NYU Langone Health

Official Title:	Effects of Cannabidiol in Alcohol Use Disorder
NCT Number:	NCT03252756
Study Number:	17-01001
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• July 20, 2021

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	June 13, 2018	Original version
1.1	July 12, 2018	Clarifications requested by the FDA as well as Local NYUSoM IRB prompting a revision of the protocol. The FDA requested adding exclusion for medications which are moderate to strong inhibitors of CYP3A4 or CYP2C19, or have a narrow therapeutic index and are substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19, CYP1A2, or CYP2B6. The NYUSoM IRB requested clarity around drug storage and importation as well as the correction of a heading title.
1.2	July 20, 2018	Clarifications requested by the NYUSoM IRB prompting a revision of the protocol. The study team removed all mention of the NYU-HHC CTSI Research Pharmacy as they will not be storing or dispensing the study medication. All mentions of medication compounding services were removed, as the investigational product will not require compounding.
1.3	July 25, 2018	Clarification requested by the NYUSoM IRB to replace mention of' pharmacy records' from page 36 of the protocol with 'study drug records'.
2.0	June 17, 2019	Documentation of change from LM to M2 study drug formulation requested by study sponsor Tilray Canada Ltd. Clarification of pharmacokinetic timepoints, collection procedure and associated statistical analyses. Clarification of additional Case Report Forms and recruitment language. Addition of Medical Managament Manual for drug dispensation and accountability. Revision of study schema and addition of full study schedule for clarity. Addition of audio-visual data collection language and consent form. Addition of generalized phone screen and associated consent form to enhance study recruitment and improve flow.
2.2	**September 13, 2019**	Changes to study schedule to include: administration of C-SSRS, urine drug screen and urine pregnancy test at every visit (except those under 24 hours from last visit) as safety measures, removal of Stroop tasks, removal of AUD-related measures from phone visits. Study reporting procedures for AEs/SAEs have been changed to reflect the DSMB's recommendations. Inclusion/Exclusion criteria have been changed to more accurately reflect the target population of participants recruited to the study.

2.3	**October 1, 2019**	Inclusion/Exclusion criteria have been changed to enhance study recruitment within the safety parameters of the research.
2.4	**November 11, 2019**	The exclusionary medication list has been changed to reflect only the limitations put in place by the FDA; the other medication types have been removed to avoid redundancy.
2.5	**December 10, 2019**	Medical management has been removed from the 1-day, 4 weeks+1 day and 9-week visits because no study drug will be dispensed at the aforementioned time points. The C-SSRS will no longer be administered at the 1-day and 4-weeks+1-day visits. The study figure has been revised to reflect these changes.
2.6	**January 10, 2020**	Drinking criteria has been changed from 10 heavy drinking days to 8 heavy drinking days in order to facilitate recruitment efforts and the attainment of target enrollment numbers.
2.7	**July 26, 2020**	Option for remote e-consent was added; option to complete initial portion of screening visit remotely added; reimbursement schedule altered to reflect two-part screening visit option; consent updated to include risk of elevated liver enzymes; recruitment dates were updated; reference to COVID-19 safety procedures SOP was added
2.8	**September 26, 2020**	Website recruitment materials added
2.9	**10/30/2020**	Changed heavy drinking inclusion from 8 heavy drinking days to 6 heavy drinking days
3.0	**February 15, 2021**	Removed exclusion of drugs that are weak-moderate 3A4 substrates Clarified exclusion criterion #8 (Significant laboratory abnormalities, including significantly impaired liver function, serious abnormalities of complete blood count or metabolic panel). Added a new exclusion for Type I Diabetes, per the DSMB's review of risks associated with cannabis use and development of ketoacidosis in Type I Diabetes.
3.1	**July 15, 2021**	Added to the procedure section 8 which states that study team may ask for release of health information if it is helpful or requested by the participant.

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

A PHASE I/II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF CANNABIDIOL FOR ALCOHOL USE DISORDER

Principal Investigator:	*Michael Bogenschutz, M.D.* *NYU SoM Department of Psychiatry* *462 First Ave, 22N11* *Michael.Bogenschutz@nyumc.org* *646-501-4026*
NYULMC Study Number:	*s17-01001*
Funding Sponsor:	*National Institute on Alcohol Abuse and Alcoholism (NIAAA/NIH)*
IND/IDE Number:	*140108*
Regulatory Sponsor:	*Michael Bogenschutz, M.D.* *NYU SoM Department of Psychiatry* *462 First Ave, 22N11* *Michael.Bogenschutz@nyumc.org* *646-501-4026*
Study Product:	*Cannabidiol*
Study Product Provider:	*Tilray*
ClinicalTrials.gov Number:	*NCT03252756*

Initial version: June 13, 2018
Amended: July 12, 2018
Amended: July 20, 2018
Amended: July 25, 2018
Amended: June 17, 2019
Amended: September 13, 2019
Amended: October 1, 2019
Amended: November 11, 2019
Amended: December 10, 2019
Amended: January 10, 2020
Amended: July 26, 2020
Amended: September 26, 2020
Amended: October 30, 2020
Amended: February 15, 2021

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.

Table of Contents

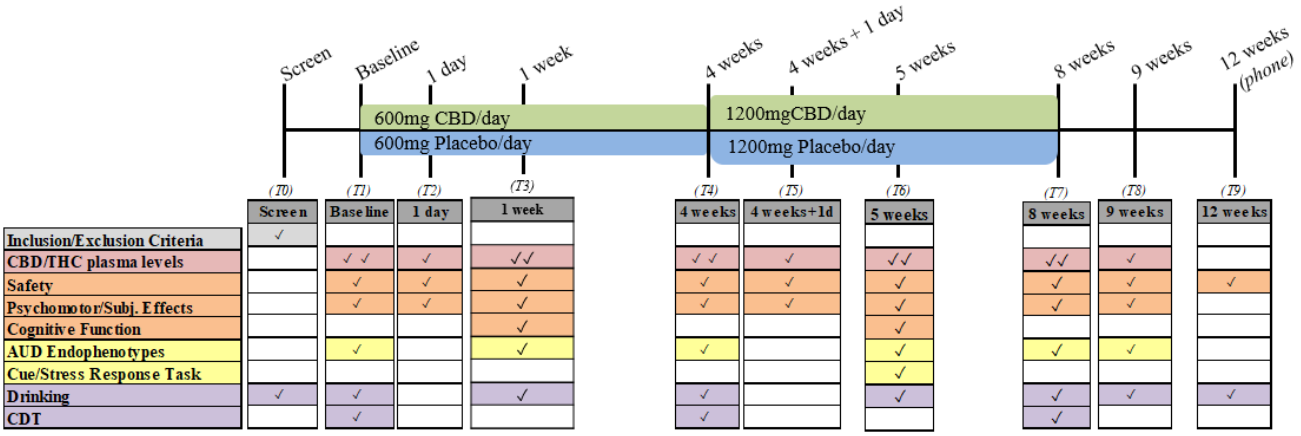
List of Abbreviations

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	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LFT	Liver Function Test
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

Protocol Summary

Title	A Phase I/II Randomized, Double-Blind, Placebo-Controlled Trial of Cannabidiol for Alcohol Use 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 drinking-related outcomes in patients with AUD. We will evaluate the safety of an extended daily CBD treatment regimen in an AUD population, assess the impact of CBD on neuropsychological and neurophysiological domains implicated in AUD, and generate preliminary data on the impact of CBD on alcohol consumption. Following screening and baseline assessments, 40 participants will be randomized in 1:1 ratio to receive either placebo or 600mg CBD/day (PO) for 4 weeks, immediately followed by 1200mg CBD/day (PO) for an additional 4 weeks (8 weeks in total).
Phase	Clinical study phase I/II
Objectives	To assess circulating cannabinoid (including CBD and THC) levels and safety of CBD administered to patients with AUD, to contrast the effects of CBD to those of placebo on several physiological and psychological domains relevant to AUD, and to assess the impact of CBD on drinking behavior
Methodology	Double-blind, placebo-controlled
Endpoint	Circulating concentrations of CBD and THC, AEs, and scores on psychomotor and cognitive tasks and alcohol consumption.
Study Duration	2 years
Participant Duration	12 weeks
Duration of IP administration	8 weeks
Population	n=40 18-65 year-old males and females with moderate to severe alcohol use disorder in the New York area
Study Sites	New York University School of Medicine
Number of participants	60 participants expected to be enrolled
Description of Study Agent/Procedure	Cannabidiol PO 600-1200mg/day
Reference Therapy	Placebo with medication management
Key Procedures	Blood draws
Statistical Analysis	Circulating levels of CBD, Anandamide, Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC will be assessed in CBD-treated participants 45 minutes after the initial administration (T1, T4), 1 day (T2, T5), 1 week (T3, T6), and 4 weeks (T4, T7) of treatment with each dose of CBD. Anandamide levels will also be assessed at these timepoints in placebo treated participants. Additionally, circulating levels of CBD and anandamide will be assessed in CBD-treated participants 12 hours after ingestion of the preceding evening dose following 1 week (T3, T6) and 4 weeks (T4, T7) of administration of each dose of CBD. Circulating levels of each analyte (mean and standard deviation) will be reported at each timepoint, and effects of dose and time-point will be evaluated. Between-group differences on psychomotor tasks (T1-T8), cognitive measures (T3, T6) and number of adverse events (T1-T9) will be assessed.

1 Schematic of Study Design



2 Key Roles

Michael Bogenschutz, MD – Principal Investigator
New York University School of Medicine
Department of Psychiatry
462 First Ave, 8th Fl. A Building
(646) 501-4026
Michael.Bogenschutz@nyumc.org

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

Stephen Ross, MD Sub-Investigator
New York University School of Medicine
Department of Psychiatry
462 First Ave, 8th Fl. A Building
(212) 562-4097
Stephen.Ross@nyumc.org

Sarah Mennenga, PhD Sub-Investigator
New York University School of Medicine
Department of Psychiatry
462 First Ave, 8th Fl. A Building
(646) 501-4037
Sarah.Mennenga@nyumc.org

3 Introduction, Background Information and Scientific Rationale

3.1 Background Information and Relevant Literature

Need for improved treatments for alcohol use disorder (AUD). Of all drugs of abuse, alcohol is possibly the most damaging in the US and globally when factoring in preventable death, premature death, disability, healthcare/societal costs, adverse medical and neuropsychiatric complications, unintentional injuries, and its significant causal link to suicidal and violent behaviors. AUDs are highly prevalent in the US, affecting up to 12% of the population at some point in their lifetimes [1]. AUDs are among the most disabling of all diseases worldwide, and alcohol use is responsible for approximately 4.6% of global disability-adjusted life-years and 36.4% of neuropsychiatric disability-adjusted life-years in 2004 [2]. In the US alcohol accounts for 12.1% of disability-adjusted life-years in men, and 4.6% in women [2]. The economic cost of alcohol use is staggering, estimated at $185 billion per annum in the US alone, vs. $158 billion for nicotine and $280 billion for illicit drugs (higher because of costs related to criminalization) [3].

Substantial progress has been made in understanding the neurobiological and neuropsychological underpinnings of the loss of control that is the hallmark of addiction. A number of pharmacological and behavioral treatments have been developed that target specific aspects of addiction, including motivation, coping skills, social support, reward/punishment, and relapse due to stress, priming doses of the drug, or exposure to conditioned cues. However, the effects of currently available treatments remain disappointingly small [4]. Although combining effective treatments (multiple pharmacotherapies or pharmacotherapy plus behavioral therapy) is an obvious strategy to increase treatment effect sizes, attempts to improve outcomes by combination therapy have been largely disappointing as well [5]. Approximately one person achieves abstinence or avoids relapse for every 9 people treated with the most effective FDA-approved pharmacotherapies for alcohol use disorder [6, 7]. Currently available medications for alcohol use disorder require adherence to treatment for relatively long periods of time, which further limits their effectiveness.

Cannabidiol. CBD is a phytocannabinoid that lacks the rewarding properties and psychoactive effects of THC [8]. CBD exerts effects both through the endocannabinoid system and through several other signaling pathways. GW pharmaceuticals is developing CBD (Epidiolex®) as a medication for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, and completed successful Phase 3 trials in 2016 [9-11]. Over the past decade, a rapidly growing body of research, summarized below, has established that CBD affects processes and behavior relevant to anxiety disorders and substance use disorders, providing strong support for exploration of the effects of CBD in humans with alcohol use disorder.

The endocannabinoid system and CBD. The endocannabinoid system includes several endogenous compounds with cannabis-like activity and their molecular targets: g-protein coupled cannabinoid receptor 1 (CB1) and 2 (CB2), and the novel cannabinoid-sensitive g-protein coupled receptor, GPR-55 [12-14]. Both CB1 and GPR-55 are highly expressed in brain regions involved in the regulation of stress, sleep, learning, memory, and reward-seeking, including: the hippocampus, amygdala, striatum, nucleus accumbens, frontal cortex, and entorhinal cortex [15-18]. CB1 is primarily expressed pre-synaptically and regulates GABAergic and glutamatergic release [17, 19], whereas GPR-55 exerts agonist- and tissue-specific actions, including regulation of intracellular calcium levels, extracellular signal-regulated kinases (ERKs), and nuclear factor of activated T-cells (NFAT), through coupling with Gαq/11 [20, 21], Gα12 [20], or Gα13 [22, 23] proteins (for review, see [24]). While the role of CB2 in the brain is unknown, neuronal expression of CB2 has been established in the substantia nigra and hippocampus, and CB2 is found in microglia [25-27].

CBD has a low affinity for CB1 and CB2 receptors [28, 29], but acts as a weak inverse agonist at CB2 receptors [30], and an antagonist at GPR-55 [22]. CBD may antagonize the effects of CB1 agonists through non-CB1 mediated mechanisms [31, 32], and indirectly facilitates endocannabinoid neurotransmission by inhibiting hydrolysis of the endocannabinoid anandamide by fatty acid amide hydrolase (FAAH) [33], and reducing anandamide uptake by the anandamide membrane transporter (AMT) [34].

Other pharmacologic targets of CBD. In addition to its impact on the endocannabinoid system, CBD also acts as an agonist at the serotonin 1A (5-HT1A) receptor [35], produces allosteric modulation of ligand-binding kinetics at μ and δ opioid receptors [36], increases intracellular calcium through activation of transient receptor potential vanilloid type 1 (TRPV1) cation channels [34], and enhances adenosinergic neurotransmission via inhibition of the adenosine transporter [37]. Moreover, CB1 receptors have been shown to regulate 5-HT1A, 5-HT2A, and 5-HT2C receptor functions in rodents [38], and there is evidence that CB2 and 5-HT1A receptors may heterodimerize, modulating their function [39].

Effects of CBD on anxiety and negative affect. In chronic addiction, increased negative affect occurs through the recruitment of the classic stress axis and aversive dynorphin-mediated systems, and negative reinforcement (relief from dysphoric states) plays an important role in maintenance of alcohol or drug use [40-42]. In animal models, alcohol withdrawal is associated with increased activity in the extended amygdala, and pharmacological inhibition of extended amygdala activity reduces both anxiety and alcohol-seeking behaviors associated with withdrawal [41, 43-47]. Higher amygdala reactivity predicts future problem drinking In AUD patients who report alcohol use to mitigate negative emotions [48].

Extensive research in animals and humans demonstrates that CBD dampens activity in circuits mediating anxiety and negative affect, suggesting a possible mechanism of its anti-addictive effects. In animal models, CBD produces anxiolytic, anti-compulsive, anti-fear-conditioning and pro-fear-extinction effects by acting at 5-HT1a and CB1 receptors within the extended amygdala [49-53] and functionally connected brain regions [54-57]. CBD indirectly increases endocannabinoid agonism at the CB1 receptor, reducing extended amygdala output and alcohol seeking [58]. In human experimental studies, CBD at doses between 300–600 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 [57, 59].

Effects of CBD on other domains relevant to addiction. Several other effects of CBD may also act to combat addiction. CBD produces several pro-cognitive effects: it protects against binge ethanol consumption-induced neurotoxicity [60], exerts neurogenerative effects in the hippocampus [61, 62], and attenuates cognitive impairments in several animal models of neurodegenerative disease, likely through its neurogenerative and anti-inflammatory properties [63-65]. In contrast to these pro-cognitive effects, CBD disrupts consolidation and facilitates extinction of fear memories [66, 67] and prevents reconsolidation of

contextual drug-related memories [68]. CBD decreases marble-burying in rodents, an analogue for obsessive-compulsive behavior [69], alters reward-seeking behavior [70], and reduces amotivational symptoms associated with anxiety, depression, and addiction [71, 72].

3.2 Name and Description of the Investigational Agent

CBD is a phytocannabinoid that lacks the rewarding properties and psychoactive effects of tetrahydrocannabinol (THC) [8]. CBD exerts effects both through the endocannabinoid system and through several other signaling pathways. GW pharmaceuticals is developing CBD (Epidiolex®) as a medication for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, and completed successful Phase 3 trials in 2016 [9-11].

Existing data suggest CBD is highly non-toxic to humans. However, clinical data are limited, and its use in the treatment of AUD is experimental. The data and safety monitoring plan is therefore designed to ensure that the risks of medications and study-related procedures are minimized for patients. 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, it has not been FDA-approved for medical use. Therefore, this study will be performed under an Investigational New Drug Application (IND #140108). Refer to the Investigator's Brochure for comprehensive drug information.

3.2.1 **Preclinical Data**

In rodent models, CBD reduces cue-induced heroin seeking, potentiates extinction of cocaine- and amphetamine-induced conditioned place preference [73], and normalizes heroin-seeking-induced changes in glutamatergic GluR1-containing amino-hydroxy-methyl-isoxazolepropionic (AMPA) receptors and CB1 receptor expression in the nucleus accumbens [74]. Work done in the laboratory of Friedbert Weiss (consultant on the current proposal) demonstrated that transdermal CBD at a dose yielding serum CBD concentrations of 300-400ng/ml reduces stress- and cue-induced alcohol- and cocaine- seeking in rodents, with effects lasting up to 138 days post-CBD treatment for alcohol [75]. This regimen also reduced anxiety-like behavior in alcohol-exposed, cocaine-exposed, and drug-naive rodents without impacting locomotor activity or cue- or stress- induced reinstatement for a sweet solution, and reversed impulsive-like behavior induced by alcohol intoxication in a delay discounting task 6-15 days after the cessation of treatment. Another recent report also demonstrated CBD's ability to reduce the reinforcing effects of alcohol at an identical dose of CBD delivered subcutaneously in a microparticle formulation also designed to provide continuous controlled release of CBD [76].

Studies of CBD's effects on addiction-related behaviors in human participants are limited. 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 [77]. However, high concentrations of CBD in cannabis are related to lower attentional bias toward drug stimuli and lower self-rated liking of cannabis-related stimuli relative to cannabis with a low ratio of CBD to THC [78], CBD may reduce cigarette smoking in dependent humans [79], and a single case study reported that daily CBD prevented marijuana withdrawal symptoms [80].

3.2.2 **Clinical Data to Date**

Studies of CBD's effects on addiction-related behaviors in human participants are limited. 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 [77]. However, high concentrations of CBD in cannabis are related to lower attentional bias toward drug stimuli and lower self-rated liking of cannabis-related stimuli relative to cannabis with a low ratio of CBD to THC [78], CBD may reduce cigarette smoking in dependent humans [79], and a single case study reported that daily CBD prevented marijuana withdrawal symptoms [80].

CBD has also been shown to produce anxiolytic and anti-epileptic effects in human participants. CBD negates the anxiogenic effects of simulated public speaking both in healthy [81] and in anxious individuals [82], and also reduces the anxiogenic effects of THC [83, 84]. CBD alters regional cerebral blood flow in limbic and paralimbic regions important for anxiety and addiction in healthy [85], and anxious [86] individuals and attenuates blood oxygenation level-dependent signal in the same structures during response inhibition [87] and presentation of

fearful faces [59]. GW pharmaceuticals is developing CBD (Epidiolex®) as a medication for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, and completed successful Phase 3 trials in 2016 [9-11].

3.2.3 **Dose Rationale (if applicable)**

CBD has been given up to 600 mg daily orally for cannabis dependence [80], and the one existing human study of CBD's impact on the acute effects of alcohol used a dose of 200 mg [88]. CBD was given to patients with schizophrenia up to 1280 mg/day [89], and Phase 3 trials of CBD for seizure disorders used doses of 20 mg/kg/day oral CBD solution (1400 mg/day for a 70 kg person) [9, 11].

Consistent and clinically significant effects on fear and anxiety in the absence of intoxicating, psychotomimetic, and psychotropic effects have been observed with oral dosing in the range of 300-600 mg/day [90]. However, preliminary work performed by Dr. Weiss and others [76] indicates that higher doses (>30mg/kg/day transdermal/subcutaneous) yielding serum CBD concentrations in the range of 300-400ng/ml are required to reduce alcohol-reinforced reward-seeking behaviors in rodents.

Oral dosing of CBD is complicated by limited oral absorption, which is similar to THC at approximately 6% [91], and by the possibility that high doses of CBD could convert to THC when delivered orally [92, 93]. However, oral delivery of CBD in a sesame-oil formulation at a dose of 12mg/kg (roughly equivalent to 1000mg/day adjusted for average human body weight) was shown to yield serum concentrations within the targeted range in rats [94]. We therefore will administer CBD vs. Placebo orally in a lipid-based formulation at 600mg/day for an initial period of 4 weeks, followed by 1200mg/day for an additional 4 weeks, to reach our target circulating levels of 300-400ng/ml in a human AUD sample. Two studies in humans have shown no progressive accumulation of CBD levels with repeated daily dosing, including following 6 weeks of oral administration of 700mg/day CBD [95, 96], and 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 circulating levels of CBD within a week.

Plasma CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC, and Anandamide levels will be assessed prior to the first dose (T1), 45 min after ingesting the first dose (T1), and 45 min after ingesting the morning dose after 1 day (T2, T5), 1 week (T3, T6), and 4 weeks (T4, T7) of treatment with each dose of CBD (600mg/day, 1200mg/day). Anandamide levels will also be assessed at these timepoints in placebo treated participants. We will also assess pre-CBD dosing plasma levels of CBD and Anandamide prior to ingesting the morning dose after 1 week (T3, T6) and 4 weeks (T4, T7) of treatment with each dose of CBD. Anandamide levels will also be assessed at these timepoints in placebo-treated participants.

3.3 Rationale

There is increasing recognition of the role of the endocannabinoid system in neurobiological processes and behavioral domains relevant to the pathophysiology and treatment of addiction. The phytocannabinioid cannabidiol has attracted considerable attention due to its lack of intoxicating effects, low abuse potential, excellent safety, and unique pharmacological profile.

CBD reliably reduces anxiety-like behavior in animals, attenuates anxiogenic effects of stressful stimuli in healthy and anxious individuals, and disrupts consolidation and facilitates extinction of fear memories. More directly relevant to addiction, CBD prevents reconsolidation of contextual drug-related memories and may decrease impulsive behaviors, craving, and withdrawal. Very recently, rodent studies have provided strong direct evidence of clinically relevant effects of CBD in models of alcohol use disorder (AUD). In two independent studies, treatment with CBD produced marked and persisting decreases in alcohol self-administration and preference for alcohol, and alcohol-, cue- and stress-induced reinstatement. These findings suggest that CBD could have potential as a treatment for AUD. However, there are few studies of the effects of CBD in humans with addictive disorders, and limited data on CBD's safety in AUD populations, particularly at doses shown to be effective in animal models of AUD.

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 drinking-related outcomes in patients with alcohol use disorder (AUD). We will evaluate the safety of an extended daily CBD treatment regimen in an AUD population, assess the impact of CBD on neuropsychological and neurophysiological domains implicated in AUD, and

generate preliminary data on the impact of CBD on alcohol consumption. Following screening and baseline assessments, 40 participants will be randomized in 1:1 ratio to receive either placebo or 600mg CBD/day (PO) for 4 weeks, immediately followed by 1200mg CBD/day (PO) for an additional 4 weeks (8 weeks in total). These doses are calculated to achieve the serum CBD levels reported to reduce alcohol-seeking behavior in animal studies. Assessments will be completed after 45 minutes, 1 day, 1 week and 4 weeks of treatment with each dose of CBD vs. placebo, and 1 and 4 weeks after the cessation of treatment. Outcomes will include circulating levels of CBD, Anandamide, Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC, safety measures (adverse events, cognitive and motoric function), and physiological and psychological domains relevant to AUD including self-reported craving, depression, and anxiety; responses to personalized scripts designed to elicit stress- and cue-induced craving and anxiety; and drinking outcomes across 8 weeks of treatment and 4 weeks of follow-up.

3.4 Potential Risks & Benefits

3.4.1 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, and convulsion. All participants in these trials were on concomitant anti-seizure medications. CBD is not noticeably psychoactive.

3.4.2 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.

4 Objectives and Purpose

4.1 Primary Objective

The primary objective of this study is to assess circulating cannabinoid levels and safety of CBD administered to patients with AUD at doses calculated to yield circulating CBD levels comparable to those that produced clinically relevant effects in animal models of AUD. We predict that within-group circulating CBD levels will stabilize within one week (i.e. pre-CBD dosing levels obtained after 1 week of treatment will not differ from those obtained after 4 weeks of treatment at each dose), that circulating CBD levels obtained at the 1200 mg/day dose will be comparable to those associated with anti-addictive effects in animal models, (i.e., in the range of 200-400 ng/ml), and that no clinically significant cognitive or motoric impairments, CBD-related serious adverse events, or persisting adverse effects will be observed.

4.2 Secondary Objectives

A secondary objective of this study is to contrast the effects of CBD to those of placebo on several physiological and psychological domains relevant to AUD. Relative to placebo, we predict that CBD will improve self-report measures of craving, anxiety, mood, and self-efficacy, and attenuate stress- and alcohol cue-induced craving and physiological stress response.

The final exploratory objective of this study is to assess the impact of CBD on drinking behavior. Relative to the placebo-treated group, we predict that CBD-treated participants will have fewer heavy drinking days during and for four weeks after treatment with 1200mg/day CBD vs. placebo.

5 Study Design and Endpoints

5.1 Description of Study Design

The proposed study is a phase I/II, single-center, double-blind, randomized proof-of-concept study designed to assess feasibility and contrast effects of CBD treatment to those of placebo on drinking-related outcomes in patients with alcohol use disorder (AUD). We will evaluate the safety of an extended daily CBD treatment regimen in an AUD population, assess the impact of CBD on neuropsychological and neurophysiological domains implicated in AUD, and generate preliminary data on the impact of CBD on alcohol consumption. Following screening and baseline assessments, 40 participants will be randomized in 1:1 ratio to receive either placebo or 600mg CBD/day (PO) for 4 weeks, immediately followed by 1200mg CBD/day (PO) for an additional 4 weeks (8 weeks in total). These doses are calculated to achieve the serum CBD levels reported to reduce alcohol-seeking behavior in animal studies.

5.1.1 Primary Study Endpoints

Circulating cannabinoid levels

Circulating levels of CBD, Anandamide, Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC will be assessed in CBD-treated participants 45 minutes after the initial administration (T1, T4), 1 day (T2, T5), 1 week (T3, T6), and 4 weeks (T4, T7) of treatment with each dose of CBD. Anandamide levels will also be assessed at these timepoints in placebo treated participants. Additionally, circulating levels of CBD and anandamide will be assessed in CBD-treated participants 12 hours after ingestion of the preceding evening dose following 1 week (T3, T6) and 4 weeks (T4, T7) of administration of each dose of CBD. Plasma CBD levels will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) by collaborators at the Nathan Kline Institute.

Safety

Safety will be assessed by collection of adverse events at all visits after treatment is initiated. LFTs will be obtained at screening, as well as weeks 4, 8, and 9 to assess liver function during and after treatment with study medication. Risk of suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) [111] by a licensed Clinical Psychologist, NP or MD as part of each study visit (except for the 1-day/T2 and 4 weeks+1-day/T5 visits).

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 [97]. The Addiction Resource Center Inventory (ARCI), 49-item version [98], 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. Between-group differences on psychomotor tasks (T1-T8), cognitive measures (T3, T6) and number of adverse events (T1-T9) will be assessed.

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 [99, 100], the Mental Rotation Task (MRT) will evaluate visuospatial ability [101, 102], a Time Reproduction Task (TRT) will measure encoding and retrieval of time intervals [88], and several WM Span tasks (OSpan, RSpan, SymSpan, RotSpan) will measure working memory capacity [103, 104].

5.1.2 Secondary Study Endpoints

Additional outcomes will include physiological and psychological domains relevant to AUD including self-reported craving, depression, and anxiety; responses to personalized scripts designed to elicit stress- and cue-induced craving and anxiety; and drinking outcomes across 8 weeks of treatment and 4 weeks of follow-up.

AUD-Related Measures:

The Penn Alcohol Craving Scale (PACS) [105] 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. Mood and Anxiety will be measured with the Beck Anxiety Inventory (BAI) [106] and Beck Depression Inventory-II (BDI-II) [107] scales before CBD treatment, at the end of treatment, and at the 2 week follow-up. Self-efficacy will be assessed using the Alcohol Abstinence Self-Efficacy Scale (AASE) [108], 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 [109, 110].

The Cue and Stress Response Task will be performed at the 5- week time-point using methodology developed in Rajita Sinha's lab, similar to those in used in past studies with alcohol dependent patients [112, 113]. Dr. Sinha will provide consultation on the implementation of these methods. Briefly, imagery scripts will be developed at baseline and again following 4 weeks of treatment. Stress imagery scripts will be based on a recent highly stressful 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 [59], suggesting threat-related sympathetic arousal may serve as a proxy for amygdala activation [114]. Participants will complete Likert scale ratings of vividness, craving, anxiety, and the 30-item Differential Emotion Scale [112, 113] 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 [112, 113]. The entire imagery protocol will take 120 minutes. The order of the sessions will be randomized and counterbalanced among participants. This task will be completed at 5 weeks, i.e. after 1 week of treatment at 1200mg daily. At this point, we expect steady-state circulating CBD levels to have been reached. It is important to assess stress- and cue- response at the high dose because it is possible that anxiolytic effects decrease at high doses of CBD, while effects on alcohol consumption are expected to increase with dose.

5.1.3 Exploratory Endpoints

Alcohol consumption will be assessed with Time-line Follow-back (TLFB) [115] and percent carbohydrate-deficient transferrin (CDT) in serum. History of trauma will be assessed with the Trauma History Questionnaire (THQ) [116] at baseline.

6 Study Enrollment and Withdrawal

6.1 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 18-65
2) DSM-5 diagnosis of moderate or severe AUD
3) Able to provide voluntary informed consent
4) At least 6 heavy drinking days (4 or more drinks for a woman, 5 or more drinks 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 duration of the study

6.2 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, Type I Diabetes)
3) DSM-5 diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder
4) High risk of adverse emotional or behavioral reaction based on investigator's clinical evaluation (e.g., evidence of serious personality disorder, antisocial behavior, serious current stressors, lack of meaningful social support)
5) Current significant suicidality (assessed using the C-SSRS), any suicidal behavior in the past 12 months, or any history of serious suicide attempts requiring hospitalization, or current significant homicidality
6) History of severe Traumatic Brain Injury (LOC > 24 hours)
7) 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
8) Significant laboratory abnormalities, including significantly impaired liver function*, serious abnormalities of complete blood count or metabolic panel
9) Active legal problems likely to result in incarceration within 12 weeks of treatment initiation
10) Pregnancy or lactation
11) 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.
12) Allergy to any ingredient of the study compound.
13) Current treatment for AUD, with exception of AA/12-step treatment
14) No inpatient psychiatric treatment in the last 12 months, with the exception of detox and extended Emergency Department stays
15) A positive urine drug screen for THC, cocaine and/or opioids at screen

*Significantly impaired liver function will be operationalized as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (All Phos) > 2.5 × upper limit of normal (ULN), or Total bilirubin > 2.0 × ULN in the absence of Gilbert's syndrome.

6.3 Strategies for Recruitment and Retention

Subjects will be approximately 60 women and men, age 18 or greater, with moderate to severe AUD, recruited from the public through local media advertisements, 40 of whom will be randomized and complete the treatment portion of the study. Participants will be recruited between approximately September 2019 and August 2021. Informed consent will be given at NYUSoM space occupied by the PI within Bellevue Hospital in New York, NY, following an initial telephone consent and screen to determine potential eligibility for the study. Participants will be asked to share information about their drinking and use of any other drugs, anxiety and mood, and undergo a full medical and psychiatric evaluation at screen by licensed providers. Participants will have the option of completing the initial portion of the screening visit remotely. In this case, participants will be asked to share information about their drinking and use of any other drugs, anxiety and mood, and undergo a full psychiatric evaluation by licensed providers remotely via Webex. If inclusion and exclusion criteria continue to be met following the remote portion of the screening visit, participants will be invited to undergo a full in-person medical evaluation by licensed providers to complete the screening visit.

Active recruitment will also take place through social media sources, including Facebook and Twitter, 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, and local universities. Recruitment materials will also be posted to the laboratory's website (centerforpsychedelicmedicine.com).

Clinicians will provide study staff with names and contact info for interested patients, who will sign an

authorization form allowing the clinic to release only their contact information to study staff (no clinical or diagnostic information will be shared). Once referrals are given, the study team will access EPIC to determine the participant's initial eligibility. Subjects will also be recruited through advertisements in local newspapers. Additionally, the study team will use NYU's DataCore service to gather information from EPIC for current NYU patients who may be eligible.

Active recruitment will also take place through social media sources, including Facebook, ResearchMatch, Craigslist, and Instagram, 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, and local universities.

Potential participants contacted through any of the above channels 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. 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 an in-person screening visit or for the remote portion of the screening visit, followed by the remaining in-person portion of the screening visit, if inclusion and exclusion criteria continue to be met.

6.4 Duration of Study Participation

Including screening and follow-up visits, the total duration of participant involvement will be approximately 12 weeks. Total time of contact during these 12 weeks is estimated at 28 hrs.

6.5 Total Number of Participants and Sites

Recruitment will end when approximately 60 participants are enrolled. It is expected that approximately 60 participants will be enrolled in order to produce 40 randomized participants.

6.6 Participant Withdrawal or Termination

6.6.1 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

6.6.2 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 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 3 times by telephone and twice by email. If the participant fails to respond, locators identified by the participant at screening will be contacted in the method specified by the participant. If participants withdraw, are terminated, or are lost to follow-up prior to the end of the 8-week treatment phase (prior to T7), they will not be replaced to allow for 40 participants to complete the 8-week treatment phase (through T7), and their partial data will be handled according to the statistical analysis plan (SAP).

6.7 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. Bogenschutz, 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.

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

7.1 Study Agent(s) and Control Description

The TN-C200M2 Oral Capsules and matching placebo for this study are provided by Tilray$_{TM}$. 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 mixture of surfactants, co-surfactants, co-solvents and carrier oils. The placebo capsules will contain no CBD.

7.1.1 **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.

7.1.2 **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.

7.1.3 **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.

7.1.4 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.

7.1.5 Dosing and Administration

Participants will self-administer CBD vs Placebo twice daily for a total of 600mg/day CBD vs. Placebo for the first four weeks of treatment and 1200mg/day CBD vs. Placebo for weeks 5-8 of treatment. For the first four weeks of treatment, 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. During weeks 5-8 of treatment, participants will self-administer three 200mg capsules every morning following a light meal at approximately the same time of day, and an additional three 200mg capsules approximately 12 hours later following a light meal.

7.1.6 Route of Administration

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

7.1.7 Starting Dose and Dose Escalation Schedule

All participants will receive 600mg/day CBD vs. Placebo for weeks 1-4 of treatment, unless contraindicated, and will be escalated to 1200mg/day CBD vs. Placebo for weeks 5-8 of treatment, unless contraindicated.

7.1.8 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 200-400mg/day every two days until symptoms are resolved or tolerable. Dose may be titrated back up toward the full dose by 200 mg/day/week as tolerated. Individuals who cannot tolerate the 600mg dose will remain on their maximum tolerable dose during the second 4-week period 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.

7.1.9 Duration of Therapy

The duration of the active treatment portion of the study is 8 weeks, followed by an additional 4-week follow-up period. In order for participants to be included in the primary statistical analyses, they must complete the 8-week treatment phase of the study (through T7).

7.2 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, 600, or 1200 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).

7.3 Study Behavioral or Social Intervention(s)

All participants will receive Medical Management from a licensed MD or NP listed as study personnel, based on the model developed for the NIAAA COMBINE trial [117]. 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 study clinician focus on: support for recovery, treatment participation, reporting possible adverse effects, and medication compliance. The PI has experience adapting this model in a prior alcohol pharmacotherapy trial [118].

7.3.1 **Administration of Intervention**

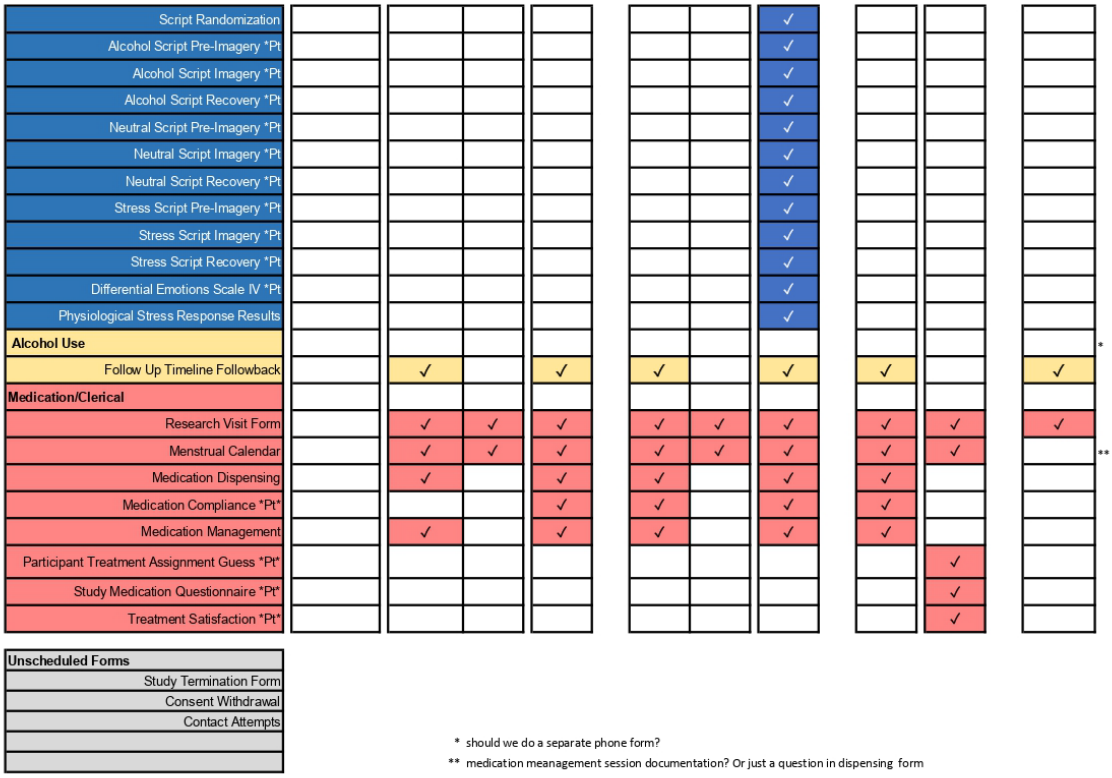
CBD (or placebo) will be administered daily for 8 weeks. The first administration of each dose of CBD vs. placebo (at T1 and T4) will take place at the study site. Participants will remain at the study site with a study team member for approximately 2 hours following the initial administration of each 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 [97]). 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 dispensed the proper quantity of study drug (CBD or placebo) to self-administer daily at home until the next scheduled study visit (i.e. a 1- or 3-week supply, depending on the visit).

7.3.2 Assessment of Subject Compliance with Study Intervention

To maximize medication compliance, we will implement a smartphone-assisted medication adherence platform [119] 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.

Bogenschutz CBD for AUD

	DOSE		600mg					1200mg			
	TIMEPOINT VARIABLE	T0	T1	T2	T3	T4	T5	T6	T7	T8	PHONE T9
	TIMELINE	Screen	Baseline	1 day	1 wk	4 wks	4wk+1d	5 wks	8 wks	9 wks	12 wks
Inclusion / Exclusion Criteria		✓									
Informed Consent Quiz		✓									
Informed Consent Documentation		✓									
Confidential Contact Information		✓									
Demographics		✓									
Medical History		✓									
Family History		✓									
Physical Examination		✓									
Phenx Quality of Life *Pt*		✓									
Phenx Sub Alc Cig		✓									
CIWA-Ar		✓									
CAPS											
SCID-5 Results		✓									
Screen Menstrual Calendar		✓									
Urine Pregnancy Test		✓	✓								
Urine Drug Screen		✓									
Screening Timeline Followback		✓									
Serum Pregnancy Test Results		✓									
Screening Blood/Urinalysis Lab Results		✓									
Concurrent Medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Inclusion Exclusion Criteria Checklist		✓									
Screen Visit Form		✓									
CBD/THC/AEA Serum Levels			✓		✓	✓		✓	✓		
Cannabinoid Blood Collection [Trough]			✓		✓	✓		✓	✓	✓	
Cannabinoid Blood Results [Trough]			✓		✓	✓		✓	✓	✓	
Cannabinoid Blood Collection [Peak]			✓	✓	✓	✓	✓	✓	✓		
Cannabinoid Blood Results [Peak]			✓	✓	✓	✓	✓	✓	✓		
CDT			✓			✓			✓		
CDT Blood Collection			✓			✓			✓		
CDT Blood Results			✓			✓			✓		
LFT		✓				✓			✓	✓	
LFT Blood Collection		✓				✓			✓	✓	
LFT Blood Results		✓				✓			✓	✓	
SAFETY & Psychomotor Effects			✓	✓	✓	✓	✓	✓	✓	✓	
Vital Signs		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	
Alcohol Breathalyzer			✓	✓	✓	✓	✓	✓	✓	✓	
Addiction Research Center Inventory *Pt*			✓	✓	✓	✓	✓	✓	✓	✓	
Field Sobriety Tests			✓	✓	✓	✓	✓	✓	✓		
Cognitive Function					✓			✓			
Rey Auditory Verbal Learning Task Results					✓			✓			
Mental Rotation Task Results					✓			✓			
Time Production Task					✓			✓			
WM Span Tasks Results					✓			✓			
AUD-Related Domains			✓		✓	✓		✓	✓	✓	
Readiness Rulers *Pt*			✓		✓	✓		✓	✓	✓	
Treatment Goal *Pt			✓		✓	✓		✓	✓	✓	
Alcohol Abstinence Self-efficacy *Pt*			✓		✓	✓		✓	✓	✓	
Short Inventory Of Problems *Pt*			✓		✓	✓		✓	✓	✓	
Penn Alcohol Craving Scale *Pt*			✓		✓	✓		✓	✓	✓	
Self-compassion Short Form *Pt*			✓		✓	✓		✓	✓	✓	
Beck Anxiety Inventory			✓		✓	✓		✓	✓	✓	
Beck Depression Inventory			✓		✓	✓		✓	✓	✓	
C-SSRS			✓		✓	✓		✓	✓	✓	
PTSD-Related Domains											
THQ			✓								
CTQ			✓								
PCL-5											
Cue/Stress Script Interview											
Imagery Scripts			✓								
Cue/Stress Task								✓			



8 Study Procedures and Schedule

8.1 Study Procedures/Evaluations

Inclusion/exclusion criteria:

Medical screening by a licensed NP or MD will include medical history and physical exam, liver function tests (LFTs), complete blood count, serum chemistries, urinalysis, serum pregnancy test, and weight. The licensed provider 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 [120]. Individuals will have the option to be audiotaped during the interview. 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 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 [121], a Urine drug screen (UDS) will be done at each in-person study 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) to verify lack of pregnancy. History of trauma will be assessed at baseline with the Trauma History Questionnaire (THQ) [116].

Confirmation of target CBD levels and determination of other cannabinoid levels:

Plasma levels of cannabinoids including CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC and Delta-9 Carboxy THC will be obtained at baseline, as well as 45 minutes, 1 day, 1 week and 4 weeks after starting each dose of treatment with CBD only. Plasma levels of anandamide will be obtained at the aforementioned timepoints after starting each dose of treatment with CBD or placebo. Anandamide and Cannabidiol will be analyzed by LC/MS/SIM. Other analytes by Capillary GC/MS/SIM/NCI in one column. Both systems using deuterated analytes as internal standards i.e. isotope dilution procedure. These analyses will be performed at the Nathan Kline Institute (NKI).

Safety:
Safety will be assessed by collection of adverse events using the Systemic Assessment for Treatment of Emergent Events (SAFTEE) [124] measure at all visits after treatment is initiated. LFTs will be obtained at screening, as well as weeks 4, 8, and 9 to assess the liver function during and after treatment with study medication. Risk of suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) [111] by a licensed psychologist, NP or MD as part of each study visit (except for the 1-day/T2 and 4 weeks+1-day/T5 visits), including screening and baseline.

Release of Health Information

The Authorization for Release of Study Information form permits research staff to communicate to listed family members designated by the participant until their participation in the study has ended. The Authorization of Release form will only release research related data. Patient's request to have family members notified of specified study related information may be useful for a variety of occasions. For example, designated family could be notified of medication related information or laboratory blood results if the participant requests such information to be shared to their designated family member. The visit schedule and medication compliance aspects of the study may be easier to navigate if unexpected situations occur, such as abnormal lab results or missed visits to pick up study medication. Hence, participants may like to have designated family members involved. The study related health information that is reported on the Authorization of Release form to be discussed with designated family members is the only information that study team members will be allowed to discuss or share. Study team members that will communicate with participant family members include the study coordinator, PI, and NP. Communication with family members will happen via phone call and email correspondence. Release of health information and study information will be done in a manner that does not un-blind participants, study staff, or designated family members. Information will be released to ensure subject confidentiality. The Authorization of Release form allows study participant's to specify health information from the study that will be released to their designated family member. Other study related information that is not designated on the release form will not be released to their designated family member. The Authorization of Release form will be kept and filed with the Informed Consent forms in the ICF Study binder for CBD-AUD. In addition, a study participant log will be kept and updated accordingly to keep track of participants who have submitted this form.

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 [97]. The Addiction Resource Center Inventory (ARCI), 49-item version [98], 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 [99, 100], the Mental Rotation Task (MRT) will evaluate visuospatial ability [101, 102], a Time Reproduction Task (TRT) will measure encoding and retrieval of time intervals [88], and several WM Span tasks (OSpan, RSpan, SymSpan, RotSpan) will measure working memory capacity [103, 104].

AUD-related domains:
The Penn Alcohol Craving Scale (PACS) [105] 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. Mood and Anxiety will be measured with the Beck Anxiety Inventory (BAI) [122] and Beck Depression Inventory-II (BDI-II) [107] before CBD treatment, 1, 4, 5, and 8 weeks into treatment, and at the end of treatment. Self-efficacy will be assessed using the Alcohol Abstinence Self-Efficacy Scale (AASE) [108], 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 [109, 110].

The Cue and Stress Response Task will be performed at the 5- week time-point using methodology developed in Rajita Sinha's lab, similar to those in used in past studies with alcohol dependent patients [112, 113]. Dr. Sinha will provide consultation on the implementation of these methods. Briefly, imagery scripts will be developed at baseline and again following 4 weeks of treatment. Stress imagery scripts will be based on a recent highly stressful 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 [59], suggesting threat-related sympathetic arousal may serve as a proxy for amygdala activation [114]. Participants will complete Likert scale ratings of vividness, craving, anxiety, and the 30-item Differential Emotion Scale [112, 113] 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 [112, 113]. The entire imagery protocol will take 120 minutes. The order of the sessions will be randomized and counterbalanced among participants. This task will be completed at 5 weeks, i.e. after 1 week of treatment at 1200mg daily. At this point, we expect steady-state circulating CBD levels to have been reached. It is important to assess stress- and cue- response at the high dose because it is possible that anxiolytic effects decrease at high doses of CBD, while effects on alcohol consumption are expected to increase with dose.

Alcohol use:
Alcohol consumption will be assessed with Time-line Follow-back (TLFB) [115] and percent carbohydrate-deficient transferrin (CDT) in serum.

8.2 Laboratory Procedures/Evaluations

Plasma will be collected at baseline, as well as 45 minutes, 1 day, 1 week and 4 weeks after starting each dose of treatment with CBD or placebo for measurement of circulating cannabinoid levels. Serum will be collected at baseline, at 4 weeks, and at 8 weeks for measurement of CDT.

8.2.1 Specimen Preparation, Handling, and Storage

Blood will be drawn at several time points to establish 45 minutes post- and pre-CBD dosing levels of CBD, according to the study's SOP. Briefly, we will measure circulating cannabinoid levels at 45 minutes, 1 day, 1 week and 4 weeks after treatment with each dose of 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. Plasma CBD levels will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) by the Nathan Kline Institute (NKI).

8.2.2 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 SOP. A specimen tracking log will be utilized to record dates and times

that each specimen was collected and shipped. Specimens may be shipped overnight between 9:00am and 5:00pm on business days except Fridays.

8.3 Study Schedule

Procedures for minimizing COVID-19 risk among participants and study team members during required in-person visits (including routine temperature checks, use of personal protective equipment, symptom checks, etc.) are outlined in the COVID Safety Procedures SOP (R:\etc-research-01\CBD-Alcohol\1. CBD-AUD\SOPs (Standard Operating Procedure)\ SOP_17-01001_COVIDSafety_Procedures_07.20.2020.docx).

8.3.1 Screening

Option 1: In-person Screening Visit (T0)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical and psychiatric history to determine eligibility based on inclusion/exclusion criteria.
- 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, alcohol, drug, and tobacco use history
- Collect urine for urine drug analysis, urinalysis, urine pregnancy test
- Collect blood for LFTs, complete blood count, serum chemistries, serum pregnancy test
  Schedule study visits for participants who are eligible and available for the duration of the study

Option 2: Two-part Remote and In-person Screening Visit (T0a/b)

Part a: Remote Screening

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical and psychiatric history to determine eligibility based on inclusion/exclusion criteria.
- Review concurrent medications to determine eligibility based on inclusion/exclusion criteria.
- Obtain demographic information, alcohol, drug, and tobacco use history
- test

Part a: In-person Screening

- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect urine for urine drug analysis, urinalysis, urine pregnancy test
- Collect blood for LFTs, complete blood count, serum chemistries, serum pregnancy
- Schedule study visits for participants who are eligible and available for the duration of the study

8.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (T1)

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, other assessments
- Record results of evaluations of safety, psychomotor effects and AUD-related domains
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD levels, before dosing, and post-CBD levels, 45 minutes after dosing)
- Collect blood for CDT (carbohydrate deficient transferrin) levels
- Administer the study treatment
- Record adverse events as reported by participant or observed by investigator
- Provide participants with sufficient study medication to administer daily until the next scheduled visit, and instructions for how to use the study medication and document their use

8.3.3 Intermediate Visits

8.3.3.1 Visit 2

1 day (T2)

- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (45 minutes post-CBD levels)
- Record adverse events as reported by participant or observed by the coordinator
- Record vital signs, results of evaluations of safety, and psychomotor effects

8.3.3.2 Visit 3

1 week (T3)

- Collect urine for urine drug analysis and urine pregnancy test
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD and 45 minutes post-CBD levels)
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, results of evaluations of safety, psychomotor/subjective effects, cognitive function, AUD-related domains and drinking
- Provide additional medication to the participant according to the study's MOP requirements
- Record participant's adherence to treatment program

8.3.3.3 Visit 4

4 weeks (T4)

- Collect urine for urine drug analysis and urine pregnancy test
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD and 45 minutes post-CBD levels), LFTs
- Collect blood for CDT levels
- Record adverse events as reported by participant or observed by investigator
- Record vital signs, results of evaluations of safety, psychomotor/subjective effects, AUD-related domains, and drinking
- Provide additional medication to the participant according to the study's MOP requirements
- Record participant's adherence to treatment program

8.3.3.4 Visit 5

4 weeks + 1 day (T5)

- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (45 minutes post-CBD levels)
- Record adverse events as reported by participant or observed by coordinator
- Record vital signs, results of evaluations of safety, psychomotor/subjective effects

8.3.3.5 Visit 6

5 weeks (T6)

- Collect urine for urine drug analysis and urine pregnancy test
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD and 45 minutes post-CBD levels)
- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of evaluations of safety, psychomotor/subjective effects, cognitive function, AUD-related domains, cue/stress response task, and drinking
- Provide additional medication to the participant according to the study's MOP requirements
- Record participant's adherence to treatment program

8.3.3.6 Visit 7

8 weeks (T7)

- Collect urine for urine drug analysis and urine pregnancy test
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD and 45 minutes post-CBD levels), LFTs
- Collect blood for CDT levels
- Record adverse events as reported by participant or observed by investigator

- Record vital signs, results of evaluations of safety, psychomotor/subjective effects, AUD-related domains, and drinking
- Provide additional medication to the participant according to the study's MOP requirements
- Record participant's adherence to treatment program

8.3.3.7 Visit 8

9 weeks (T8)

- Collect urine for urine drug analysis and urine pregnancy test
- Collect blood for CBD, Delta-9 THC, 11-Hydroxy Delta-9 THC, Delta-9 Carboxy THC and Anandamide levels (pre-CBD levels), LFTs
- Record adverse events as reported by participant or observed by coordinator
- Record vital signs, results of evaluations of safety, psychomotor/subjective effects, AUD-related domains, and drinking

8.3.4 Final Telephone Follow-Up

12 weeks (T9)

- Record adverse events as reported by participant
- Record drinking

8.3.5 Unscheduled Visit

Unscheduled visits will be documented on an unscheduled visit form.

8.4 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.

8.5 Prohibited Medications, Treatments, and Procedures

Treatment with medications including cannabinoids; treatments for addictions including alcohol; moderate to strong inhibitors of CYP3A4 or CYP2C19; medications metabolized primarily by CYP3A4, CYP3A5, or CYP3A7: and medications with a narrow therapeutic index which are substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19, CYP1A2, or CYP2B6 will not be permitted unless discussed with and approved by the PI.

9 Definitions of Key Terms

An adverse event (AE; also referred to as an adverse experience) 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.

10 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.

11 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) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

11.1 Solicitation of AEs

At all follow-up visits occurring after study medication has been administered, the SAFTEE questionnaire [124] will be used to assess AEs through the following three prompts:

> *"Have you had any physical or health problems since our last visit?"*
>
> *"Have you noticed any changes in your physical appearance since our last visit?"*
>
> *"Have you cut down on the things you usually do because of not feeling well physically since our last visit?"*

If the subject responds *"yes"* to any of these questions then the following question will be asked:

"Could you describe in more detail what this effect means to you?"

The presence or absence of specific AEs should not be solicited from subjects.

11.2 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).

11.3 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.

11.4 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.

12 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.

12.1 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.

12.2 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

12.3 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.

13 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).

14 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.

15 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.

16 Reporting Procedures

16.1 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 o*n 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 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).

16.2 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.

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.

16.3 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.

16.4 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.

17 Reporting of Investigational Medicinal Product Quality Complaints

17.1 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.

17.2 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.

18 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.

19 Safety Oversight

Medical and Safety Monitoring

The research team (project manager, coordinators, and research assistants) will submit any adverse events to the PI. The PI is 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. All AEs will be reviewed on a weekly basis to observe trends or unusual events.

The PI will generate and present reports for Data Safety Monitoring Board (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 individuals appointed by the PI. The members of the DSMB will have the following backgrounds/expertise: one member with expertise in clinical trials for alcohol use disorder, one member with expertise in clinical trials involving pharmacological interventions, one member with expertise in clinical trials for mood disorders, and one member with expertise in clinical trials for anxiety disorders. 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.

20 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.

21 Statistical Considerations

21.1 Statistical and Analytical Plans (SAP)

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

21.2 Statistical Hypotheses

Hypothesis 1a: Within-group circulating CBD levels will stabilize within one week, i.e. pre-CBD dosing (12 hour) levels obtained after 1 week of treatment will not differ from those obtained after 4 weeks of treatment at each dose.
Hypothesis 1b: Circulating CBD levels obtained at the 1200 mg/day dose will be comparable to those associated with anti-additive effects in animal models, i.e., in the range of 200-400 ng/ml.
Hypothesis 1c: No clinically significant cognitive or motoric impairments, CBD-related serious adverse events, or persisting adverse effects will be observed.
Hypothesis 2a: Relative to placebo, CBD will improve self-report measures of craving, anxiety, mood, and self-efficacy.
Hypothesis 2b: Relative to placebo, CBD will be associated with decreased stress- and alcohol cue-induced craving and physiological stress response
Hypothesis E: Relative to the placebo-treated group, CBD-treated participants will have fewer heavy drinking days during and for four weeks after treatment with 1200mg/day CBD vs. placebo.

21.3 Description of Statistical Methods

21.3.1 General Approach

The distributional characteristics of the measures used to investigate the aims of the study will be assessed and data transformations will be explored if necessary. For all hypotheses, linear mixed effects models will be constructed including treatment group as a fixed between-subjects factor, time (T0-T9) as a fixed within-subjects factor, and subject as a random effect. Treatment groups will also be compared on baseline measures of alcohol consumption (% drinking days and % heavy drinking days), alcohol craving (PACS), anxiety (BAI), mood (BDI-II), and self-efficacy (AASE), and baseline scores on these measures will be utilized as covariates for hypothesis evaluation.

21.3.2 Analysis of the Primary Endpoint(s)

For Hypothesis 1a, acute circulating levels of CBD will be assessed in CBD-treated participants 45 minutes after initial administration (T1, T4), and 45 minutes after administration of the morning dose of medication following 1 day (T2, T5), 1 week (T3, T6), and 4 weeks (T4, T7) of treatment with each dose of CBD. Additionally, circulating levels of CBD will be assessed in CBD-treated participants 12 hours after ingestion of the preceding evening dose following 1 week (T3, T6) and 4 weeks (T4, T7) of administration of each dose of CBD. Levels of CBD (mean and standard deviation) will be reported at each timepoint and effects of dose and timepoint will be evaluated. For Hypothesis 1b, circulating CBD levels (mean and standard deviation) 45 minutes after administration of the morning dose of medication following 1 week (T3, T6) and 4 weeks (T4, T7) of treatment with each dose of CBD will be reported in CBD-treated participants. For Hypothesis 1c, between-group differences on psychomotor tasks (T1-T8), cognitive measures (T3, T6) and number of adverse events (T1-T9) will be assessed.

21.3.3 Analysis of the Secondary Endpoint(s)

For Hypothesis 2a, between- and within- group differences on measures of craving, anxiety, depression, and self-efficacy (T1, T3, T4, T6, T7, T8) will be evaluated. For Hypothesis 2b, linear mixed effects models will be constructed as described by Sinha et al. [123] with treatment group (CBD vs. placebo) included as a fixed

between-subjects factor, time (nested factor including pre-imagery, imagery, and recovery periods at both T3 and T6) and script type (stress, alcohol cue, neutral) as fixed within-subjects factors, with subject as a random effect. Between- and within- group comparisons and interactions for measures of craving, anxiety, and physiological stress response will be assessed.

21.3.4 Safety Analyses

Means and standard deviations of acute circulating CBD and THC levels within CBD-treated participants 45 minutes after initial administration (T1, T4), and 45 minutes after administration of the morning dose of medication following 1 day (T2, T5), 1 week (T3, T6), and 4 weeks (T4, T7) of treatment with each dose of CBD will be assessed to determine whether target circulating levels of CBD have been achieved, and whether metabolic transformation of CBD to THC has occurred.

Means and standard deviations of change in 12 hour circulating CBD levels from 1 week to 4 weeks of treatment (T3 to T4, and T6 to T7) within CBD-treated participants will be presented to determine whether extended treatment with CBD results in accumulation of CBD.

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 [97]) within 2 hours of the initial administration of each dose of CBD vs. placebo (T1 and T4) 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.

21.3.5 Adherence and Retention Analyses

Adherence to the protocol will be assessed with a smartphone-assisted medication adherence platform [119] 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. Circulating concentrations of CBD will also be collected at T1-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 T9), 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.

21.3.6 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), and self-efficacy (AASE). Categorical data will be tallied, and means and standard deviations of continuous scores will be calculated.

21.3.7 Planned Interim Analysis

21.3.7.1 Safety Review

The DSMB will meet (in person or by teleconference) 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.

21.3.8 **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.

21.3.9 **Tabulation of Individual Response Data**

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

21.3.10 **Exploratory Analyses**

Hypothesis E will be assessed by comparing within- and between- group differences in percent heavy drinking days from baseline (T1) to week 8 of treatment with study medication (T7) and during the 4-week period following administration of study medication (T8-T9)

21.4 Sample Size

We will enroll approximately 60 participants, and randomize approximately 40 participants to meet our recruitment goal (through week 8/T7). Sensitivity to detect effects with the proposed study design was calculated for each hypothesis at power = 0.95 for univariate outcomes with 40 participants in 2 groups at alpha = 0.05 for the analyses described above. Hypotheses 1a and 1c are powered to detect effect sizes of approximately d = 0.2. Hypothesis 2a and 2b are powered to detect effect sizes of d = 0.2 and d = 0.3, respectively. Hypothesis E (exploratory hypothesis) is powered to detect an effect size of d = 0.6, therefore we are only powered to detect substantial impacts on drinking outcomes for this exploratory aim.

22 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.

23 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.

24 Ethics/Protection of Human Subjects

24.1 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.

24.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form 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 regarding whether previously consented participants need to be re-consented.

24.3 Informed Consent Process

24.3.1 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.

The following consent materials are submitted with this protocol:

- Advertisement
- Telephone Screening Consent Form
- Telephone Screening Script
- Informed Consent Form
- Consent Quiz
- Audio-Visual Release Form

24.3.2 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 will be referred for informed consent.

Interested patients will be provided with an informed consent form including all pertinent details of the study including description 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. The investigator 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 prior to signing.

In the event the participant cannot be at the study site to participate in the consent process in person, it can be conducted via telephone or NYULH-approved Secure Video Conferencing (i.e. WebEx). An electronic copy of the consent form will be shared with the participant via SendSafe email and participants will still be given adequate time to read, review and ask questions about the informed consent document. Participants can electronically sign and date the consent form and authorization documents by typing their names, initials and date and/or using a valid electronic signature wherever indicated. Once signed, participants will return the informed consent form and authorization documents to the consenting study team member via SendSafe email. The consenting study team member will then electronically sign the informed consent form and authorization forms where indicated and return the completed and double-signed consent documents to the participant for their personal record keeping via SendSafe email correspondence. Should the participant prefer, they can print and sign a hard copy of the document to be mailed or scan and email the documents via SendSafe back to the consenting study team member.

The participants may withdraw consent at any time throughout the course of the trial. 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.

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) audio-recorded at the initial visit (see Audio Recording Consent). If a patient does not sign the Audio Recording Consent, then we will not audio-record the patient's interview.

24.4 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 and genetic tests 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 study drug records for the participants in this study. 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.

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® and REDCap, programs designed specifically 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.

24.4.1 **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 cannabinoids. 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 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.

24.5 Future Use of Stored Data

Data collected for this study will be analyzed and in locked cabinets in NYU space 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.

25 Data Handling and Record Keeping

25.1 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 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. DO 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 "Research Electronic Data Capture" (TrialMaster®), 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.

The audiotaped recordings will be kept as confidential as possible. No individual identities will be used in any reports or publications resulting from this study. The researchers are committed to protecting the confidentiality of subject responses and have taken a number of steps in this regard. For example, the audio recordings will be coded with a code number unique to the study and all information will be kept on secure servers and/or in locked files. Only NYU study personnel, with the permission of the principal investigator, will have access to the file linking the subject name and study ID code. All digital data will be double pass code protected and stored on a secure server at NYU. Digital video and audio recordings of clinical interviews conducted at NYU as part of this study will be stored on the secure NYU server.

25.2 Study Records Retention

Study documents and/or recordings 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.

25.3 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 participant, 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.

25.4 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.

26 Study Finances

26.1 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).

26.2 Costs to the Participant

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

26.3 Participant Reimbursements or Payments

Participants will receive monetary compensation for research assessments as follows:
Screen:
Option 1 (T0): In-person = $40,
Option 2 (T0a/b): Two-part Remote and In-person Screen:
Part a: Remote portion = $20
Part b: In-person portion = $20
Total = $40
Baseline (T1) = $60,
1-day assessment (T2) = $20,
1-week assessment (T3) = $60,
4-week assessment (T4) = $60,
4-week+1-day assessment (T5) = $20,
5-week assessment (T6) = $60,
8-week assessment (T7) = $40,
9-week assessment (T8) = $40.

Participants completing all of the assessments would therefore receive a total of $400, equivalent to roughly $20 per hour of time required to complete the assessments.

27 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.

28 References

1. Hasin, D.S., et al., *Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions.* Arch Gen Psychiatry, 2007. **64**(7): p. 830-42.
2. Rehm, J., et al., *Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders.* Lancet, 2009. **373**(9682): p. 2223-33.
3. Volkow, N.D. and T.K. Li, *Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences.* Pharmacol Ther, 2005. **108**(1): p. 3-17.
4. Berglund, M., *A better widget? Three lessons for improving addiction treatment from a meta-analytical study.* Addiction, 2005. **100**(6): p. 742-50.
5. Anton, R.F.O.M., S. S.; Ciraulo, D. A.; Cisler, R. A.; Couper, D.; Donovan, D. M.; Gastfriend, D. R.; Hosking, J. D.; Johnson, B. A.; LoCastro, J. S.; Longabaugh, R.; Mason, B. J.; Mattson, M. E.; Miller, W. R.; Pettinati, H. M.; Randall, C. L.; Swift, R.; Weiss, R. D.; Williams, L. D.; Zweben, A., *Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial.* J Stud Alcohol Drugs, 2003. **69**: p. 5-13.
6. Rosner, S., et al., *Opioid antagonists for alcohol dependence.* Cochrane Database Syst Rev, 2010(12): p. CD001867.
7. Rosner, S., et al., *Acamprosate for alcohol dependence.* Cochrane Database Syst Rev, 2010(9): p. CD004332.
8. Devinsky, O., et al., *Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders.* Epilepsia, 2014. **55**(6): p. 791-802.
9. Thiele, E.A., et al. *Cannabidiol (CBD) Significantly Reduces Drop Seizure Frequency in Lennox-Gastaut Syndrome (LGS): Results of a Multi-center, Randomized, Double-blind, Placebo-controlled Trial (GWPCARE4)*. in *The American Epilepsy Society Annual Meeting*. 2016. Houston, TX.
10. Wong, M.H., et al. *A Dose Ranging Safety and Pharmacokinetic Study of Cannabidiol (CBD) in Children With Dravet Syndrome (GWPCARE1)*. in *The American Epilepsy Society Annual Meeting*. 2016. Houston, TX.
11. Cross, J.H., et al. *Cannabidiol (CBD) Significantly Reduces Convulsive Seizure Frequency in Dravet Syndrome (DS): Results of a Multi-center, Randomized, Double-blind, Placebo-controlled Trial (GWPCARE1)*. in *The American Epilepsy Society Annual Meeting*. 2016. Houston, TX.
12. Sharir, H. and M.E. Abood, *Pharmacological characterization of GPR55, a putative cannabinoid receptor.* Pharmacol Ther, 2010. **126**: p. 301-313.
13. Hu, S.S. and K. Mackie, *Distribution of the Endocannabinoid System in the Central Nervous System*, in *Endocannabinoids, Handbook of Experimental Pharmacology*, R.G. Pertwee, Editor. 2015, Springer International Publishing Switzerland. p. 59-93.
14. Di Marzo, V. and F. Piscitelli, *The Endocannabinoid System and its Modulation by Phytocannabinoids.* Neurotherapeutics, 2015. **12**: p. 692-698.
15. Tsou, K., et al., *Immunohistochemical Distribution of Cannabinoid CB1 Receptors in the Rat Central Nervous System.* Neuroscience, 1998. **83**(2): p. 393-411.
16. Moldrich, G. and T. Wenger, *Localization of the CB1 cannabinoid receptor in the rat brain. An immunohistochemical study.* Peptides, 2000. **21**: p. 1735-1742.
17. Freund, T.F., I. Katona, and D. Piomelli, *Role of Endogenous Cannabinoids in Synaptic Signaling.* Physiol Rev, 2003. **83**: p. 1017-166.
18. Hillard, C.J., M. Beatka, and J. Savaido, *Endocannabinoid Signaling and the Hypothalamic-Pituitary-Adrenal Axis.* Comprehensive Physiology, 2017. **7**: p. 1-156.
19. Katona, I., et al., *Presynaptically Located CB1 Cannabinoid Receptors Regulate GABA Release from Axon Terminals of Specific Hippocampal Interneurons.* J Nerosci, 1999. **19**(11): p. 4544-4558.
20. Lauckner, J.E.J., J. B.; Chen, H. Y.; Lu, H. C.; Hille, B.; Mackie, K., *GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current.* PNAS, 2008. **105**(7): p. 2699-2704.
21. Waldeck-Weiermair, M., et al., *Integrin clustering enables anandamide-induced Ca2+ signaling in endothelial cells via GPR55 by protection against CB1-receptor-triggered repression.* J Cell Sci, 2008. **121**(Pt 10): p. 1704-17.

22. Ryberg, E., et al., *The orphan receptor GPR55 is a novel cannabinoid receptor.* Br J Pharmacol, 2007. **152**(7): p. 1092-101.
23. Henstridge, C.M., et al., *The GPR55 ligand L-alpha-lysophosphatidylinositol promotes RhoA-dependent Ca2+ signaling and NFAT activation.* FASEB J, 2009. **23**(1): p. 183-93.
24. Ross, R.A., *The enigmatic pharmacology of GPR55.* Trends Pharmacol Sci, 2009. **30**(3): p. 156-63.
25. Brusco, A., et al., *Postsynaptic Localization of CB2 Cannabinoid Receptors in the Rat Hippocampus.* Synapse, 2008. **62**: p. 944-949.
26. Stella, N., *Endocannabinoid signaling in microglial cells.* Neuropharmacology, 2009. **56**(Suppl 1): p. 244-253.
27. Atwood, B.K. and K. Mackie, *CB2: a cannabinoid receptor with an identity crisis.* British J Pharmacol, 2010. **160**: p. 467-479.
28. Showalter, V.M.C., D. R.; Martin, B. R.; Abood, M. E., *Evaluation of Binding in a Transfected Cell Line Expressing a Peripheral Cannabinoid Receptor (CB2): Identification of Cannabinoid Receptor Subtype Selective Ligands.* The Journal of Pharmacology and Experimental Therapeutics, 1996. **278**: p. 989-999.
29. Thomas, B.F.G., A. F.; Burch, D. F.; Roche, M. J.; Seltzman, H. H., *Comparative Receptor Binding Analyses of Cannabinoid Agonists and Antagonists.* The Journal of Pharmacology and Experimental Therapeutics, 1998. **285**: p. 285-292.
30. Thomas, A., et al., *Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro.* Br J Pharmacol, 2007. **150**(5): p. 613-23.
31. Pertwee, R.G.R., R. A.; Craib, S. J., Thomas, A., *(-)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens.* Eur J Pharmacol, 2002. **456**: p. 99-106.
32. Pertwee, R.G.G., G.; Lainton, J. A. H.; Huffman, J. W., *Pharmacological characterization of three novel cannabinoid receptor agonists in the mouse isolated vas deferens.* Eur J Pharmacol, 1995. **284**: p. 241-247.
33. Watanabe, K.K., Y.; Matsunaga, T.; Yamamoto, I.; Yoshimura, H., *Inhibition of Anandamide Amidase Activity in Mouse Brain Microsomes by Cannabinoids.* Biol Pharm Bull, 1996. **19**(8): p. 1109-1111.
34. Bisogno, T.H., L.; De Petrocellis, L.; Tchilibon, S.; Ponde, D. E.; Brandi, I.; Moriello, A. S.; Davis, J. B.; Mechoulam, R.; Di Marzo, V., *Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide.* British J Pharmacol, 2001. **134**: p. 845-852.
35. Gomes, F.V., E.A. Del Bel, and F.S. Guimaraes, *Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT1A receptor activation in mice.* Prog Neuropsychopharmacol Niol Psychiatry, 2013. **46**: p. 43-47.
36. Kathmann, M., et al., *Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors.* Naunyn-Schmiedeberg's Arch Pharmacol, 2006. **372**: p. 354-361.
37. Pandolfo, P., et al., *Cannabinoids inhibit the synaptic uptake of adenosine and dopamine in the rat and mouse striatum.* Eur J Pharmacol, 2011. **655**(1-3): p. 38-45.
38. Mato, S., et al., *CB1 knockout mice display impaired functionality of 5-HT1A and 5-HT2A/C receptors.* J Neurochem, 2007. **103**(5): p. 2111-20.
39. Pazos, M.R., et al., *Mechanisms of cannabidiol neuroprotection in hypoxic-ischemic newborn pigs: role of 5HT(1A) and CB2 receptors.* Neuropharmacology, 2013. **71**: p. 282-91.
40. Wise, R.A. and G.F. Koob, *The development and maintenance of drug addiction.* Neuropsychopharmacology, 2014. **39**(2): p. 254-62.
41. Koob, G.F., *The dark side of emotion: the addiction perspective.* Eur J Pharmacol, 2015. **753**: p. 73-87.
42. Koob, G.F. and N.D. Volkow, *Neurobiology of addiction: a neurocircuitry analysis.* Lancet Psychiatry, 2016. **3**(8): p. 760-73.
43. Gilpin, N.W., *Corticotropin-releasing factor (CRF) and neuropeptide Y (NPY): effects on inhibitory transmission in central amygdala, and anxiety- & alcohol-related behaviors.* Alcohol, 2012. **46**(4): p. 329-37.
44. Gilpin, N.W. and M. Roberto, *Neuropeptide modulation of central amygdala neuroplasticity is a key mediator of alcohol dependence.* Neurosci Biobehav Rev, 2012. **36**(2): p. 873-88.
45. Kallupi, M., et al., *Neuropeptide YY(2)R blockade in the central amygdala reduces anxiety-like behavior but not alcohol drinking in alcohol-dependent rats.* Addict Biol, 2014. **19**(5): p. 755-7.

46. Roberto, M., N.W. Gilpin, and G.R. Siggins, *The central amygdala and alcohol: role of gamma-aminobutyric acid, glutamate, and neuropeptides.* Cold Spring Harb Perspect Med, 2012. **2**(12): p. a012195.
47. de Guglielmo, G., et al., *Recruitment of a Neuronal Ensemble in the Central Nucleus of the Amygdala Is Required for Alcohol Dependence.* J Neurosci, 2016. **36**(36): p. 9446-53.
48. Nikolova, Y.S., et al., *Divergent responses of the amygdala and ventral striatum predict stress-related problem drinking in young adults: possible differential markers of affective and impulsive pathways of risk for alcohol use disorder.* Mol Psychiatry, 2016. **21**(3): p. 348-56.
49. Hsiao, Y.T., et al., *Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats.* Neuropharmacology, 2012. **62**(1): p. 373-84.
50. Alves, F.H., et al., *Cannabidiol injected into the bed nucleus of the stria terminalis modulates baroreflex activity through 5-HT1A receptors.* Pharmacol Res, 2010. **62**(3): p. 228-36.
51. Gomes, F.V., et al., *Cannabidiol administration into the bed nucleus of the stria terminalis alters cardiovascular responses induced by acute restraint stress through 5-HT(1)A receptor.* Eur Neuropsychopharmacol, 2013. **23**(9): p. 1096-104.
52. Gomes, F.V., L.B. Resstel, and F.S. Guimaraes, *The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors.* Psychopharmacology (Berl), 2011. **213**(2-3): p. 465-73.
53. Norris, C., et al., *Cannabidiol Modulates Fear Memory Formation Through Interactions with Serotonergic Transmission in the Mesolimbic System.* Neuropsychopharmacology, 2016. **41**(12): p. 2839-2850.
54. Soares Vde, P., et al., *Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors.* Behavioural brain research, 2010. **213**(2): p. 225-9.
55. Do Monte, F.H., et al., *Infusion of cannabidiol into infralimbic cortex facilitates fear extinction via CB1 receptors.* Behav Brain Res, 2013. **250**: p. 23-7.
56. Campos, A.C., et al., *The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system.* The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum, 2013. **16**(6): p. 1407-19.
57. Blessing, E.M., et al., *Cannabidiol as a Potential Treatment for Anxiety Disorders.* Neurotherapeutics, 2015. **12**(4): p. 825-36.
58. Roberto, M., et al., *The endocannabinoid system tonically regulates inhibitory transmission and depresses the effect of ethanol in central amygdala.* Neuropsychopharmacology, 2010. **35**(9): p. 1962-72.
59. Fusar-Poli, P.C., J. A.; Bhattacharyya, S.; Borgwardt, S. J.; Allen, P.; Martin-Santos, R.; Seal, M.; Surguladze, S. A.; O'Carrol, C.; Atakan, Z.; Zuardi, A. W.; McGuire, P. K., *Distinct Effects of Delta9-Tetrahydrocannabinol and Cannabidiol on Neural Activation During Emotional Processing.* Arch Gen Psychiatry, 2009. **66**(1): p. 95-105.
60. Hamelink, C., et al., *Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity.* J Pharmacol Exp Ther, 2005. **314**(2): p. 780-8.
61. Campos, A.C., et al., *The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system.* Int J Neuropsychopharmacol, 2013. **16**(6): p. 1407-19.
62. Wolf, S.A., et al., *Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis.* Cell Commun Signal, 2010. **8**: p. 12.
63. Fagherazzi, E.V., et al., *Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders.* Psychopharmacology (Berl), 2012. **219**(4): p. 1133-40.
64. Cheng, D., et al., *Long-term cannabidiol treatment prevents the development of social recognition memory deficits in Alzheimer's disease transgenic mice.* J Alzheimers Dis, 2014. **42**(4): p. 1383-96.
65. Cheng, D., et al., *Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1E9 mice.* Psychopharmacology (Berl), 2014. **231**(15): p. 3009-17.
66. Bitencourt, R.M., F.A. Pamplona, and R.N. Takahashi, *Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats.* Eur Neuropsychopharm, 2008. **18**: p. 849-859.

67. Norris, C., et al., *Cannabidiol Modulates Fear Memory Formation Through Interactions with Serotonergic Transmission in the Mesolimbic System.* Neuropsychopharmacology, 2016. **41**: p. 2839-2850.
68. Ribeiro de Carvalho, C. and R.N. Takahashi, *Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats.* Addict Biol, 2016: p. 1-10.
69. Deiana, S., et al., *Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Delta(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour.* Psychopharmacology (Berl), 2012. **219**(3): p. 859-73.
70. Kasidoni, V., I. Anagnostou, and G. Panagis, *Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus.* Addict Biol, 2012. **18**: p. 286-296.
71. Zlebnik, N.E. and J.F. Cheer, *Beyond the CB1 Receptor: Is Cannabidiol the Answer for Disorders of Motivation?* Annu. Rev. Neurosci, 2016. **39**: p. 1-17.
72. Lawn, W., et al., *Localization of the CB1 cannabinoid receptor in the rat brain. An immunohistochemical study.* Psychopharmacology, 2016. **233**: p. 3537-3552.
73. Parker, L.A., et al., *Effect of low doses of delta9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats.* Psychopharmacology (Berl), 2004. **175**(3): p. 360-6.
74. Ren, Y., et al., *Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances.* J Neurosci, 2009. **29**(47): p. 14764-9.
75. Weiss, F., et al., *Cannabidiol: Long-lasting amelioration of vulnerability states associated with relapse risk as determined in animal models of drug seeking, anxiety, and impulsivity.* Alcohol and Alcoholism, 2014. **49**(S1): p. i1-i69.
76. Viudez-Martínez, A., et al., *Cannabidiol reduces ethanol consumption, motivation and relapse in mice.* Addict Biol, 2017: p. 1-11.
77. Consroe, P., et al., *Interaction of cannabidiol and alcohol in humans.* Psychopharmacology (Berl), 1979. **66**(1): p. 45-50.
78. Morgan, C.J., et al., *Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis.* Neuropsychopharmacology, 2010. **35**(9): p. 1879-85.
79. Morgan, C.J., et al., *Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings.* Addict Behav, 2013. **38**(9): p. 2433-6.
80. Crippa, J.A., et al., *Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report.* J Clin Pharm Ther, 2013. **38**(2): p. 162-4.
81. Zuardi, A.W.C., R. A.; Graeff, F. G.; Guimaraes, F. S., *Effects of ipsapirone and cannabidiol on human experimental anxiety.* British Association for Psychopharmacology, 1993. **7**(1): p. 82-88.
82. Bergamaschi, M.M., et al., *Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients.* Neuropsychopharmacology, 2011. **36**(6): p. 1219-26.
83. Karniol, I.G.S., I.; Kasinski, N.; Pfeferman, A.; Carlini, E. A., *Cannabidiol Interferes with the Effects of Delta9-Tetrahydrocannabinol in Man.* Eur J Pharmacol, 1974. **28**: p. 172-177.
84. Zuardi, A.W.S., I.; Finkelfarb, E.; Karniol, I. G., *Action of Cannabidiol on the Anxiety and Other Effects Produced by delta9-THC in Normal Subjects.* Psychopharmacology, 1982. **76**: p. 245-250.
85. Crippa, J.A., et al., *Effects of cannabidiol (CBD) on regional cerebral blood flow.* Neuropsychopharmacology, 2004. **29**(2): p. 417-26.
86. Crippa, J.A., et al., *Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.* J Psychopharmacol, 2011. **25**(1): p. 121-30.
87. Borgwardt, S.J., et al., *Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition.* Biol Psychiatry, 2008. **64**(11): p. 966-73.
88. Consroe, P.C., E. A.; Zwicker, A. P.; Lacerda, L. A. , *Interaction of cannabidiol and alcohol in humans.* Psychopharmacology, 1979. **66**(1): p. 45-50.
89. Zuardi, A.W.H., J. E. C.; Dursun, S. M.; Morais, S. L.; Sanches, R. F.; Musty, R. E.; Crippa, J. A. S., *Cannabidiol monotherapy for treatment-resistant schizophrenia.* British Association for Psychopharmacology, 2006. **20**(5): p. 683-686.

90. Campos, A.C., et al., *Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders.* Philos Trans R Soc Lond B Biol Sci, 2012. **367**(1607): p. 3364-78.
91. Huestis, M.A., *Human cannabinoid pharmacokinetics.* Chem Biodivers, 2007. **4**(8): p. 1770-804.
92. Watanabe, K., et al., *Conversion of cannabidiol to ∆9-tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice.* Forensic Toxocol, 2007. **25**: p. 16-21.
93. Merrick, J., et al., *Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid.* Cannabis and Cannabinoid Research, 2016. **1**(1): p. 102-112.
94. Zgair, A., et al., *Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines.* Am J Trans Res, 2016. **8**(8): p. 3448-3459.
95. Consroe, P., et al., *Controlled Clinical Trial of Cannabidiol in Huntington's Disease.* Pharmacol Biochem Behav, 1991. **40**: p. 701-708.
96. Stott, C.G., et al., *A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray.* Eur J Pharmacol, 2013. **2013**(69).
97. Burns, M., *An Overview of Field Sobriety Research.* Perceptual and Motor Skills, 2003. **97**: p. 1187-1199.
98. Martin, W.R., et al., *Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man.* Clin Pharmacol Ther, 1971. **12**: p. 245-258.
99. Rey, A., *L'examen psychologique dan les cas d'encephalopathie traumatic.* Archives de Psycholegie, 1941. **28**(112): p. 286-340.
100. Rosenberg, S.J., J.J. Ryan, and A. Prifitera, *Rey Auditory-Verbal Learning Test Performance of Patients With and Without Memory Impairment.* J. Clin. Psych., 1984. **40**(3): p. 785-787.
101. Vandenberg, S.G. and A.R. Kuse, *Mental Rotations, A Group Test of Three-Dimensional Spatial Visualization.* Perceptual and Motor Skills, 1978. **47**: p. 599-604.
102. Peters, M., et al., *A Redrawn Vandenberg and Kuse Mental Rotations Test: Different Versions and Factors That Affect Performance.* Brain and Cog., 1995. **28**: p. 39-58.
103. Conway, A.R.A., et al., *Working memory span tasks: A methodological review and user's guide.* Psychonomic Bulletin & Review, 2005. **12**(5): p. 769-786.
104. Unsworth, N., G.J. Spillers, and G.A. Brewer, *Examining the relations among working memory capacity, attention control, and fluid intelligence from a dual-component framework.* Psychology Science Quarterly, 2009. **51**: p. 388-402.
105. Flannery, B.A., J.R. Volpicelli, and H.M. Pettinati, *Psychometric properties of the Penn Alcohol Craving Scale.* Alcohol Clin Exp Res, 1999. **23**(8): p. 1289-95.
106. Beck, A.T., et al., *Use of the Beck Anxiety and Depression Inventories for Primary Care with Medical Outpatients.* Assessment, 1997. **4**(3): p. 211-9.
107. Beck, A. T., Steer, R. A., & Brown, G. K. (1996) Beck depression inventory-II. San Antonio, 78(2), 490-498.
108. DiClemente, C.C., et al., *The Alcohol Abstinence Self-Efficacy scale.* J Stud Alcohol, 1994. **55**(2): p. 141-8.
109. Project MATCH Research Group, *Project MATCH secondary a priori hypotheses.* Addiction, 1997. **92**(12): p. 1671-98.
110. Vielva, I. and I. Iraurgi, *Cognitive and behavioural factors as predictors of abstinence following treatment for alcohol dependence.* Addiction, 2001. **96**(2): p. 297-303.
111. Posner, K., et al., *The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* Am J Psychiatry, 2011. **168**(12): p. 1266-77.
112. Sinha, R., *Modeling relapse situations in the human laboratory.* Curr Top Behav Neurosci, 2013. **13**: p. 379-402.
113. Seo, D., et al., *Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk.* JAMA Psychiatry, 2013. **70**(7): p. 727-39.
114. Phelps, E.A., et al., *Activation of the left amygdala to a cognitive representation of fear.* Nature Neurosci, 2001. **4**(4): p. 437-441.

115. Sobell, L.C., et al., *Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations.* British Journal of Addiction, 1988. **83**: p. 393-402.
116. Hooper, L., Stockton, P., Krupnick, J., & Green, B., *Development, use, and psychometric properties of the Trauma History Questionnaire.* Journal of Loss and Trauma, 2011. **16**: p. 258-283.
117. Anton, R.F., et al., *Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence.* JAMA, 2006. **295**(17): p. 2003-2017.
118. Bogenschutz, M.P., et al., *Coadministration of disulfiram and lorazepam in the treatment of alcohol dependence and co-occuring anxiety disorder: an open-label pilot study.* Am J Drug and Alcohol Abuse, 2016. **42**(5): p. 490-499.
119. Mooney, L.J., et al., *Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder.* J Addict Med, 2016. **10**(4): p. 236-243.
120. First, M.B., et al., *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition*. 1997, New York, NY: Biometrics Research Department, New York State Psychiatric Institute.
121. Sullivan, J.T., et al., *Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar).* British Journal of Addiction, 1989. **84**: p. 1353-1357.
122. Beck, A.T. and D.A. Clark, *An information processing model of anxiety: automatic and strategic processes.* Behav Res Ther, 1997. **35**(1): p. 49-58.
123. Sinha, R., et al., *Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings.* Psychopharmacology (Berl), 2007. **190**(4): p. 569-74.
124. Johnson, B.A., Ait-Daoud N., & Roache, J.D., *The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field.* Journal of studies on alcohol, 2005. **14:** p. 157-67.

29 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
- Informed Consent Form
- Study Procedures Flowchart/Table
- Study Monitoring Plan
- Specimen Preparation And Handling (e.g. for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for shipment)