-up visit, we will follow procedures that have been successful in retaining patients with similar demographics, e.g. drug using emergency department patients, for whom we have achieved follow-up rates of 85% at 6 months. If follow-up rates at 10 weeks are below 90%, we will reexamine our tracking procedures, and consider altering the reimbursement and/or completing community-based follow-ups.

We expect the population to be approximately 50% male, 50% female; 7% Hispanic, 60% Non-Hispanic Caucasian, 30% Non-Hispanic African American, and 3% other.

5.5 Duration of Study Participation

Including screening and follow-up visits, the total duration of participant involvement will be approximately 9 weeks. Total time of contact during these 9 weeks is estimated at 30-35 hrs.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 150 participants are enrolled. It is expected that approximately 48 participants who fully meet study criteria will be randomized in a 5:3 ratio to receive either 600mg CBD/day (PO) or placebo respectively (N=30 participants on CBD and N=18 participants on placebo).

5.7 Participant Withdrawal or Termination

5.7.1 **Reasons for Withdrawal or Termination**

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant fails to adhere to protocol requirements

5.7.2 Handling of Participant Withdrawals or Termination

Every effort will be made to undertake the protocol-specified safety follow-up procedures to capture AEs, SAEs, and UPs. The investigator will attempt to obtain at a minimum safety/survival data on all participants lost to follow-up. If a participant is lost to follow-up, they study team will attempt to contact the participant up to 15 times by telephone, email, or text message. If the participant fails to respond, locators identified by the participant at screening will be contacted up to three times in the method specified by the participant. If participants withdraw, are terminated, or are lost to follow-up prior to the end of the 6-week treatment phase (prior to T8), they will not be replaced to maintain 48 randomized participants to complete the 6-week treatment phase (through T8) and their partial data will be handled according to the statistical analysis plan (SAP).

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Marmar, NIH/NIAAA, the FDA, the DEA, and the NY State BNE. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

The TN-C200M2 Oral Capsules and matching placebo for this study are provided by TilrayTM. The CBD is derived from cannabis and processed according to CGMP standards (see Quality Overall Summary document provided by Tilray). The active capsules will include CBD (the active ingredient) at a quantity of 200mg per capsule, as well as a mix of surfactants, co-surfactants, co-solvents and carrier oils. The placebo capsules will only include the same excipients, with no CBD.

6.1.1 Acquisition

The investigational product, CBD, will be imported from Tilray, which is located at 1100 Maughan Road, Nanaimo, British Columbia, Canada V9X 1J2. The IND & DEA schedule I researcher, Michael P. Bogenschutz, MD, will acquire a New York State Bureau of Narcotic Enforcement Class 9 license to import controlled substances as well as a DEA Schedule I import permit. Tilray will then obtain a DEA export permit that will allow them to ship CBD to Michael P. Bogenschutz, MD. Once all permits and licensure is in place, Michael P. Bogenschutz will send a DEA 222 form to Tilray requesting the shipment of the investigational product. All shipping, importation and exportation of the investigational product will occur in line with local, state and federal regulations.

6.1.2 Formulation, Appearance, Packaging and Labeling

The drug product to be used in this study (TN-C200LM Oral Capsule) is a formulation of CBD dissolved in a mix of surfactants, co-surfactants, co-solvents and carrier oils at a concentration of 400mg/g. The formulation is designed to act as a self-emulsifying drug delivery system (SEDDS). Hard gelatin size-zero capsules are filled with the formulation to a fill weight of 500mg, providing a single capsule dose of 200mg CBD. This product in investigational and will be acquired as described above in 6.1.1. The TN-C200M2 Oral capsules are packaged in pharmaceutical grade 100mL polyethylene terephthalate (PET) bottles and lid, with a fill of 20 capsules.

6.1.3 Product Storage and Stability

The study drug, CBD, will be stored securely by study personnel under the PI's individual schedule 1 DEA registration and New York Bureau of Narcotics Enforcement (BNE) class 7 license in accordance with all applicable laws and regulations. Additionally, a NYS BNE class 9 importer license and a DEA importer permit will be obtained prior to importation of study drug and study initiation. CBD will be stored in a double-locked refrigerator. The refrigerator is located in a designated research room with limited access to the PI and study staff only, within the NYU-HHC CTSI Facility, which is located at 462 1st Avenue, 27th Street, C-D Building 4th floor, New York, NY 10016. The drug is to be stored between 2-8 degrees Celsius. It is recommended that the investigational product be reassayed at 9-months. The Principal Investigator will oversee the appropriate storage, accountability and dispensing of the study medication and all study drug administration to the patients will be done by the PI or treating co-investigators.

Tilray™ has provided stability data for RSM-CBD Lots P56/8/116, P56/8/116, p56/17/017 and P56/44/057 at 4, 25 and 40 degrees Celsius. 12-months data has been generated on the first two batches and 9-months data has been generated on the second two batches. There is no evidence of degradation for any of the samples stored at 4, 25 and 40 degrees Celsius after 9-months. Additional and detailed stability data can be found in the accompanying Quality Overall Summary (QOS) document.

6.1.4 Preparation

Because the investigational product is going to be shipped and received in its ready-for-dispensation formulation, there will not be any preparation required prior to dispensation. The study drug will be dispensed by qualified study personnel.

6.1.5 Dosing and Administration

Participants will self-administer CBD vs Placebo twice daily for a total of 600mg/day CBD vs. Placebo for six-weeks. Participants will self-administer two 200mg capsules every morning following a light meal at approximately the same time of day, and an additional single 200mg capsule approximately 12 hours later following a light meal.

6.1.6 Route of Administration

CBD will be administered orally in capsules that each contain 200mg CBD vs. Placebo.

6.1.7 Starting Dose and Dose Escalation Schedule

All participants will receive 600mg/day CBD vs. Placebo for weeks 1-6 of treatment (T1-T8), unless contraindicated.

6.1.8 Dose Adjustments/Modifications/Delays

If participants report AEs that are determined by the PI to be treatment-related during administration of study medication and are intolerable to the participant or represent a significant risk to the participant, daily administration will be reduced by 200mg/day every two days until symptoms are tolerable or clinical abnormalities are resolved. For self-described symptoms, tolerability will be determined by a joint decision between the PI and the participant, based upon of whether this symptom is tolerable or treatment related. For laboratory abnormalities, all values outside of the normal range will be regarded as presenting a risk, as evaluated by the PI. All reported AEs will be recorded. Dose will be titrated back up toward the full dose by 200 mg/day/week as tolerated, based upon a repeat assessment by the PI, including laboratory tests.

Individuals who cannot tolerate the 600mg dose will remain on their maximum tolerable dose for the remainder of the study. Treatment will be discontinued immediately if continuing the medication places the participant at significant risk in the medical judgement of the PI.

6.1.9 Duration of Therapy

The duration of the active treatment portion of the study is 6 weeks, followed by an additional 3-week follow-up period. In order for participants to be included in the primary statistical analyses, they must complete the 6-week treatment phase of the study (through to T8).

6.2 Study Agent Accountability Procedures

CBD will be stored by the study personnel securely under the PI's individual schedule 1 DEA registration and New York Bureau of Narcotics Enforcement (BNE) class 7 license in accordance with all applicable laws and

regulations. Additionally, a NYS BNE class 9 importer license and a DEA importer permit will be obtained by the schedule I license and registration holder prior to importation of study drug and study initiation. CBD will be stored in a double-locked refrigerator. The refrigerator is located in a designated research room, with limited access to the PI and study staff only, within the NYU-HHC CTSI Facility, which is located at 462 1st Avenue, 27th Street, C-D Building 4th floor, New York, NY 10016. The Primary Investigator will oversee the appropriate storage, accountability and dispensing of the study medication and all study drug administration to the patients will be done by the PI or treating co-investigators. In order to preserve the blind, medication will be administered in identical capsules containing 0 or 200 mg of CBD dissolved in a mixture of self-emulsifying excipients; participants will be delivered multiple 200mg capsules/day for a total of 0 or600 mg CBD/day.

Study medication will be received under a Schedule 1 import license obtained by the PI and will be logged into the approved storage facility upon arrival. Study medication will be re-packaged by unblinded study personnel from the original Tilray bottles into blinded and appropriately labeled bottles for dispensation. The re-bottled, blinded study medication will then be dispensed to participants under the direct supervision of the PI or a designated coinvestigator, as approved by the BNE and DEA. Participants will be required to return all un-used medication, which will be kept securely at the drug storage site until it is sent to a reverse distributor for destruction.

Designated study personnel will keep a log of the study drug accountability and dispensing in accordance with New York State Bureau of Narcotic Enforcement and DEA policies (see below). This process will provide strict safeguarding and accounting of the agent both for internal and external regulatory agencies.

As per Schedule I drug compliance, a biennial inventory shall be prepared and maintained in accordance with New York State and federal statutes. A copy of the inventory will be kept on file with other controlled substance records and shall be kept available for inspection for at least 5 years. The number of study drug-containing capsules will be checked on a weekly basis by two designated study staff members and it will be recorded on a Controlled Substance Accountability Log which includes the following information: 1) date and time of recording, 2) name of controlled substance, 3) amount received (number of capsules), 4) amount dispensed, and 5) amount returned. All other information will be included in the Study Drug Dispensation Log as each individual subject's dose is dispensed. The information included in the Study Drug Dispensation Log is: 1) subject initials/number (plus date of birth as a double identifier), 2) date and time of study drug dispensation, 3) drug name, 4) lot number, and 5) dose. Two designated study team members will sign the Study Drug Dispensation Log. The balance of the remaining medication and any amount returned will be recorded in the Controlled Substance Accountability Log (see above).

6.3 Study Behavioral or Social Intervention(s)

All participants will receive Medical Management by a licensed MD or NP, based on the model developed for the NIAAA COMBINE trial [92]. This model provides a low intensity intervention that has some efficacy over no intervention, and is designed to enhance compliance in the context of a clinical trial. Brief counselling sessions provided by a licensed MD or NP focus on: support for recovery, treatment participation, reporting possible adverse effects, and medication compliance. The co-investigator Dr. Bogenschutz has experience adapting this model in a prior alcohol pharmacotherapy trial [93].

6.3.1 **Administration of Intervention**

CBD (or placebo) will be administered daily for 6 weeks. The first administration of CBD vs. placebo (at T1) will take place at the study site. Participants will remain at the study site with a study team member for approximately 2 hours following the initial administration of each dose of CBD, and participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test (a walk-and-turn task, one-leg stand, Romberg's test, finger-finger test, and counting backwards [85]). If there are no AEs during this time-period or lasting intoxicating effects of the study drug (i.e. participants are able to pass field sobriety tests 2-3 hours after study drug administration), participants will be given a 1- or 2-week supply of the study drug (CBD or placebo) to self-administer daily at home until the next scheduled study visit.

6.3.2 **Assessment of Subject Compliance with Study Intervention**

To maximize medication compliance, we will implement an optional smartphone-assisted medication adherence platform [94] in which the subject takes a video of drug administration at each dose, and transmits this to study personnel. This program has been used successfully in previous studies and includes security provisions that ensure protection of confidentiality and privacy. If the participant is unable to use the smartphone-assisted platform then medication adherence will be ensured using pill counting and meeting with the study nurse practitioner at each visit.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Inclusion/exclusion criteria:
Medical screening by an NP or MD will include medical history and physical exam, liver function tests, complete blood count, urinalysis, menstrual calendar (if female except those menopausal for >1 year since last menstrual period and/or had a bilateral oophorectomy), pregnancy test (if female except those menopausal for >1 year since last menstrual period, had a hysterectomy, and/or had tubal ligation), and vital signs for safety. The licensed provider (NP or MD) will also review participants' controlled substance prescription history using the online Prescription Monitoring Program (PMP) Registry to inform study eligibility. The Structured Clinical Interview for DSM-5 (SCID) will be used to determine substance use disorder diagnoses and exclusionary psychiatric disorders {First, 1997 #114}. The Life Events Checklist (LEC) and Clinician Administered PTSD Scale (CAPS) for DSM 5 will be used to assess PTSD symptoms [101]. The Concussion Symptom Inventory (CSI) and a modified version of the Ohio State University TBI Identification Method (TBI OHIO) will be used to assess for Traumatic Brain Injury (TBI). The clinical interviews will be conducted by SCID and CAPS trained study clinicians, masters-level study team members and bachelors-level study team members with sufficient psych-assessment training as approved by the study PI. Individuals will have the option to be audiotaped during the screening interview. If the participant consents, audio recordings will be used to ensure quality control and clinical adherence to the protocol. Audio recordings will also be used for voice-marker analysis. If a participant voices that he/she is uncomfortable with the audiotaped interview, he/she can tell a study team member that he/she does not wish to participate in this component of the study. In that case, the participant could still participate in the study but would not complete the audiotaped interview.

PhenX Tier 1 measures and a Locator form will be completed at screening to collect contact information, demographics, BMI, quality of life, HIV risk and status, and substance use measures (age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco, and other substances; www.phenxtoolkit.org). The Clinical Institute Withdrawal Scale- Alcohol, revised (CIWA-Ar) will be used to verify lack of alcohol withdrawal [95], a urine drug screen (UDS) will be done at every in-person study visit (except for visits less than 24 hours from the last visit; i.e. 1 day visit) to verify lack of recent cannabinoid and other drug use, and a urine pregnancy test will be done at each in-person study visit (for women of childbearing potential: if female except those menopausal for >1 year since last menstrual period, had a hysterectomy, and/or had tubal ligation) to verify lack of pregnancy. If subjects are found to have suicidal intentions based on screening tests, appropriate referrals to mental health professionals will be made by the PI.

7.1.1 **Confirmation of target CBD plasma levels and measurement of THC levels:**
Circulating levels of CBD, THC and THC metabolites (Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC) will be obtained from CBD-treated participants baseline (pre-CBD levels), following 45 minutes (T1- 45min post-CBD levels), 1 day (T2- 45min post-CBD levels), 1 week (T3- 45min post-CBD and pre-CBD levels), 2 weeks (T4- 45min post-CBD and pre-CBD levels), 4 weeks (T6- 45min post-CBD and pre-CBD levels),6 weeks (T8- 45min post-CBD and pre-CBD levels), and 7 weeks (T9- pre-CBD levels) after the first CBD vs. placebo dose. All of these levels (CBD, THC and THC metabolites) will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) at Dr. Thomas Neubert's Lab at the Department of Cell Biology at NYU Langone Health..

7.1.2 **Measurement of plasma Anandamide levels:**
Plasma AEA levels will be obtained at baseline (pre-CBD levels), following 45 minutes (T1- 45min post-CBD levels), 1 day (T2- 45min post-CBD levels), 1 week (T3- 45min post-CBD and pre-CBD levels), 2 weeks (T4- 45min post-CBD and pre-CBD levels), 4 weeks (T6- 45min post-CBD and pre-CBD levels),6 weeks (T8- 45min post-CBD and pre-CBD levels), and 7 weeks (T9- pre-CBD levels) after the first CBD vs. placebo dose. Plasma AEA levels will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS)at Dr. Thomas Neubert's Lab at the Department of Cell Biology at NYU Langone Health .

7.1.3 **Safety:**

Safety will be assessed by collection of adverse events using the Systemic Assessment for Treatment of Emergent Events (SAFTEE) [103] measure at all visits after treatment is initiated. LFTs will be obtained at screening, as well as weeks 2, 6 and 7 to assess the liver function during and after treatment with study medication. Risk of suicidality will be assessed by a licensed MD, NP, Psychologist, or C-SSRS certified study team member using the Columbia-Suicide Severity Rating Scale (C-SSRS) [98] as part of each study visit, including screening and baseline. If the patient endorses significant suicidality/homicidality, a safety assessment will be conducted, referrals provided, and if indicated, a case report form will be written if indicated, a follow-up phone call within 48 business hours of providing referrals will be completed. If and when appropriate, the clinicians will then contact the overall study PI (Charles Marmar, MD) for further consultation. The appropriate procedures for all study team members to follow in the case of a psychiatric or medical emergency are outlined in detail in the Medical and Psychiatric Emergencies SOP.

7.1.4 **Psychomotor and subjective effects of CBD:**

Basic motoric and cognitive function will be evaluated throughout treatment with several established field sobriety tests, including a walk-and-turn task, one-leg stand, Romberg's test, finger-finger test, and counting backwards [85]. The Addiction Resource Center Inventory (ARCI), 49-item version [86], will be used as a measure of the intoxicating effects and abuse potential of CBD. Breath Alcohol Concentration (BAC) will also be measured to ensure participants are not under the influence of alcohol during administration of these tasks.

7.1.5 **Cognitive Function:**

Several established neuropsychiatric and cognitive tasks will be administered to evaluate the impact of CBD vs. placebo treatment on cognitive domains potentially affected by CBD and/or THC. The Rey Auditory Verbal Learning Task (RAVLT) will be used to assess episodic memory [87], the Mental Rotation Task (MRT) will evaluate visuospatial ability [88] [89], a Time Reproduction Task (TRT) will measure encoding and retrieval of time intervals [67] and several WM Span tasks (OSpan, RSpan, SymSpan, RotSpan) will measure working memory capacity [90, 91]. Cognitive function will be assessed one day after CBD or placebo treatment and at 6 weeks following treatment.

7.1.6 **AUD-related measures:**

The Penn Alcohol Craving Scale (PACS) [79] will be used to assess craving. This scale has 5 Likert-scaled items with excellent internal consistency and evidence of predictive, construct, and discriminant validity. Craving will be assessed before CBD or placebo treatment (baseline), at weeks 1, 4 and 6 of treatment, and one week after the completion of treatment (week 7). Mood and Anxiety will be measured with the Beck Anxiety Inventory (BAI) [99] and Beck Depression Inventory-II (BDI-II) [100] scales before CBD or placebo treatment (baseline), at weeks 1, 4 and 6 of treatment, and one week after the completion of treatment (week 7). Self-efficacy will be assessed using the Alcohol Abstinence Self-Efficacy Scale (AASE) [81], a self-report questionnaire which has been used widely in the alcohol treatment research, both as a predictor of outcome and as a patient-treatment matching variable [82]. Self-efficacy will be assessed before CBD or placebo treatment (baseline), at weeks 1, 4 and 6 of treatment, and one week after the completion of treatment (week 7).

7.1.7 **PTSD-related measures:**

PTSD symptoms will be assessed with the PTSD checklist for the DSM-5 (PCL-5) [96]. Baseline PTSD symptoms will be defined as the total PCL-5 score at baseline. The primary PTSD outcome is the total score of the PCL-5 for each week administered. PTSD symptoms will be assessed before CBD or placebo treatment (baseline), at weeks 2, 4 and 6 of treatment, and one week after the completion of treatment (week 7).

7.1.8 **Cue and Traumatic Stress Response Task**

The Cue and traumatic stress Response Task will be performed using methodology developed in Rajita Sinha's lab, similar to that in used in past studies with alcohol dependent patients and AUD+PTSD/subthreshold PTSD patients [84].. Imagery scripts will be developed at baseline. Traumatic stress imagery scripts will be based on a recent highly stressful situation that the participant identifies as traumatic. Alcohol cue scripts will be derived from a recent event that included alcohol-related stimuli and led to alcohol use. Neutral or relaxing scripts will also be developed. All scripts will be developed by obtaining specific details of stimulus and response, including contextual details, cognitive and verbal content, affective experience, and bodily sensations. These details form the basis of a 5-minute imagery script, which will be developed for each of the three conditions. Imagery sessions will be structured with a 5-minute pre-imagery period, a 5-minute imagery period, and a 5-minute recovery period. Pulse, skin conductance, heart rate variability, and blood pressure

will be monitored during each imagery session with an ADInstruments PowerLab 4/30 Galvanic Skin Response device and a Contec Patient Monitor. In Human laboratory studies with CBD, skin conductance and amygdala activation were reduced by CBD in a closely correlated manner [52], suggesting threat-related sympathetic arousal may serve as a proxy for amygdala activation [53]. Participants will complete Likert scale ratings of vividness, craving, anxiety, and the 30-item Differential Emotion Scale [84] following each of the three periods. After each condition, a progressive relaxation procedure will be implemented to facilitate return to baseline of vital signs, craving and anxiety, an approximate period of 10 minutes, as shown in previous research from the Sinha lab [97]. The entire imagery protocol will take 120 minutes. The order of the sessions will be randomized and counterbalanced among participants. The task will be administered at T6, following 4 weeks of treatment with CBD or placebo. At this point, we expect steady- state plasma CBD levels to have been reached.

7.1.9 **Alcohol use:**

Alcohol consumption will be assessed with a constellation of measures from Time-line Follow-back (TLFB) [78], percent carbohydrate-deficient transferrin (CDT), and breath alcohol concentration (BAC).

7.2 Laboratory and Voice-markers Procedures/Evaluations

Plasma will be collected at baseline before treatment, and 45 minutes, 1 day, 1 week, 2 weeks, 4 weeks 6 weeks, and 7 weeks after the first dose of treatment with CBD or placebo. CBD, THC and THC metabolite levels will be obtained from the CBD group only. Anandamide levels will be obtained from both the CBD and placebo groups. Serum will be collected at baseline, at 4 weeks, and at 6 weeks for measurement of CDT.

7.2.1 **Specimen Preparation, Handling, and Storage**

Blood will be drawn at several time points to establish 45 minutes post- and pre-dosing levels of CBD, according to the study's SOP. Briefly, we will measure plasma CBD, THC and THC metabolite levels at baseline, 45 minutes, 1 day, 1 week, 2 weeks, 4 weeks, 6 weeks, and 7 weeks after treatment with CBD. Plasma (1ml/sample) will be stored at -20 °C for no longer than 6 months, and will be labeled with study number, participant number, and timepoint as specified in the MOP. Plasma CBD levels will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) by collaborators at Dr. Thomas Neubert Lab at the Department of Cell Biology at NYU Langone Health.

7.2.2 **Specimen Shipment**

Specimens will be shipped monthly on dry ice with appropriate labeling for shipment of biological specimens on dry ice, according to the study's MOP. Medical screening labs will be labelled according to CTSI protocols and processed by LabCorp. Plasma for anandamide, CBD, THC and THC metabolite testing will be sent to Dr. Neubert laboratory at the Department of Cell Biology at NYU Langone Health. A specimen tracking log will be utilized to record dates and times that each specimen was collected and shipped. Specimens may be shipped overnight or walked to Dr. Neubert lab between 9:00am and 5:00pm on business days .

7.2.3 **Voicemarkers Procedure**

Voice-markers: Clinical interviews (in-person and remote) will be audio and/or video-taped to ensure quality control and clinical adherence. De-identified audio recordings of participants who consent to participate in the voice-markers analysis will be encrypted and sent via secure sites to HIPAA compliant labs for analysis.

7.2.4 **Data Storage and Sharing of Voice-markers Data**

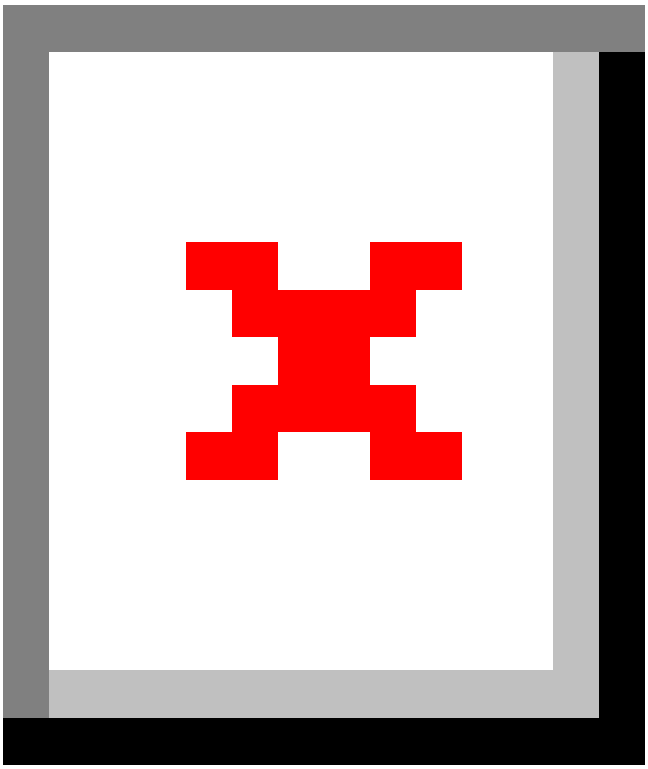
Only the investigator and authorized study personnel will have access to the digital audio recordings to ensure quality control, clinical adherence during calibration and to study voice-markers. Under no circumstances will any unauthorized personnel listen to or view the tapes without the written permission of the participant.

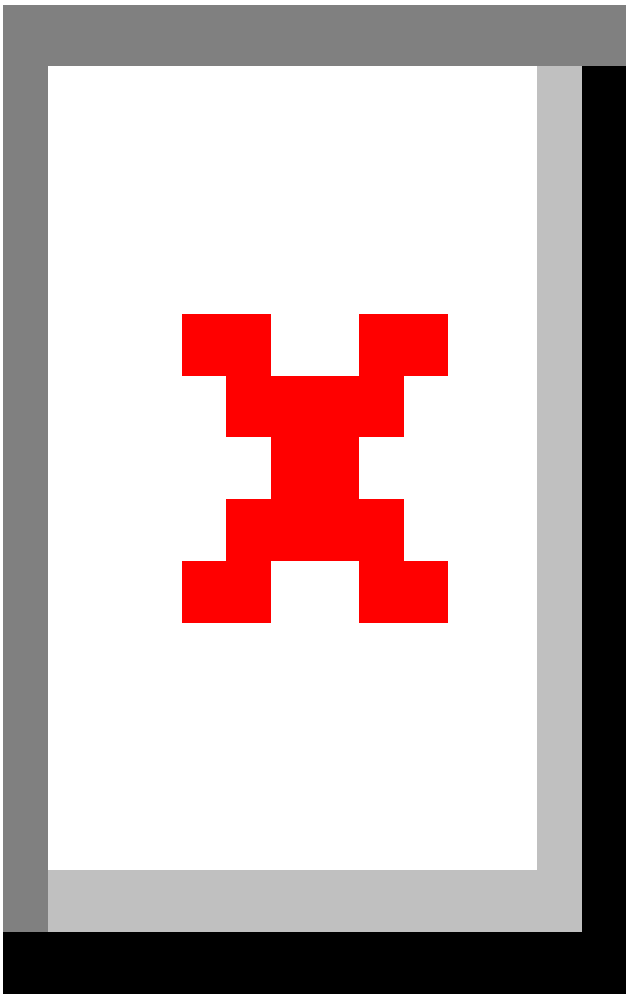
The study team will collect speech data from audio recordings collected from the clinical interview at the screening visit. The digital audio recordings will then be transferred for analysis via encrypted CDs or secure NYU sites and stored on secure servers. All the recordings will be de-identified and labeled with a unique study code number for each participant in the study. The study team will identify a professional, specialized entity to conduct the voice-markers analysis; any authorized entity will only receive de-identified data without any PHI or linking information and will store the data on secure servers.

No individual identities will be used in any reports or publications resulting from the study. Study information, such as the digital audio recordings will be coded with a code number unique to the study. Only authorized

NYUMC study personnel, with the permission of the principal investigator, will have access to the files that links the identifying information and study ID codes. Digital audio recordings of interviews will be encrypted and pass-code protected while retained on a secure NYU server until the conclusion of the study; at that point they will be deleted. Only the investigator and study personnel will have access to the digital audio recordings in order to compare the ratings on the standardized interview format. Sessions will be recorded digitally. All files will be secured using a digital encryption key. No unauthorized persons will be able to access this key to open the audio files. These encrypted audio files will be de-identified , stored and password protected on a secure server. Any identifying information embedded in the audio recordings will be deleted during the transcription process. Any data sharing will follow all the NYU data security requirements. Identifiable data will not be stored on laptops, PDA's, flash drives or other portable devices. De-identified data will be shared via mailed encrypted CDs, encrypted emails, or via a VPN access and secure access to the secure NYU server.

7.3 Study Schedule





7.3.1 **Screening Visit (S1) (2 Options)**

Option 1: Screening Visit – In-Person

- Administer consent quiz (up to 2 administrations) and obtain informed consent of potential participant verified either by signature on written informed consent for screening form or through electronic signature.
- Obtain consent of participant on audio/visual consent form, either by signature on audio/visual consent form or through electronic signature.
- Perform alcohol breathalyzer to obtain BAC
- Review medical and family to determine eligibility based on inclusion/exclusion criteria
- Perform psychiatric assessments to determine eligibility based on inclusion/exclusion criteria
- Audio-record clinical interview (if participant consents to this component) to ensure clinical quality control, and study voice-markers for participants that consent to voice-marker analysis. Audio recordings can be waived per PI discretion.
- Review concurrent medications to determine eligibility based on inclusion/exclusion criteria
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria
- Obtain demographic information, contact information, alcohol, drug, and tobacco use history and quality of life
- Collect urine for urine drug analysis, urinalysis, urine pregnancy test (if applicable)
- Collect blood at either the One Park site or at CTSI for hepatic function panel/liver function tests (LFT), complete blood count with differential, basic metabolic panel, and serum pregnancy test (if female)
- Record vital signs
- Schedule study visits for participants who are eligible and available for the duration of the study

NOTE: The in-person screening visit may be split into two or more sessions to accommodate participants' schedules, provider availability, etc. All portions of the screening visit must be complete within 1 month.

Option 2: Screening Visit – Two-part: Clinical Screen Remote; Medical Screen In-Person

To reduce participant burden and minimize in-person screening visits, we will offer participants the option of splitting the screening visit into two or more sessions. The first session will be completed remotely (phone or WebEx) to establish that minimal inclusion criteria and no exclusion criteria are met. Participants will be invited to a second session, which will be completed in-person, if they meet minimum inclusion/exclusion criteria standards. All portions of the screening visit must be complete within 1 month.

Session 1: Clinical Screen – Remote

- Administer consent quiz (up to 2 administrations) and obtain informed consent of potential participant verified either by signature on written informed consent for screening form or through electronic signature .
- Obtain consent of participant on audio/visual consent form, verified either by signature on audio/visual consent form or through electronic signature.
- Review medical and family history to determine eligibility based on inclusion/exclusion criteria
- Perform psychiatric assessments to determine eligibility based on inclusion/exclusion criteria
- Review concurrent medications to determine eligibility based on inclusion/exclusion criteria
- Obtain demographic information, contact information, alcohol, drug, and tobacco use history and quality of life

Session 2 – In Person

- Perform alcohol breathalyzer to obtain BAC
- Review medical and family history
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria
- Collect urine for urine drug analysis, urinalysis, urine pregnancy test (if applicable)
- Collect blood at either the One Park site or at CTSI for hepatic function panel/ liver function tests (LFT), complete blood count with differential, basic metabolic panel, and serum pregnancy test (if female)
- Assess withdrawal using CIWA-Ar
- Record vital signs
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.3.2 **Enrollment/Baseline (B1) (Day 0, 1-30 days after Screening Visit)**

- Perform alcohol breathalyzer to obtain BAC
- Record vital signs, results of examination, other assessments, concurrent medications and menstrual calendar (if applicable)
- Record AUD-related and PTSD related measures
- Collect imagery scripts for the cue/traumatic stress response task
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- Collect baseline plasma for baseline CBD, THC, and AEA levels (pre-CBD dosing levels)
- Collect blood for carbohydrate deficient transferrin (CDT) test
- Record results of evaluations of safety and psychomotor effects and AUD, PTSD related domains
- Record adverse events as reported by participant or observed by investigator
- Evaluate and record alcohol use
- Administer medical management session
- Provide participants with study medication to administer at visit
- Provide participants with sufficient study medication to administer daily until the next scheduled visit (1 week), and instructions for how to use the study medication and document their use

7.3.3 **Intermediate Visits**

Intermediate visits that do NOT include safety labs may be conducted remotely via phone or WebEx.

7.2.2.1 Visit 3

45 minutes +/- 10 minutes (T1)

- Collect blood and plasma for CBD, THC, and AEA levels at 45 minutes post medication (post-CBD levels)
- Record adverse events as reported by participant or observed by investigator
- Results of evaluations of safety, and psychomotor effects
- Record participant's adherence to treatment program

7.2.2.2 Visit 4 (1 day after Baseline/Enrollment Visit +5 days)

1 day (T2)

- Perform alcohol breathalyzer to obtain BAC
- Collect blood and plasma for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (45 minutes post-CBD levels).
- Collect urine for urine drug analysis
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, and results of evaluations of safety, cognitive function and psychomotor effects
- Record participant's adherence to treatment program
- Evaluate and record alcohol use

7.2.2.3 *Visit 5*

1 week (T3)

+/- 5 days

- Perform alcohol breathalyzer to obtain BAC
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- **C**ollect blood and plasma for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (post- and pre-CBD dosing levels)
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety, psychomotor/subjective effects
- Evaluate and record AUD related measures
- Evaluate and record alcohol use
- Provide participants with sufficient study medication to administer daily until the next scheduled visit (1 week), and instructions for how to use the study medication and document their use
- Record participant's adherence to treatment program
- Administer medical management session

7.3.3.2 Visit 6

2 weeks (T4)

+/- 5 days

- Perform alcohol breathalyzer to obtain BAC
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- **C**ollect blood and plasma for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels(post- and pre-CBD levels)
- Collect blood for liver function tests (LFT)
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety, psychomotor/subjective effects
- Evaluate and record alcohol use
- Evaluate PTSD-related measures
- Provide participants with sufficient study medication to administer daily until the next scheduled visit (2 weeks), and instructions for how to use the study medication and document their use
- Record participant's adherence to treatment program
- Administer medical management session

7.3.3.3 Phone call 1

3 weeks (T5)

+/- 5 days

- Record adverse events as reported by participant
- Record participant's adherence to treatment program
- Record concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety

7.3.3.4 Visit 7

4 weeks (T6)

+/- 5 days

- Perform alcohol breathalyzer to obtain BAC
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- **C**ollect blood, plasma and serum for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (post- and pre-CBD levels)
- Collect blood for carbohydrate deficient transferrin (CDT) test
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety, psychomotor/subjective effects
- Evaluate and record alcohol use
- Evaluate and record AUD and PTSD-related measures
- Administer the cue/traumatic stress response task and record response
- Provide participants with sufficient study medication to administer daily until the next scheduled visit (2 weeks), and instructions for how to use the study medication and document their use
- Record participant's adherence to treatment program
- Administer medical management session

7.3.3.5 Phone call 2

5 weeks (T7)

+/- 5 days

- Record adverse events as reported by participant
- Record participant's adherence to treatment program
- Record concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety

7.3.3.6 Visit 8

6 weeks (T8)

+/- 5 days

- Perform alcohol breathalyzer to obtain BAC
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- Collect blood, plasma and serum for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels(post- and pre-CBD levels)
- Collect blood for carbohydrate deficient transferrin (CDT) test and liver function tests (LFT)
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, menstrual calendar (if applicable), and results of evaluations of safety, psychomotor/subjective effects
- Evaluate and record alcohol use
- Evaluate and record AUD and PTSD-related measures
- Collect information for cognitive function changes
- Provide participants with morning dose of study medication at the study visit and 1 pill to take in the evening.
- Record participant's adherence to treatment program
- Administer medical management session

7.3.3.7 Visit 9

7 weeks (T9)

+/- 5 days

- Perform alcohol breathalyzer to obtain BAC
- Collect urine for urine drug analysis and urine pregnancy test (if applicable)
- Collect blood and plasma for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels(pre-CBD levels)
- Collect blood for liver function tests (LFT)
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, concurrent medications, menstrual calendar (if applicable), results of evaluations of safety, psychomotor/subjective effects
- Evaluate and record alcohol use
- Evaluate and record AUD and PTSD-related measures

7.3.4 **Final Telephone Follow-Up**

9 weeks (T10)

+/- 5 days

- Record adverse events as reported by participant
- Evaluate and record alcohol use
- Record evaluations of safety
- Administer treatment completion questionnaires

7.3.5 **Unscheduled Visit**

Unscheduled visits will be documented on an unscheduled visit form.

7.3.6 **Clinical Re-Screen**

If there is a delay of ~2-3 months between an eligible participant's screening visit and baseline visit, the following measures/procedures will be administered during a "clinical re-screen" at a separate visit or completed on the same day as the baseline visit (prior to baseline procedures) to confirm continued study eligibility as applicable:

The following measures/procedures will be conducted at the clinical re-screen:

- BAC
- Urine toxicology screen and urine pregnancy test (if applicable)
- PCL-5 (past month)
- TLFB (past 30 days)
- CIWA-Ar
- CSSRS (since last visit)
- Current medications

- Vital signs
- If determined necessary by the study clinicians, we may collect urine for urine analysis and blood at either the One Park site or at CTSI for hepatic function panel/liver function tests (LFT), complete blood count (CBC) with differential, basic metabolic panel, and serum pregnancy test (if female)

If there is a delay of over 3 months between an eligible participant's screening visit and their baseline visit, then the specific measures/procedures listed above (with the exception of the CSSRS since last visit) will be re-administered. The LEC/CAPS5, CSSRS baseline/screening, and relevant sections of the SCID5 will also be re-administered to confirm continued study eligibility and to confirm previously collected data. The TBI Ohio/CSI form will also be updated with any new head injuries. Re-screen procedures will be conducted remotely except blood draws and urine analysis, if applicable.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Prohibited Medications, Treatments, and Procedures

Treatment with medications acting on serotonergic pathways, cannabinoids, treatments for addictions including alcohol, and medications metabolized primarily by CYP3A4, CYP3A5, or CYP3A7 will not be permitted unless discussed with and approved by the PI.

8 Definitions of Key Terms

An adverse event (AE; also referred to as an adverse event) is any untoward medical occurrence associated with the use of a drug (pharmaceutical investigational product) in humans, which does not necessarily have a causal relationship with that treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding or test result), symptom, disease, accident, or worsening (increase in severity or frequency) of a pre-existing abnormality, temporally associated with the use of the drug, whether or not considered related to the drug. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug and from any route of administration, formulation, or dose, including overdose).

A serious adverse event (SAE) is an adverse drug or biologic or device experience occurring during any study phase (i.e., screening, admission, treatment, or follow-up), and at any dose of the study drug, comparator or placebo, that results in one or more of the following criteria:

- Results in death
- Is life-threatening*
- Requires in-patient hospitalization (i.e., admission) or prolongation of existing hospitalization
- Results in persistent or significant disability** or incapacity
- Is a congenital abnormality or birth defect (in an offspring)
- Is an important medical event that may not result in death, be life-threatening, or require or prolong hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of important medical events include events requiring intensive treatment in an emergency department, convulsions that do not require in-patient hospitalization, or the development of drug dependency or drug abuse (see Section 8, Other Significant Adverse Events).

**Life-threatening:* Any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.

***Disability:* A substantial disruption of a person's ability to conduct normal life functions.

9 Specification of Safety Variables

Safety and toxicity monitoring will be performed throughout the study for all subjects. Safety variables to be assessed include AEs, vital signs, and safety laboratory values, when collected.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each study visit following screening, designated study team members will inquire about the occurrence of AE/SAEs since the last visit.

10 General Guidelines

All AEs, regardless of causality or severity, must be immediately recorded on the AE CRF when volunteered by the subject or solicited through a study assessment questionnaire. The CRC will record all AEs, regardless of causality or severity, with start dates occurring any time after informed consent is obtained until 7 (for AEs) or 30 (for SAEs) days after the last day of study participation on the AE case report forms (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At the last scheduled visit, the CRC should instruct each subject to report any subsequent event(s).

10.1 Solicitation of AEs

At all follow-up visits occurring after study medication has been administered, the SAFETEE questionnaire [Johnson et al., 2005] will be used to assess AEs. The presence or absence of specific AEs should not be solicited from subjects.

10.2 Preplanned Hospitalization or Procedure

During the study, if a subject has a hospitalization or procedure (e.g., elective surgery) that was due to a preexisting condition that has not worsened since enrollment in the study (i.e., since the subject [or the subject's legal representation] signed the informed consent), the hospitalization or procedure is considered a therapeutic intervention and not the results of an AE. However, if the event/condition worsens during the study, it must be reported as an AE (or SAE, if the event/condition results in a serious outcome, such as hospitalization).

10.3 Reports of Cancer

Cancer is no longer considered an FDA criterion for an SAE (unless an event occurs with a serious outcome). If a new diagnosis of cancer has a serious outcome, then the reporting time frame for an SAE (48 hours) must be met. Progression of disease is not considered new cancer and is therefore not an AE.

10.4 Specific guidelines for assessing laboratory values as adverse events

Any laboratory abnormality, including leukopenia, absolute neutropenia, or thrombocytopenia, will not be considered an AE unless this abnormal laboratory value results in clinical sequelae, such as infection, bleeding, or an intervention. If an abnormal laboratory value results in a clinical event, then the clinical event, not the abnormal laboratory value, must be recorded as an AE. The clinical event must be reviewed to determine if it meets the criteria for an SAE.

11 Assessment of Adverse Events

The following definitions, developed in accordance with the US Code of Federal Regulations (CFR) and the International Committee on Harmonization (ICH), will be used for the purpose of identifying AEs in this clinical study.

11.1 Expectedness

Unexpected: An AE is considered unexpected if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed, or not previously observed in animal toxicity studies for psilocybin. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug, but are not specifically mentioned as occurring with psilocybin.

11.2 Severity

The determination of severity must be made with the appropriate involvement of a medically qualified investigator. The investigator will evaluate the severity of each AE using the following three terms and definitions:

- Minimal: single occurrence that is not distressing and does not limit activities
- Mild: multiple occurrences, awareness of sign or symptom but easily tolerated, usually does not require intervention or limit activities
- Moderate: discomfort sufficient to cause interference with normal activities; intervention may be needed
- Severe: incapacitating, with inability to perform normal activities; treatment or other intervention usually needed

11.3 Relatedness

This category provides the opportunity to indicate the reasons for suspecting a drug-related effect. If no such effect is suspected, check “No.” The following reasons for possible relationship to drug are to be assessed by the medically qualified investigator.

- Dose-response: indicates that the intensity of the event is related to the dosage level.
- Timing of onset: is used if the onset of the event has some regular relationships to drug administration (e.g., it always occurs 1 hour after taking the drug).
- Known drug effect: is another reason for suspecting a drug relationship.

The relationship of each AE to study drug will be assessed using the following terms and definitions:

- Probable (must have first two): This category applies to AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered probable, if:
    - It follows a reasonable temporal sequence from administration of the drug.
    - It cannot be reasonably explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
    - It follows a known pattern of response to the suspected drug.
- Possible: This category applies to those AEs in which the connection with the study drug administration is possible. An AE may be considered possible if, or when, any of the above reasons have been selected.
- Unrelated: This category is applicable to those AEs that are judged to be due only to extraneous causes (e.g., disease, environment, etc.) and do not meet any of the criteria for a possible drug relationship.

The determination of the relationship of the AE to the use of the study drug(s) rests on careful medical consideration of the PI.

12 Monitoring Adverse Events

The investigator will follow all AEs until the event is resolved, stabilized, or the subject is lost to follow-up. Relevant

clinical assessments and laboratory tests may be performed as determined by the PI or a qualified designee, appropriate medical intervention should be provided and, if necessary, the subject may be excluded from additional treatment with the study drug.

Any actions taken and follow-up results must be recorded on the appropriate page of the CRF and in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

13 Known Potential Toxicities of Study Drug

Overall, no preclinical results have been identified that preclude the development of cannabidiol for the treatment of alcohol use disorder, or suggest that serious AEs are likely in clinical studies. Refer to the IB for toxicology findings and information on AEs observed to date.

14 Other Significant Adverse Events

Should any AE occur that is considered significant, but does not meet the criteria for an SAE, the CRC and PI should be notified immediately.

15 Reporting Procedures

15.1 AE Reporting

To the FDA: In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the PI or IND Sponsor. On an annual basis, as part of the update to the study IND, the IND Sponsor will submit to the FDA:

- A list of all AEs that have occurred during the reporting period
- A summary of all IND safety reports submitted during the past year
- A list of all subjects who died during the participation in the investigation, listing cause of death for each,
- And a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

To the IRB: In accordance with local IRB requirements, all AEs occurring during the course of the clinical trial regardless of relationship to study activities will be collected, documented, and reported by the PI or designee to the IRB on an annual basis in the application for the study's continuation renewal. Staff education, re-training or appropriate corrective action plan will be implemented when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting.

To the DSMB: All AEs occurring during the course of the clinical trial regardless of relationship to study activities will be reported to the DSMB at regular meetings. Prior to each DSMB meeting, the PI will prepare a report to the Board including review of aggregate analysis of AEs and SAEs.

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study. This report will then be submitted to the FDA as part of the annual report to the study IND, and the IRB in the application for the study's annual continuation renewal.

To the Study Sponsors:

Tilray

The PI shall promptly inform Tilray of any significant safety issues occurring during the course of the study that might affect the performance of the study and of any AEs and SAEs experienced by subjects during the study. The PI shall share with Tilray any associated CRFs and source data, safety reports related to such AEs and SAEs,

and permit access to anonymized pharmacokinetic data of study subjects.

PI shall provide all reports issued by the DSMB according to protocol (e.g. annually for the duration of the trial, including prior to enrollment of the first participant, following completion of treatment for the first 5 completers, after completion of treatment for the first 20 completers, and upon completion of enrollment for the trial).

NIH/NIAAA

All AEs occurring during the course of the clinical trial regardless of relationship to study activities will be collected, documented, and reported by the PI or designee to NIH/NIAAA on an annual basis in the annual Research Performance Progress Report (RPPR).

15.2 SAE Reporting

SAEs will be promptly reported to the CRC and PI. The PI or qualified designee will distinguish Serious Adverse Events (SAEs) from Adverse Events (AEs). The details of the event will be documented and reported as follows:

To the FDA: The PI is required to report certain study events in an expedited fashion to the FDA. These written notifications of AEs are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected, and
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous AE that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. This is not applicable for us as we are not using animals in this study.

Each written notification must be submitted on an FDA Form 3500A. The PI is also required to identify in IND safety reports all previous reports concerning similar AEs and to analyze the significance of the current event in light of the previous reports.

To the IRB: The IRB Chair or Administrator will be notified immediately for SAEs that are at least possibly related to study participation only. If the IRB administrator determines that reporting of the incident/issue is required, it will be submitted to the IRB within 48 hours of the IRB direction/response.

The team will also submit summary information related to all SAEs, AEs, and UPs in the annual application for continuation to the IRB.

To the Study Sponsors:

NIH/NIAAA

SAEs considered at least possibly related to study participation will be documented and reported to NIAAA within 48 hours with copies included in the participant's file.

Tilray

If an SAE occurs after the subject signs informed consent through the end of study participation, the PI or a qualified designee will complete the Tilray SAE Form and send it via email to contacts designated by Tilray within

24 hours of the site becoming aware of the SAE. The form must be completed and submitted to Tilray any time a serious medical event has occurred in a participant during the clinical trial, whether or not it is considered related to the study treatment, including active comparators and placebo.

Ensure that an investigator has reviewed and signed the SAE form prior to submission.

Every exposure during pregnancy (participant) should be reported on an SAE worksheet as a case of special interest from the time of study enrolment to the end of study participation.

The following timelines describe when Tilray, as the manufacturer of IP, has to report ADRs to Health Canada:

- Fatal or life-threatening unexpected ADRs require notification of regulatory agencies as soon as possible but no later than 7 calendar days after first knowledge by Tilray that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. The report will include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.
- All other serious, unexpected ADRs must be filed as soon as possible but no later than 15 calendar days after first knowledge by Tilray that the case meets minimum criteria for expedited reporting.

15.3 UP Reporting

Incidents or events that meet the OHRP criteria for UPs involving risks to subjects or others require notification of the local IRB. The phrase “unanticipated problems involving risks to subjects or others” is found but not defined in the HHS regulations at 45 CFR part 46. Any incident, experience, or outcome that meets all of the following criteria is considered to be Reportable New Information (RNI) and is required to be promptly reported to the local IRB:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means that, in the opinion of the PI, the incident, experience, or outcome was more likely than not caused by procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

The RNI report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

UPs must be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor according to SAE reporting procedures described above (within 48 hours of the investigator becoming aware of the event).
- UPs that meet the requirements for RNI will be reported to the IRB as soon as possible and within 5 working days of the site becoming aware of the event.

- All other UPs not related to study activities or that do not result in harm to participants will be reported to the IRB annually in the application for the study's continuation renewal.

15.4 Pregnancy Reporting

Pregnancy information on clinical study subjects is collected by the investigator. If a subject should become pregnant during the course of the study, the investigator or qualified designee will contact the IRB within 5 working days of the PI or qualified designee first becoming aware of the pregnancy.

Tilray Pregnancy Reporting Requirements: Every exposure during pregnancy (participant) should be reported on a Tilray SAE worksheet within 24 hours of the site becoming aware of the pregnancy as a case of special interest from the time of study enrollment to the end of study participation. If an SAE occurs in conjunction with the pregnancy, then the Tilray reporting timeframe for an SAE (24 hours) must be met. In the event of a pregnancy, administration of study medication will be discontinued, but all other follow-up data, including safety data, will be collected.

Pregnancies resulting in congenital abnormalities or birth defects in offspring meet the requirements for an SAE and will be collected, documented, and reported according to the procedures outlined above for SAEs.

16 Reporting of Investigational Medicinal Product Quality Complaints

16.1 Defect or Possible Defect in the IP

Any defect or possible defect in the investigational medicinal product (defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial) must be reported by the PI or qualified designee to Tilray within 48 hours of first becoming aware of the possible defect. This report to Tilray may be made by telephone or by email. The product and packaging components in question, if available, must be stored in a secure area under specific storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

16.2 Temperature Deviations

In the event that the temperature at which the IP is stored is less than 2°C or greater than 8°C, the CRC and PI will be notified immediately and a temperature deviation form will be completed and sent via email to contacts designated by Tilray as soon as possible. Tilray will provide further guidance on how to proceed on a case-by-case basis.

17 Study Halting Rules

When three severe AEs are determined to be "probably related" to the study agent, the DSMB will be informed and asked to convene in order to determine whether action should be taken. The Principal Investigator will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the Principal Investigator. The Principal Investigator will inform the FDA of the DSMB's decision and the disposition of the study. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study.

18 Safety Oversight

The research team (project manager, coordinators, and research assistants) will submit any adverse events to the PI and the Data and Safety Monitoring Board (DSMB). The PI and the DSMB members are responsible for reviewing all AEs and serious adverse events (SAEs) reported. All SAEs will be reviewed at the time they are reported in the electronic data capture system. Where further information is needed, the DSMB will discuss the

event with the research team. All AEs will be reviewed on a weekly basis to observe trends or unusual events.

The PI will generate and present reports for DSMB meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Data and Safety Monitoring Board (DSMB)
A Data and Safety Monitoring Board (DSMB) will be established, comprising three to five individuals appointed by the PI. The committee will include Dr. Don Goff, Dr. Dan Iosifescu and Dr. Kathlene Tracy. This committee will meet (in person or by teleconference) prior to enrollment of the first participant, and at least annually thereafter, including meetings following completion of treatment of the first 5 completers, after completion of treatment of the first 20 completers, and upon completion of enrollment for the trial. Prior to each meeting, the PI will prepare a report to the Board including review of:

- Protocol and ICF changes
- Protocol violations and deviations
- Documentation of informed consent
- Enrollment and retention
- Investigator or key personnel changes
- Aggregate analysis of adverse events/serious adverse events
- Protection of confidentiality

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study. Reports will be submitted to the IRB on at least an annual basis.

19 Clinical Monitoring

Site staff will be required to audit source documentation, including informed consent forms and HIPAA forms, regulatory documents and case report forms on a biannual basis. Site staff will be responsible for local quality assurance and will verify that study procedures are properly followed and that site staff are trained and able to conduct the protocol appropriately. If the site staff's review of study documentation indicates that additional training of study personnel is needed, this will be arranged as per the PI. Study team members will review each other's data for completeness, accuracy, and fidelity to the protocol.

20 Statistical Considerations

20.1 Statistical and Analytical Plans (SAP)

A formal SAP will be developed prior to database lock and unblinding.

20.2 Statistical Hypotheses

Hypothesis 1a Safety and tolerability: CBD will be safe and well tolerated and will not lead to increased plasma THC. No clinically significant cognitive or motoric impairments, CBD-related serious adverse events, persisting adverse effects or treatment associated increases in plasma THC will be observed.

Hypothesis 1b: Alcohol use. Relative to the placebo-treated group, CBD-treated participants will have fewer drinks per day during the 6 weeks of treatment with CBD vs placebo.

Hypothesis 2: PTSD symptoms. Relative to the placebo-treated group, CBD-treated participants will lower PTSD symptoms during the 6 weeks of treatment with CBD vs placebo.

Hypothesis 3a: Mechanism, traumatic stress-induced craving: Relative to placebo, CBD will be associated with a greater reduction between baseline and end of treatment in trauma induced alcohol craving, negative emotion, and psychophysiological arousal in response to the task.

Hypothesis 3b: Mechanism, AUD and PTSD related measures and cognition: Relative to placebo, CBD will improve self-report measures of craving, anxiety, mood, self-efficacy and cognitive performance.

Hypothesis 3c: Mechanism, anandamide: Relative to placebo, CBD will be associated with a greater increase

in plasma anandamide levels.

Hypothesis 4: CBD plasma levels. Within-group plasma CBD levels will stabilize within one week, i.e. 45 minutes post-CBD dosing levels obtained after 1 week of treatment will not differ from those obtained after 4 weeks of treatment at each dose.

Exploratory Hypothesis 1: Relationship between effects on PTSD symptoms and alcohol use. The onset of reduction in PTSD symptoms will precede the onset of reduction in alcohol use.

20.3 Description of Statistical Methods

20.3.1 **General Approach**

We recognize that the relatively small sample sizes proposed in the RCT are not likely to produce statistical significance, unless the effect sizes are remarkably high. We will carry out a full Mixed Model Repeated Measures (MMRM) statistical analysis in case CBD does perform so well. However, the main focus of the statistical analysis of the results of the trial will be to characterize the effect sizes and response rates across the various measurement domains and the profiles of individuals who are treatment successes. The intent to treat (ITT) population will contain all randomized patients who receive at least one dose of double-blind study medication and from whom at least one post-baseline (B1) efficacy measurement is obtained while on study medication. The efficacy analysis will be based on the ITT population. Two-sided hypothesis testing will be utilized. Tests with p-values less than or equal to 0.05 will be considered statistically significant, while those less than equal to 0.10 will be considered suggestive. Since this trial is the first use of this treatment for this diagnostic indication, no adjustments of p-values for multiple comparisons will be made. Thus, all control of type 1 error is contrast-wise. All confidence intervals will be two-sided with 95% confidence. Mean treatment effect, standard errors, and 95% confidence intervals will be derived from fully adjusted models on outcomes averaged across the treatment period. Cohen's d and p-values will be calculated from fully adjusted models with appropriately transformed outcome variables. For dichotomous drinking outcomes, prevalence rates will be calculated. Odds ratios (ORs) and *p*-values will be derived from logistic regression models including treatment group.

20.3.2 **Analysis of the Primary Endpoint(s)**

For Hypothesis 1a, Safety and tolerability, the frequency of adverse events will be analyzed for the entire sample at all time points, tabulated for each treatment group, and compared using chi-squared tests. The safety analysis will be largely descriptive of outcomes for the entire study population. The incidence of AEs will be summarized by system organ class, preferred term, the likelihood of its relationship to the treatment, and severity for each treatment group. Clinical laboratory data will be summarized by type of test. Frequency and percentage of patients whose values fall outside of reference ranges will be presented for each measurement.

For Hypothesis 1b, Alcohol Use. The Primary outcome measure, number of drinks per day, will be analyzed with an MMRM to assess differences in change from baseline. The primary contrast is change from baseline (B1) at week 6 (T8). The model at each time point will include terms for treatment, time and treatment by time interaction as factors and the baseline value for each score as a covariate. Parameter estimation will be based on REML and to begin an unstructured covariate matrix will be used. If the model fails to converge, the form of the covariance matrix will be chosen based on Akaike's Information Criteria, and Schwarz' Bayesian Criterion. Model-based LS means will be obtained for change from baseline to each time point for each treatment group. At each time point, contrasts between CBD and placebo will be obtained. Secondary alcohol use measures will be tested with MMRM sequentially in a closed testing union intersection paradigm in the order listed in section C.8.3. Validity of the p-value will extend until the first test fails to have a p-value smaller than a two-sided alpha of 0.05. The analyses will continue for all measures but the resulting p-value will be nominal.

For Hypothesis 2, PTSD symptoms, the primary outcome measure, total score of the PCL-5, will be analyzed in the same way as the primary outcome for alcohol use. The primary contrast is change from baseline (B1) at week 6 (T8).

20.3.3 **Analysis of the Secondary Endpoint(s)**

For hypothesis 3a: Mechanism, traumatic stress-induced craving: The primary outcome measure will be alcohol craving. Alcohol craving outcomes within a session will be examined in terms of a created measure of a difference of difference scores: first, the difference score of the alcohol craving response to trauma and to neutral challenges calculated for the Pre and for the Post session time points, and second, the difference of the

scores between Post and Pre. This difference measure of alcohol craving will be calculated at Baseline, and at week 6 of the clinical trial (T8). The outcome analysis will be conducted with an MMRM model that includes fixed effects for treatment C, (CBD vs. placebo) and clinical trial time T, a random effect for subjects, and a treatment by clinical trial time interaction (C*T). The model will provide least-square mean estimates of difference scores at each session for each treatment. Between treatment outcome contrasts will be performed at Baseline, as a measure of the equivalence of the groups, and at T6 and for the difference between T6 and Baseline. For parameter estimation, the form of the covariance matrix will follow the procedures described for the analysis of Aim 1. Secondary outcome measures will be Negative Emotion, and Psychophysiological arousal. These outcomes will be analyzed in a similar manner to the primary outcome, alcohol craving.

For Hypothesis 3b: Mechanism, AUD and PTSD related measures and cognition (craving, self-efficacy, anxiety, cognitive measures) will be analyzed in the same way as the primary outcome for alcohol use. The primary contrast is change from baseline (B1) at week 6 (T8).

For Hypothesis 3c: Mechanism, anandamide, within- and between-group comparisons of plasma anandamide levels will be assessed following 45 minutes (T1), 1 day (T2), 1 week (T3), 2 weeks (T4), 4 weeks (T6), 6 weeks (T8) of treatment with CBD vs. placebo, and one week (T9) after the completion of treatment. Effects of dose will be assessed and the interaction between group and time- point will be evaluated.

For Hypothesis 4, plasma CBD and THC levels will be analyzed in the same manner as anandamide in Hypothesis 3c.

20.3.4 **Safety Analyses**

Means and standard deviations of plasma CBD and THC levels within the CBD treatment group will be presented following 45 minutes (T1), 1 day (T2), 1 week (T3), 2 weeks (T4), 4 weeks (T6),6 weeks (T8) of treatment with CBD vs. placebo, and one week (T9) after the completion of treatment to determine whether target plasma levels of CBD have been achieved, and whether metabolic transformation of CBD to THC has occurred.

The number of participants within each treatment group that were able to pass a battery of psychomotor field sobriety tasks (walk-and-turn task, one-leg stand, Romberg's test, finger-finger test, and counting backwards [85]) within 2 hours of the initial administration of CBD vs. placebo (T1) will be analyzed as summary statistics during treatment.

AEs and SAEs, when present, will be collected on an AE Case Report Form at study visits. The form will include an assessment of clinical significance and study relatedness. Serious Adverse Events (SAEs) will be documented on an additional SAE form. These CRFs will be based on those used in recent NIDA Clinical Trials Network trials. To further assess abuse potential, visual analog scales will be used to assess abuse potential. Scales will include desire to use the study medication again, desire to use the study medication again for pleasurable intoxication ("to get high"), and craving for the study medication.

The study may be stopped if there are untoward and concerning levels of Adverse Event (AE) or Serious Adverse Event (SAE) outcomes attributable to CBD or study participation. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study.

The frequency of adverse events will be analyzed for the entire sample tabulated for each treatment group and compared using chi-squared tests. The safety analysis will be largely descriptive of outcomes for the entire study population. The incidence of AEs will be summarized by system organ class, preferred term, the likelihood of its relationship to the treatment, and severity for each treatment group. Clinical laboratory data will be summarized by type of test. Frequency and percentage of patients whose values fall outside of reference ranges will be presented for each measurement.

20.3.5 **Adherence and Retention Analyses**

Adherence to the protocol will be assessed with a smartphone-assisted medication adherence platform [94] in which the subject takes a video of drug administration at each dose, and transmits this to study personnel.

This program has been used successfully in previous studies, and includes security provisions that ensure protection of confidentiality and privacy. If the participant is unable to use the smartphone-assisted platform then medication adherence will be ensured using pill counting and meeting with the study nurse practitioner

at each visit. Plasma concentrations of CBD will also be collected at all in-person visits (T1-T4, T6, and T8) to verify treatment adherence.

Number of participants that complete the treatment phase of the study (through T8), complete the follow-up phase of the study (through T10), and are lost to follow-up will be collected. Frequency of and reasons for discontinuation of the intervention or study follow-up will also be tallied.

20.3.6 **Baseline Descriptive Statistics**

Treatment groups will be compared on several baseline characteristics, including sex, age, race/ethnicity, education level, baseline measures of alcohol consumption (% drinking days and % heavy drinking days), alcohol craving (PACS), anxiety (BAI), mood (BDI-II), CAPS total, and self-efficacy (AASE). Categorical data will be tallied, and means and standard deviations of continuous scores will be calculated.

20.3.7 **Planned Interim Analysis**

20.3.7.1 Safety Review

The DSMB will meet (in person or by teleconference) at least annually, including prior to enrollment of the first participant, following completion of treatment of the first 5 completers, after completion of treatment of the first 20 completers, and upon completion of enrollment for the trial. Prior to each meeting, the PI will prepare a report to the Board including review of the aggregate analysis of adverse events/serious adverse events.

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study. The study may be stopped if there are untoward and concerning levels of AE or SAE outcomes attributable to CBD or study participation. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study.

20.3.8 **Multiple Comparison/Multiplicity**

Because our primary outcomes are safety data, in which we hypothesize a null difference between treatment groups, we will not employ a correction for Type I error/alpha inflation.

20.3.9 **Tabulation of Individual Response Data**

Aside from AEs/SAEs, individual response data will not be presented.

20.3.10 **Exploratory Analyses**

For Exploratory Hypothesis 1, relationship between PTSD/subthreshold PTSD and AUD symptom change

Symptom onset is defined to be the first week in which the patient has 50% reduction in the number of drinks per day for the primary alcohol outcome and a 30% reduction in the Total Score of the PCL-5 that is sustained for at least two weeks. Onset of a positive clinical outcome will be described by a "cure model." The form of a cure model is $H(t) = 1- p + pS(t)$; where $H(t)$ is the probability of onset at a time greater than t, p represents the probability of success and $S(t)$ is the distribution of time to success, conditional on success occurring. The parameters will be estimated based both on Kaplan Meier methods and parametrically. The equality of the values of p for the two treatment arms will be tested using a nonparametric likelihood ratio test. For the parametric test, a logistic will be used to model p and a Weibull survival distribution will be used to model time to failure, $S(t)$. Both allow the use of covariates. The comparison will be based on a likelihood ratio test and the median time to onset of $S(t)$.

20.4 Sample Size

We will phone screen approximately 600 participants, and enroll approximately 150 participants to randomize a total of 48 participants (through week 6/T8). In this pilot study sample sizes are obviously quite limited. A simple t test of mean differences requires an effect size of .939 to have .8 power. We have chosen an unbalanced design with more subjects on CBD to maximize the ability to characterize response to treatment for use in planning future confirmatory trials and still have valid hypotheses tests.

20.5 Measures to Minimize Bias

20.5.1 **Enrollment/Randomization/Masking Procedures**

Enrolled participants that pass screening will be randomized using a 5:3 ratio to receive either 600mg CBD/day (PO) or placebo respectively for 6 weeks (N=30 participants on CBD and N=18 participants on placebo). Treatment assignment will be known only to a designated unblinded study staff member in charge of dispensing study medication under direct PI supervision, but the blind can be broken if necessary, e.g., in case of a serious reaction during drug administration.

20.5.2 **Evaluation of Success of Blinding**

In order to assess the integrity of the blind, following the treatment portion of the study (T8), participants will be asked to guess 1) what medication was administered (CBD or placebo), and 2) degree of confidence in this guess.

20.5.3 **Breaking the Study Blind/Participant Code**

The blind can be broken for an individual participant if necessary, e.g., in case of a serious reaction during drug administration or in the event of a SAE likely to be related to the study medication.

21 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, study medication dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the dispensation site, at the laboratories, and at medico- technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. dispensation site, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

22 Quality Assurance and Quality Control

Data quality assurance (QA) includes all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements(s) (ICH E6 1.46). Data quality control (QC) includes the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 1.47).

QC procedures will be implemented beginning with the data entry system, and data QC checks on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated,

documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

23 Ethics/Protection of Human Subjects

23.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

23.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant-facing materials will be submitted to the IRB for review and approval. Study approval must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made by the IRB regarding whether previously consented participants need to be re-consented.

23.3 Informed Consent Process

23.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

23.3.2 Consent Procedures and Documentation

An IRB-approved pre-screening form will be used to pre-screen individuals expressing interest in the study, to assess whether they are likely to qualify for the study. Interested patients who pass the pre-screening (conducted via phone) will be referred for a screening visit.

- Participants will be provided with an informed consent form, COVID-19 information sheet, audio and video consent form, and health release form at or prior to their screening visit. Understanding of the study procedures will be assessed using a consent quiz.

Subjects will be electronically consented via a 21CFR Part 11-compliant electronic consent method. The U.S. Food and Drug Administration (FDA)'s MyStudies mobile application is a Part 11-compliant electronic consent method which allows our study team to review study informed consent forms with the participants remotely and obtain the participant's electronic signatures on the study's informed consent forms via the mobile application. The app is available in the US in English on both Apple and Android smartphones. Secure registration allows participants to enter a unique enrollment code specific to our study to prevent people outside of the study from enrolling. The application allows for the storage of signed electronic consent forms on HIPAA and FISMA compliant servers; the participant is able to receive secure copies of their electronically signed consent form PDF by email directly after they sign the consent. Designated research staff can easily access and download all signed consent forms for secure storage on the shared drive by logging into a portal. The FDA MyStudies e-consent application will not be used until a link to the informed consent form has been submitted and approved by NYU's IRB. We will also utilize REDCap (accompanied with REDCap Cloud, a Part 11-compliant electronic consent method) to obtain the participant's electronic signatures on the study's informed consent forms remotely.

Alternatively, remote consent may be obtained via SendSafe email. In this case, a copy of the consent form will be sent via SendSafe email. The subject's signature will be captured electronically on the document provided, or the subject may print and sign a physical copy that is scanned and returned via the SendSafe method. Subjects who do not have access to email or scanner may choose to have a hard copy of the consent mailed to them and return via a self-addressed stamped envelope provided by the study team.

At or prior to their first visit, participants will be provided with an informed consent form including all pertinent details of the study including descriptions of the following: the assessment interview and questionnaires; the follow-up interviews; description of experimental treatment; risks and benefits of study procedures; alternatives

to participation in the study; confidentiality; emergency treatment and compensation for injury; payment for participation; a statement that patients will be informed of any new findings affecting the risks or benefits of the study; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions or in case of emergency. The consent form will also include assurances of confidentiality and a statement that participation is entirely voluntary, that the decision to participate will in no way influence other aspects of the patient's treatment, and that the participant is free to withdraw participation at any time. Study staff will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions of the study team.

Participants must pass a consent quiz with a score of 90% or higher prior to signing. Participants who score less than 90% may take the quiz a second time after the study team has reviewed content and answered all questions. Participants who are unable to score 90% or higher on the quiz after two attempts will be given a copy of the consent to take home and may return for a screening visit on a later date. If the participant is unable to score 90% or higher on the third attempt, they will be excluded from the study unless otherwise determined by senior management or the PI. If a decision is made to retain the subject despite failure to attain a 90% or higher on the consent quiz, the rationale will be documented in the subject's binder via a note to file.

A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participants may withdraw consent at any time throughout the course of the trial.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Patients who consent to participate in the study will also be invited to consent to having their remote and/or in-person screening assessments (i.e. SCID and CAPS) audio-recorded at the initial visit (see Audio Recording Consent) for quality control and for voice-markers analysis. If a patient does not sign the Audio Recording Consent, then we will not audio-record the patient's interview.

Re-Contacting Screen Failures
In the event the protocol inclusion and exclusion criteria are updated, previously screened participants will be reconsidered for inclusion in the study. If a previously screened participant is eligible under the updated inclusion and exclusion criteria, they will be contacted via phone or email to ascertain whether they are still interested in participation. If interested, the participant will be brought in for re-consent and a Clinical Re-Screen or a new Screening Visit if 3 months or greater have passed since the initial screening.

Re-Consent
If the consent is revised (e.g.: new procedures, risk information, compensation, data sharing, etc.), participants will be re-consented with the most updated version of the consent form at their next visit. New information that could substantially affect a participant's desire to continue in the study will be communicated via phone, followed by re-consent at the next study visit.

23.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains

the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and records of drug dispensation for the participants in this study. Records will be housed in a secured space in 1 Park, A, C-D, and H buildings of Bellevue Hospital Center with limited access to study PI and designated study staff only. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations as described in section 24.2.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

Confidentiality of research material will be ensured by storing the research materials in locked cabinets. Material will be available only to project staff, and only as needed. All project staff will be thoroughly trained in issues relating to confidentiality. Participants will be identified in case report forms (CRFs) by initials and an identification code. Data will be entered into TrialMaster™, a program provided by NYU's Datacore designed specifically for clinical trials to protect patient privacy and confidentiality. Published reports will be based on group data; no individual data will be reported.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

If the study participant has previously participated in a research study at NYU, we will ask the participant's permission to link their previously collected data to the data collected in this research study in order to retain longitudinal information on the participant.

23.4.2 **Research Use of Stored Human Samples, Specimens, or Data**

- Intended Use: Samples and data collected under this protocol may be used to evaluate study eligibility and plasma concentrations of CBD and THC. No genetic testing will be performed.
- Storage: Access to stored samples will be limited by storing samples in a securely locked area. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using paper and electronic logs.
    - Disposition at the completion of the study: All stored samples will be sent to GRM Document Management. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

23.5 Future Use of Stored Data

Data collected for this study will be analyzed and in locked cabinets in NYU space at One Park and within the A, C-D, and H buildings of Bellevue Hospital Center. After the study is completed, the de-identified, archived

data will be transmitted to and stored at GRM Document Management for use by other researchers including those outside of the study. Permission to transmit data to GRM Document Management will be included in the informed consent.

When the study is completed, access to study data will be provided through GRM Document Management.

24 Data Handling and Record Keeping

24.1 Data Collection and Management Responsibilities

Data collection, interpretation, analysis, review, and reporting is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink will be used to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. We will not erase, overwrite or use correction fluid or tape on the original.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents will be consistent with the source documents or the discrepancies will be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster™ Electronic Data Capture (EDC), a 21 CFR Part 11- compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

24.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

24.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents and reported to NIAAA Program Official.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible

for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

24.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

25 Study Finances

25.1 Funding Source

This study is financed through a grant from the US National Institutes of Health (NIH)/National Institute on Alcohol Abuse and Alcoholism (NIAAA).

25.2 Costs to the Participant

Participants will not incur any costs as a result of participating in the study.

25.3 Participant Reimbursements or Payments

Participants will receive monetary compensation for research assessments as follows:

- Option 1 Screen (S1)= $70
- Option 2 Screen Session 1 = $50
- Option 2 Screen Session 2 = $20
- Baseline (B1)= $70
- 1-day assessment (T2)= $40
- 1-week assessment (T3)= $60
- 2-week assessment (T4)= $60
- 4-week assessment(T6) = $70
- 6-week assessment (T8)= $70
- 7-week assessment (T9)= $40

Participants completing all the assessments would therefore receive a total of $480. Participants will also be provided with a gift card or $12 cash compensation for the purchase of a meal for visits that are 5 hours or longer. If requested, compensation will also be provided for travel and transportation for study-related visits. Participants may receive partial compensation for portions of study visits completed as applicable. Participants may also receive a $15 compensation for time/effort spent as a “standby” for a potential screening visit; participants will only receive the one-time $15 compensation once the clinical screen visit is completed as part of the study.

In the case of a clinical re-screen or partially completed visits, participants will be compensated $25-$40 depending on the length of the visit. The amount is determined by senior management.

Payment may be made in cash, check, or ClinCard.

26 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIAAA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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