A Phase 2B, 8-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety and Tolerability of the Fatty Acid Amide Hydrolase (FAAH) Inhibitor PF-04457845 in Adults with DSM-5 Current Cannabis Use Disorder (CUD)

STUDY PROTOCOL

National Clinical Trial (NCT) Identified Number: NCT03386487

Principal Investigator: Deepak Cyril D'Souza, M.D.

IND Coordinating Center: IND#114,017 Mohini Ranganathan, M.D.

Funded by: National Institute of Drug Abuse (NIDA)

Protocol Version: 5.0
February 8, 2022

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

TABLE OF CONTENTS

LIST OF APPENDICES

1.0 ADMINISTRATIVE INFORMATION:

1.1 Yale University Statement of Compliance:

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Coordinating Center. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonization, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- Regulatory requirements for reporting serious adverse events defined in Section 12.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator as per FDA (Appendix J)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____ _____

Deepak Cyril D'Souza, M.D. Date
Lead Principal Investigator
Professor of Psychiatry
Yale University, School of Medicine

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

1.2 Columbia University Statement of Compliance:

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Coordinating Center. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonization, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- Regulatory requirements for reporting serious adverse events defined in Section 12.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator as per FDA (Appendix J)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____ _____

Frances Levin
Site Principal Investigator
Psychiatrist II
Research Foundation for Mental Hygiene
Columbia University Medical College

Date

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

1.3 Johns Hopkins Statement of Compliance:

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Coordinating Center. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonization, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- Regulatory requirements for reporting serious adverse events defined in Section 12.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator as per FDA (Appendix J)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____ _____

Ryan Vandrey
Site Principal Investigator
Associate Professor
John Hopkins University

Date

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

1.4 Medical University of South Carolina Statement of Compliance:

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Coordinating Center. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonization, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- Regulatory requirements for reporting serious adverse events defined in Section 12.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator as per FDA (Appendix J)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____ _____

Kevin Gray, M.D.
Site Co-Principal Investigator
Professor of Psychiatry
Medical University of South Carolina

Date

_____ _____

Aimee McRae-Clark, M.D.
Site Co-Principal Investigator
Professor of Psychiatry
Medical University of South Carolina

Date

*1.2 **Contacts*:**

Please refer to Table 2 for the complete study organization chart. A separate contact information list will be provided to each site.

Investigators will be provided with emergency medical contact information cards to be carried by each participant. General advice on protocol procedures should be obtained through the Coordinating Center.

Coordinating Center – Yale University:

Deepak Cyril D'Souza, M.D.
Lead Principal Investigator

Christina Luddy, BS
Study Coordinator

Mohini Ranganathan, M.D.
Coordinating Investigator / Medical Monitor

Patrick D. Skosnik, Ph.D.
Actigraphy Investigator

Ralitza Gueorguieva, Ph.D.
Senior Statistician

Jose Cortes-Briones, Ph.D.
Statistician/Analyst

Research Foundation for Mental Hygiene (Columbia University):

Frances Levin, M.D.
Site Principal Investigator:

John Mariani, M.D.
Site Co-Investigator

Johns Hopkins University:

Ryan Vandrey, Ph.D.
Site Principal Investigator

Dustin Lee, Ph.D.
Site Co-Investigator

Medical University of South Carolina:

Kevin Gray, M.D.
Site Principal Investigator

Aimee McRae-Clark, PharmD.
Site Co-Principal Investigator

1.3 Protocol Summary Synopsis:

Title:	**A Phase 2B, 8-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety and Tolerability of the Fatty Acid Amide Hydrolase (FAAH) Inhibitor PF-04457845 in Adults with DSM-5 Current Cannabis Use Disorder (CUD)**
Study Description:	The efficacy, safety and tolerability of the FAAH Inhibitor PF-0447845 in reducing cannabis use will be studied in a 4-site randomized, double-blind, placebo-controlled, parallel-group, outpatient clinical trial comparing PF-04457845 (4mg) and placebo in DSM-5 CUD individuals. Participants will be randomized in a 1:1 ratio to either PF-04457845 or placebo using random block sizes of 2 and 4, stratified by site and degree of cannabis use (CUD at the level of moderate (4-7 [of 11] symptoms) or severe (8-11 [of 11] symptoms)). Participants will receive motivational interviewing for 2 weeks before being randomized to receive study medication to make a quit attempt within the first week of treatment. For a self-reported quit attempt, participants will be rewarded. Participants will receive active or placebo PF-04457845 for 8 weeks during which time they will be evaluated weekly with either in person or remote study visits. In addition, daily assessment of adherence to study medication and cannabinoid use will be conducted by cellphone. Measures of cannabinoid exposure, and problems related to the use of cannabis, will be assessed.
Primary Objective:	To determine whether PF-04457845 is superior to placebo in reducing self-reported frequency (number of times per day) of cannabis use.
Primary Endpoint:	Change in the average number of times per day of self-reported cannabis consumption.
Study Population:	Up to approximately 260 individuals diagnosed with DSM5 Cannabis Use Disorder
Phase:	Phase 2B
Description of Sites Enrolling Participants:	This multi-center trial will take place at four sites: Yale University School of Medicine, Columbia University Medical Center, John Hopkins University, & Medical University of South Carolina.
Description of Study Interventions:	For 8 weeks participants will receive 4mg daily of PF-04457845 or placebo.
Study Duration:	The duration of this study is approximately 3 years.
Participant Duration:	This trial is 14 weeks total, including: 1) a 2-week screening phase, 2) randomization to PF-04457845 or placebo for 8 weeks, and 3) a 4 week follow up phase for safety especially because the effects of the drug take ~ 2 weeks to washout.

1.4 Protocol Summary Schema:

Table 1: Schematic of Study Design

		Screening		Treatment Phase **Outpatient**								Follow–up Phase				
Weeks (days)		(-14)	(-7)	1 (Quit Attempt after day 2)	2	3	4	5	6	7	8	9	10	11	12	End
Visit		1	2	3	5	6	7	8	9	10	11	12	13	14	15	16
Visit Type	**In Person**		X	X		X		X		X		X				X
	Remote	X			X		X		X		X		X	X	X	
Drug Condition	**PF-04457845**			x	x	x	x	x	x	x	x					
	Placebo			x	x	x	x	x	x	x	x					

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

1.5 Schedule of Procedures:

Table 2: Schedule of Procedures

**Weekly visits after randomization occur every 7 days ± 3 days*

Visit* *(R=Remote ; IP= In-Person)*		Remote Screening	In-Person Screening	Week 1 IP / R	Week 2 R	Week 3 IP / R	Week 4 R	Week 5 IP / R	Week 6 R	Week 7 IP / R	Week 8 R	Week 9 IP / R	Week 10 R	Week 11 R	Week 12 R	End of Study IP / R
Study Phase		**Pre-Randomization**		**Treatment Phase**								**Follow Up Phase**				
Day*		**-14**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**
Informed Consent & Supplement to Consent Questionnaire		x														
Psychiatric Evaluation	SCID	x														
	Demographic data	x														
Safety	Chemistry, hematology, LFTs		x (IP)	x (IP)				x (IP)		x (IP)		x (IP)				x (IP)
	DNA Sample collection		x (IP)													
	UTOX (spot - on site)	x	x (IP)	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)				x (IP)
	Urine Pregnancy Test for WOCBP	x	x (IP)	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x	x	x (IP)
	Urinalysis		x (IP)	x (IP)				x (IP)		x (IP)		x (IP)				x (IP)
	Physical Examination		x (IP)									x				
	EKG		x (IP)	x (IP)								x				
	Concomitant medication check	x		x	x	x	x	x	x	x	x	x	x	x	x	x
	Columbia Suicide Severity Rating Scale	x		x	x	x	x	x	x	x	x	x	x	x	x	x
	Adverse Events (SAFTEE)	x	x (IP)	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x	x	x (IP)
	Licensed Clinician (MD, RN, APRN, PA) check-in	x	x (IP)	x (IP)	x (IP)	x	x	x	x	x	x	x	x	x	x	x
MJ Use Quantification	Lifetime Cannabis Use (SALCU)	x														
	Urine Creatinine: THC-COOH Quantification		x (IP)	x (IP)		x (IP)		x (IP)		x (IP)		x (IP)				x (IP)
	TLFB-cannabis (30 day, 7 day)	-30	-7 (IP)	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7
	$ spent on MJ	-30	-7 (IP)	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7
	CAROMA (daily TLFB)			x	x	x	x	x	x	x	x					
Willingness to Attempt Quitting (signed statement)		x	x (IP)	x (IP)												
Contingency management for self-reported quit attempt				$50												
Motivational Interviewing		x	x (IP)													
Randomization of Participant				x (IP)												
Marijuana Problems	Desire to Quit	x	x (IP)	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)	x	x (IP)				x (IP)
	Marijuana Problems Scale	x	x (IP)	x								x		x		x
	MJ Withdrawal Checklist		x (IP)	x	x	x	x	x	x	x	x	x				x
	MJ Craving Scale		x (IP)	x	x	x	x	x	x	x	x	x				x
	VAS -Marijuana Ladder	x	x (IP)	x	x	x	x	x	x	x	x	x				x
	PRISM		x (IP)					x				x				
Tobacco	FTND		x (IP)	x			x				x					
	TLFB-Nicotine/Tobacco (30 day, 7 day)	-30	-7 (IP)	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7
Alcohol	TLFB-Alcohol (30 day, 7 day)	-30	-7 (IP)	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7	-7
Cognitive	Cogstate Battery (Attention, V. Memory, Exe Func)			x (IP)								x (IP)				
Behavioral	VAS-Mood States		x (IP)	x	x	x	x	x	x	x	x	x				x
	Quality of Life Enjoyment and Satisfaction			x								x				
	Weight		x (IP)	x (IP)		x (IP)		x (IP)		x (IP)		x				x
	Vital Signs		x (IP)	x (IP)		x (IP)		x (IP)		x (IP)		x				x
	24-Hour Actigraphy		x (IP)	x	x	x	x	x	x	x	x	x	x	x	x	x
Sleep	Evening/Morning Sleep Questionnaire	x	x (IP)	x	x	x	x	x	x	x	x	x				x
	Pittsburgh Sleep Quality Index	x	x (IP)	x	x	x	x	x	x	x	x	x				x
Medication Dispensing				xx (IP)		xx (IP)		xx (IP)		xx (IP)						
Study Medication Adherence	Weekly Pill Count			x	x	x	x	x	x	x	x	x				
	CAROMA (daily)			x	x	x	x	x	x	x	x					
	PF-04457845 Assay			x (IP)				x (IP)				x (IP)				
	Serum Endocannabinoids			x (IP)				x (IP)				x (IP)				

2.0 STUDY RATIONALE AND BACKGROUND

2.1 Cannabis use disorder (CUD) is an increasingly recognized problem for which there are no FDA-approved or clinically-accepted pharmacological treatments: Cannabis is the most widely used illicit substance in the United States (1) and globally. Globally, cannabis consumption has increased in the last quarter of the twentieth century (2). In the U.S., cannabis use rates have doubled in the last decade (3, 4) particularly in young people (5, 6). The 2015 National Survey on Drug Use and Health (NSDUH) estimated that 22.2 million Americans aged 12 or older were current users of cannabis (7). Moreover, the NSDUH reported that approximately 4.0 million people aged 12 or older had a cannabis use disorder in the past year. The legalization of "medical" and recreational cannabis use is sweeping across the U.S. (8, 9). To date, the District of Columbia and 28 states have legalized cannabis for the treatment of medical conditions and the District of Columbia and 8 states have also legalized cannabis for nonmedical (recreational use). The potency of cannabis has been steadily increasing (10), and a number of high-THC-containing products (e.g., wax, shatter) are commercially available. In parallel, there is growing recreational use of potent synthetic cannabinoids (11, 12).

Diagnostic, epidemiological, laboratory and clinical studies provide compelling evidence for the existence of a cannabis dependence syndrome, currently termed cannabis use disorder (CUD) in DSM-5, that is characterized by and includes 1) the development of tolerance (13-16), 2) the emergence of withdrawal symptoms on cessation of exposure (17-19), and 3) compulsive use, impaired control and continued use despite physical and psychological problems caused or exacerbated by such drug use (20-22). Individuals with CUD have difficulty containing use, spend too much time or money acquiring, using, or recovering from the effects of cannabis, make many failed attempts to quit or reduce use, have cravings and a desire to use, and use in contexts that are potentially dangerous (e.g., driving). The regular use of cannabis has been associated with a number of negative outcomes including cognitive deficits (23-26), motor vehicle accidents (27, 28), psychiatric symptoms and disorders (29-32), poor quality of life (33) and substantial comorbidity and disability (34). While not all cannabis users experience problems, nearly 3 of 10 marijuana/cannabis users manifested a cannabis use disorder in 2012-2013 (3).

While cannabis may be less likely than other drugs to produce dependence, after alcohol, it has the highest rate of dependence or abuse among all drugs (1)**.** In fact, it is twice as prevalent as cocaine or opioids (35) likely because more people use cannabis. Around 10% of people who use cannabis will become dependent on it (36, 37), and that increases to about 17 % in those who start using in their teens. In the US, cannabis was the illicit drug with the highest rate of past year dependence or abuse in 2009 (38) and there were more treatment admissions for cannabis related problems than for cocaine or heroin (39, 40). As reviewed by Hall et al., chronic cannabis use is associated with many negative outcomes (41, 42) including cognitive dysfunction (43-48), psychosis (49), and possible structural brain abnormalities (50-56).

There is increasing demand for effective treatments for CUDs. The US Treatment Episode Data Set (TEDS) reported that 17% of all admissions to substance abuse facilities were for cannabis (57), second only to opioids. Further, this represents a doubling of the rate since 1993. The rates of CUDs and CUD-related problems highlights the need for effective treatments. However, there are no FDA-approved or clinically-accepted pharmacological treatments for cannabis CUD as yet.

2.2 Changes associated with cannabis use disorder: Exposure to natural and synthetic agonists of the brain cannabinoid receptor (CB1R) is associated with a number of changes manifesting as behavioral tolerance that is accompanied by changes in the endocannabinoid (eCB) system. Furthermore, discontinuation following prolonged exposure to CB1R agonists leads to a withdrawal syndrome. *The eCB system* is a neuromodulatory system consisting of

two G-protein–coupled receptors, CB1R and CB2R; lipid ligands including anandamide (AEA) and 2-arachidonoylglycerol (2-AG); and enzymes involved in eCB biosynthesis and degradation (fatty acid amide hydrolase [FAAH], monoacylglycerol lipase [MAG-L] and 2-arachidonoylglycerol hydrolase [ABHD6]) (for reviews see (58-60)). eCBs are synthesized and released on demand, following which they travel back to activate presynaptic CB1Rs resulting in braking the further release of neurotransmitters. eCBs are rapidly removed by a transport system that is yet to be fully characterized. CB1Rs are critical in mediating the psychoactive effects of cannabis and are expressed mainly in the brain whereas CB2Rs are mostly expressed peripherally.

2.3 <u>Tolerance:</u> In humans, tolerance develops to the effects of CB1R agonists on mood, memory and cognition, heart rate, blood pressure and hormones, etc., (61-66) and the magnitude of tolerance is proportional to the dose and duration of exposure. The rate and time-course of the development of tolerance to the various effects of CB1R agonists varies. In animals, tolerance to the analgesic, hypothermic and hypomotor effects develop within days (67, 68), while tolerance to the memory (69) and endocrine effects (70) take longer to develop.

Exposure to CB1R agonists is accompanied by receptor downregulation, desensitization of receptor-mediated G-protein activation, and alterations in CB1R mRNA levels (13, 19, 71-77). These changes have a distinct regional and temporal profile and are related to the duration and magnitude of exposure to cannabinoids (77-79). While CB1R downregulation occurs within days, there are regional differences in the time course of these changes. Hippocampal CB1Rs exhibit the greatest magnitude of desensitization and downregulation in response to repeated THC administration while striatal CB1R adaptations develop more slowly and recover more quickly than in regions such as the hippocampus (71, 74-77).

It is now clear from *in vivo* brain imaging studies by us (**Figure 1**) and others that repeated cannabis exposure is associated with downregulation of CB1Rs which tends to "*normalize*" with prolonged abstinence (80-82).

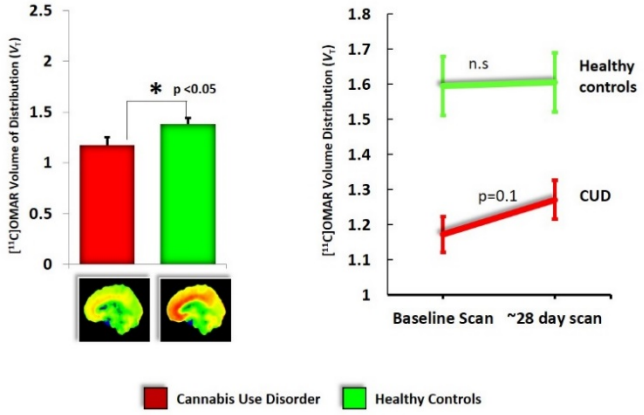


Figure 1: *CB1R Availability in CUDs vs. HCs at Baseline, and after 28 days of abstinence (D'Souza et al., 2016); Fig 1A: Reduced (15%) reduction in CB1R levels CUDs vs Controls; Fig 1B: CB1R levels increase with 28 days of abstinence from cannabis, but remain stable in controls*

Furthermore, and specifically relevant to the mechanism of action of the proposed treatment, in a recent *in vivo* imaging study, Boileau et al., showed that FAAH binding measured with positron emission tomography and [^{11}C]CURB was significantly lower by 14-20% in the brains of chronic cannabis users (83). Furthermore, lower FAAH binding was negatively correlated with measures of cannabis exposure (cannabinoid concentrations in blood and urine). They suggested that lower FAAH binding levels in the brain may be a consequence of chronic and recent cannabis exposure and could contribute to cannabis withdrawal. Taken collectively, the lower FAAH binding in CUD may reflect a compensatory effort to increase AEA in response to low CB1R availability with chronic cannabis exposure.

Interestingly, in animals, prolonged activation of CB1Rs with THC leads to decreased AEA levels in the striatum (84), and consistent with these findings, human cannabis users show reduced cerebrospinal fluid AEA levels (85). Thus, an alternative explanation for the low FAAH binding in chronic cannabis users, is that it might reflect an attempt to compensate for the reduction in striatal AEA levels associated with chronic downregulation of AEA release. *<u>Thus, if</u>*

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

reduced FAAH activity reflects a compensatory attempt to maintain endocannabinoid tone, treatment with inhibitors of FAAH, might be beneficial.

2.4 Cannabis withdrawal syndrome: Abrupt discontinuation of CB1R agonists in cannabinoid dependent animals or the administration of CB1R antagonist to cannabinoid dependent animals leads to a withdrawal syndrome (86-91). In humans, a cannabis withdrawal syndrome has been reported from retrospective self-report studies (72), prospective outpatient studies (73, 74), and human laboratory studies involving the administration and discontinuation of cannabinoids (49, 50, 75, 76). The typical withdrawal symptoms include anger, aggression, appetite change, weight loss, irritability, anxiety, restlessness, altered sleep, strange dreams, cannabis craving and physical discomfort (11, 49, 50, 73, 75, 77-80). Most symptoms appear within 1 day of abstinence, peak within 2–3 days, and typically resolve within 1–2 weeks. However, other studies (73, 80) suggest that withdrawal symptoms may persist longer than 4 weeks, and specifically sleep disturbances may persist for longer (92-94). Characteristic of a true withdrawal syndrome, abstinence symptoms occur with blind discontinuation and resolve with CB1R agonist re-administration (49, 75, 77, 81, 82). Avoidance of CWS might be one factor that contributes to the persistence of chronic cannabis use, and thus, medications that attenuate CWS may also improve treatment outcomes among individuals with CUD.

2.5 Sleep disturbances are an important manifestation of cannabis withdrawal: Several lines of experimental evidence suggest a role of CB1R in sleep (95, 96); therefore, it is not surprising that sleep disturbance is a common symptom of cannabis withdrawal and is clinically meaningful. About 76% of daily cannabis users who abruptly discontinue the use of cannabis report sleep disturbance (92, 93, 97). Difficulty sleeping and strange dreams have been reported with high cross-study reliability (92). These generally occur within 24 to 72 hours of discontinuation of cannabis use and persist for 6–7 weeks (93, 98). Resumption of cannabis use or administration of oral THC improves sleep or even reinstitutes subjectively normal sleep (66, 99-102). Sleep disturbance is reported as a reason why individuals resume smoking cannabis (103) or use alcohol, sedative/hypnotic drugs, or illicit drugs in attempts to treat their sleep disturbance (98, 104). Similarly, certain drugs of abuse may be more rewarding in insomniacs (105), and preferred to a greater degree in persons who are sleep-restricted or deprived (106-108).

However, self-reports do not always accurately reflect actual sleep quality e.g. (109) and do not provide information about sleep architecture. A number of studies have used polysomnography (PSG) to complement self-report measures of sleep and to study sleep architecture during the period immediately following the abrupt cessation of cannabis use reviewed in (110-113). PSG studies of cannabis withdrawal have demonstrated increases in sleep onset latency and wakefulness after sleep onset reviewed in (110-112, 114-117). Total sleep time (TST), sleep efficiency (SEff), and slow-wave sleep (SWS) time is reduced (111, 112, 115, 118, 119). REM sleep is increased (REM rebound) (99, 114, 116-118, 120) and REM latency is shorter (111, 114). Changes in sleep architecture during CWS can begin as early as the first night of abstinence (118). Changes during withdrawal are more evident in heavy users (111). With continued abstinence, TST, SEff, and amount of REM sleep decline, while wake after sleep onset (WASO) increases. These disturbances progress over the first 2 weeks of cannabis abstinence (93, 97, 111) and persist for more than ~6 weeks (93). PSG evidence of sleep disturbance increase, as levels of THC-COOH decrease, suggesting an association between declining levels of cannabis and increasing sleep disturbance. Furthermore, quantity (joints/week) and duration (years) of cannabis use were positively associated with more PLMs. Vandrey et al., replicated most of the findings of Bolla et al., except that they showed increased sleep latency and time spent in REM sleep (14) which may be a result of differences in the samples studied. As stated by Bolla: **"***The treatment of sleep disturbance is a potential target for*

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

the management of cannabis use disorders since poor sleep could contribute to treatment failure in heavy MJ users" (112).

Relief of withdrawal is a negative reinforcer for continued substance use (102, 103). Thus, individuals who experience CWS may use cannabis to relieve or avoid withdrawal (16). Since CWS may serve as negative reinforcement for relapse to cannabis use (121, 122), treatments aimed at alleviating cannabis withdrawal might prevent relapse and reduce dependence.

2.6 There is a need for effective treatments for cannabis use disorder: In parallel with the increase in cannabis use disorders, there is increasing demand for effective treatments for cannabis use disorders. For example, the percentage of hospital admissions for cannabis between 1993 and 2004 doubled (105).

2.6.1 Psychotherapeutic approaches: Despite progress in developing interventions, these approaches which include motivational enhancement (MET), motivational interviewing (MI), cognitive behavioral treatment (CBT) and contingency management (CM) have had limited success reviewed in(17, 123). Most CUD patients do not achieve abstinence with these interventions (124-127). Even with the most efficacious treatment – combination of MET, CBT and CM, only ~50% achieve an initial 2-week period of abstinence, and of those who do, about half relapse within a year (128, 129).

2.6.2 Pharmacotherapeutic approaches: As reviewed by Hart et al., (2005), precipitated cannabinoid withdrawal syndrome (CWS) in laboratory animals has been used to test the efficacy of various drugs (THC, clonidine, prostaglandin E2, and lithium) (130-133). The results of these animal studies have provided the rationale for some of the clinical trials in humans.

Almost every class of psychotropic drug has been tested for CUD (134-139) including drugs that 1) directly target the CB-1R system such as **CB-1R agonists** e.g., 9-delta-tetrahydrocannabinol (THC) to substitute cannabis (101, 102, 140, 141), Nabiximols (142), Sativex (143) or **CB1R antagonists** to block cannabis effects (144, 145), 2) **Anti-depressants**: Bupropion (146), Nefazodone (147, 148), Fluoxetine (149), Escitalopram (150),Venlafaxine (151), Lofexidine (152), Baclofen (153) and Mirtazapine (154), Buspirone (155-157), and Vilazodone (158), 3) **Mood stabilizers**: Lithium (159) and Divalproex (101, 160), 4) **Antipsychotics**: Pericyazine (161), Aripiprazole (162), Quetiapine (163), 5) **Other** drugs: Gabapentin (164), Naltrexone (165-169), N-acetylcysteine (170, 171), Atomoxetine (172, 173), Entacapone (174) and some unpublished reports of pregnenolone, cannabidiol (CBD), Aprepitant, Citicholine, Guanfacine, Progesterone, and Nabilone.

Most pharmacological trials have focused on the initial and immediate goal of alleviating the unpleasant abstinence symptoms associated with CWS. Few studies have targeted the long-term goal of relapse prevention or reducing consumption. The study designs were mostly randomized, double-blind, placebo-controlled, counter balanced, with the exception of a few open label studies (139). The studies had small sample sizes (mean 60, range 6-300 participants) and were of varying duration (1-13 weeks). None of the medications that have been tested for cannabis withdrawal and/or dependence have been shown to be consistently effective (134-139, 155, 175, 176). Most of the approaches yielded negative results. The few that did yield promising results have not all been consistently replicated. The evidence base for the gabapentin and N-acetylcysteine while showing some promise needs further investigation. Substitution treatment with CB1R agonists (e.g., THC) reduces cannabis withdrawal in a dose-dependent manner (101, 102, 141). However, the reduction in cannabis withdrawal does not appear to translate into any reduction in relapse but may result in higher treatment retention (141). However, CB1R agonists such as THC and Nabilone have potent psychoactive effects

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

and other side effects that limit tolerability and are not without risk. THC is unlikely to be a useful treatment for under age 21 CUD patients because THC cannot be given to individuals who are under the age of 21, a group that has high rates of CUD. While low doses of oral THC might attenuate withdrawal symptoms, similar doses of THC have been shown to exhibit reinforcing properties in cannabis users, suggesting that abuse liability remains a concern with substitution therapy (177). Furthermore, substituting cannabis with THCs does not address the underlying changes in CB1R function associated with CUD. ***Thus, at present there are no FDA approved or clinically-accepted pharmacological treatments for cannabis use disorders.***

2.7 Potentiating endocannabinoid signaling as a treatment for CUD: The endogenous cannabinoid system consists of at least two receptor subtypes (CB1R and CB2R) and several endogenous signaling molecules (endocannabinoids = eCBs) that bind to these receptors (178, 179). The two best characterized endogenous ligands, anadamide (AEA) and 2-arachindonoylglycerol (2-AG) are synthesized from membrane phospholipid precursors on-demand by the enzymes *N*- Acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), respectively.

Endocannabinoids are rapidly synthesized and released on demand. Endocannabinoid function can be potentiated via several pathways including by increasing levels of the principal eCBs, anandamide (AEA) and 2-AG. Levels of AEA and 2-AG are regulated by related synthases, degrading enzymes, and transporters. Fatty Acid Amide Hydrolase (FAAH) is the primary enzyme for hydrolysis of AEA (180-183). Thus, AEA levels can be increased by inhibiting FAAH. Genetic deletion of the FAAH gene or pharmacological inhibition of FAAH activity impairs AEA hydrolysis, resulting in up to 10-fold increases in brain AEA levels (184, 185). FAAH knockout mice exhibit normal CB1R expression despite constitutively higher levels of endogenous fatty acid amides including AEA (186, 187). FAAH knockout mice also display wild-type behavioral responses in most tests, with mild to moderate hypoalgesic and anxiolytic-like phenotypes (188, 189). There are a number of FAAH inhibitors available including URB597, OL-135, PF-04457845 and PF-622 reviewed in(190). FAAH Inhibitors have shown promising therapeutic efficacy in a variety of pathologies (191) without the psychoactive effects or the abuse liability of cannabis (192-194) and PF-04457845 has shown promising results for CUD.

2.8 Compared to THC, increased anandamide levels produce lower adaptive changes at the CB1R: Anandamide and THC might differentially regulate CB1Rs. When FAAH-knockout mice were repeatedly administered equivalent maximally effective doses of anandamide or THC, those given THC demonstrated reduced cannabinoid-stimulated G-protein activity and receptor binding levels, which was associated with tolerance to *in vivo* effects and CB1R antagonist-precipitated withdrawal (187). In contrast, repeated anandamide administration produced receptor levels and receptor-mediated G-protein activity intermediate between vehicle- and THC-treated FAAH-knockout mice. Rimonabant precipitated a markedly reduced withdrawal in FAAH knockout mice treated sub-chronically with anandamide as compared with mice treated repeatedly with THC. Collectively, these findings suggest that unlike repeated exposure to direct acting CB1R agonists, repeated anandamide administration is not associated with the CB1R adaptive changes.

2.9 FAAH inhibitors have several advantages over THC or cannabis:

2.9.1 FAAH-inhibitors are not rewarding: Animals treated sub-chronically with the FAAH inhibitor URB597 do not show CB1R antagonist precipitated withdrawal suggesting that unlike THC, FAAH inhibitors do not induce dependence (195). Furthermore, URB597 does not elicit conditioned place preference (196) and also does not generalize in rats trained to discriminate the drug effects of THC (193, 196). Also, unlike THC, URB597 is not self-administered by

monkeys does not prime reinstatement, and fails to increase self-administration in monkeys receiving either THC or cocaine (192). FAAH inhibitors such as URB597 do not elicit rewarding effects in the conditioned place preference test, and are not self-administered by monkeys (192). Furthermore, PF-04457845 does not elicit effects on motility, catalepsy and body temperature, which are the signature effects of cannabinoids (197).

2.9.2 FAAH Inhibitors do not have negative interactions with THC: Despite having consistently elevated anandamide levels nearly 10-fold above that of the wild-type animals, FAAH-deficient mice have previously been demonstrated to display similar responses to acute THC administration in a battery of cannabinoid-sensitive behaviors as wild-type animals (184). This has some important implications for the use of FAAH inhibitors in individuals who are using cannabis, suggesting that in individuals receiving FAAH inhibitor treatment there should be no safety concerns if they were to use cannabis (relapse).

2.9.3 FAAH inhibitors have several advantages: The approach of substituting cannabis with THC or other direct acting CB1R agonists for CUD essentially creates a state of controlled dependence without addressing the underlying adaptive changes associated with CUD. Compared to THC or cannabis, FAAH inhibitors 1) do not have psychoactive effects, 2) are not rewarding, 3) do not increase the abuse liability of other addictive drugs, and 4) are not associated with tolerance or withdrawal.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

3.0 PRELIMINARY RESEARCH

PF-04457845, a potent and selective FAAH-inhibitor, is an orally active, long-acting, time-dependent, highly efficacious and selective covalent inhibitor of FAAH (198-201). It has undergone preclinical and clinical (phase 2) testing by Pfizer. PF-04457845 inhibits human FAAH with high potency (*k*inact/*Ki* = 40300 M-1s-1; IC50 = 7.2 nM).

***3.1 Animal Studies**:* PF-04457845 has potent and long lasting antinociceptive effects in rats with oral administration. At 1 mg/kg PF-04457845 displays in vivo efficacy for over 24 hours with concomitant FAAH-inhibition, elevation of brain and plasma anandamide, *N*-palmitoyl ethanolamine (PEA), and *N*-oleoyl ethanolamine (OEA). Furthermore, unlike direct CB1R agonists even at high doses PF-04457845 does not have effects on motility, catalepsy, or body temperature, which are the classic central nervous system effects of CB1R agonists.

***3.2 Human Phase 1 Studies*:** Randomized, double-blind, placebo-controlled Phase 1 studies have been conducted in healthy male participants (n=64), aged 21 to 55 to characterize the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of single and multiple oral doses of PF- 04457845 in healthy participants. Dose regimens included single doses from 0.1 to 40 mg and multiple doses from 0.5 to 8 mg once daily (QD) for 14 days. Blood and urine were collected for PK analysis.

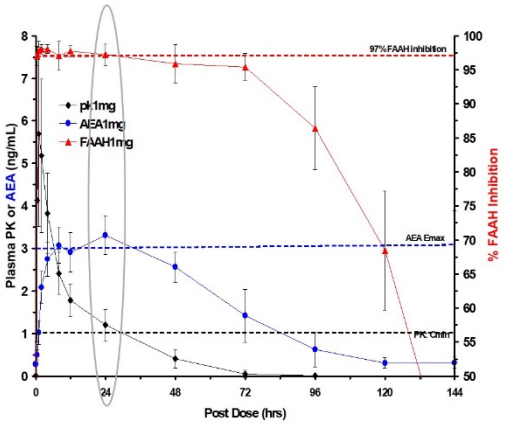


Figure 2: *Almost complete FAAH inhibition with 1mg dose in humans*

3.2.1 Pharmacokinetics: With single doses, absorption of PF-04457845 is rapid, and concentrations peak (C_{max}) within an average of 2 hours post dose. Elimination of PF-04457845 is multi-phasic, with a half-life (t1/2) ranging from 12-23 hours. With multiple dosing, steady-state plasma concentrations were attained by Day 7. An approximate 2-3 fold accumulation in exposure was observed between days 1 and 14. PK at steady-state appeared dose-proportional. There are no major food effects on PF-04457845. Urine excretion of PF-04457845 as intact parent was negligible. PK is commensurate with QD dosing.

3.2.2 Pharmacodynamics: Peripheral FAAH activity was measured ex vivo in blood leukocytes. Plasma concentrations of anandamide, PEA, OEA and *N*-linoleoylethanolamide (LEA) were measured as pharmacodynamic biomarkers. PEA, OEA, and LEA may have anti-inflammatory, sleep inducing, and appetite inducing effects. Inhibition of FAAH activity and elevation of a number of fatty acids has been demonstrated with single and multiple doses. Pharmacological washout takes 10 days after multiple dosing with 4 mg due to a combination of the time it takes for the drug to clear and the time that it takes for FAAH activity to recover. This slow pharmacological washout may offer the advantage of being less likely to result in withdrawal symptoms.

The effects of 5 doses of PF-04457845 (0, 0.5, 1, 4 and 8 mg) on cognitive function were tested in a randomized, double-blind, placebo-controlled, parallel group study of healthy volunteers (Pfizer; on file). Participants were repeatedly assessed several times a day and several days over 2 weeks using the CogState battery, a battery that assesses psychomotor function, visual attention, learning, executive function, and delayed recall, as well as a global measure of cognition across domains (202). While PF-04457845 was not associated with

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

changes in cognitive function in healthy adults when given over 14 days, it is not clear what effects it might have on cognitive function in cannabis dependent individuals who are known to have cognitive deficits. Of note, oral THC attenuated some of the cognitive deficits associated with CWS (101).

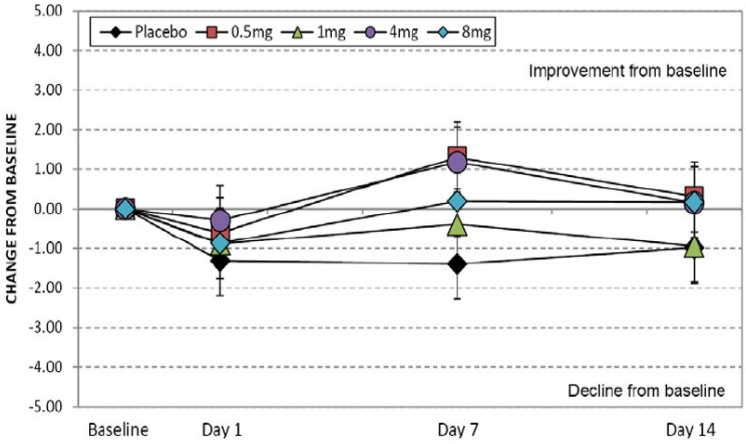


***Figure 3**: Effects of 5 doses of PF-04457845 on cognitive test performance over time in healthy individuals. Composite score performance remained within plus or minus one standard deviation unit across the study period.*

3.3 <u>Human Phase 2 Osteoarthritis Study</u>: The effects of 2 weeks of daily oral administration of PF-04457845 on pain relief in patients with osteoarthritis of the knee were studied in a phase 2a randomized, double-blind, double-dummy, placebo- and active-controlled, 2-way cross-over, multi-center clinical trial (Pfizer; on file). An interim analysis was completed after 56 participants completed the study; 36 participants received PF-04457845 (4-mg) for 2 weeks. PF-04457845 was well tolerated in patients with OA, with a safety profile that was indistinguishable from placebo. The study was conducted in 5 centers in Canada, Sweden, and the United States of America and randomized 76 participants. During the study, no participant died or had a Serious Adverse Event (SAE). No participant was permanently withdrawn due to an Adverse Event (AE). A total of 136 AEs (all causalities) were reported in 51%, 58%, and 51% of participants treated with PF-04457845, naproxen, and placebo, respectively. There were no clinically significant trends or clinically significant abnormalities in clinical laboratory tests, vital signs measurements, or ECG findings. Most AEs (97) were mild in severity; 31 AEs were moderate, and 2 AEs were severe (nightmare and headache in the placebo treatment group). Furthermore, PF-04457845 caused substantial increase in all of the FAAH concentrations (means of 3.4 to 13.5-fold increases) compared to placebo.

***Table 3**: Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in Any Treatment Group - All Causality/Treatment-Related*

	Number (%) of Subjects					
	PF-04457845 N = 37		Naproxen N = 36		Placebo N = 70	
MedDRA (v13.0) Preferred Term	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Upper respiratory tract infection	6 (16.2)	0	3 (8.3)	0	6 (8.6)	0
Headache	1 (2.7)	0	2 (5.6)	1 (2.8)	10 (14.3)	3 (4.3)
Diarrhea	1 (2.7)	0	2 (5.6)	0	3 (4.3)	1 (1.4)
Back pain	2 (5.4)	0	2 (5.6)	0	2 (2.9)	0
Fatigue	0	0	1 (2.8)	1 (2.8)	4 (5.7)	3 (4.3)
Dizziness	2 (5.4)	1 (2.7)	2 (5.6)	1 (2.8)	1 (1.4)	0
Constipation	1 (2.7)	0	3 (8.3)	3 (8.3)	0	0
Dyspepsia	0	0	3 (8.3)	2 (5.6)	0	0

Includes data up to 14 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
This table includes data up to 14 days after the last dose of study drug.
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, v = version, N = number of subjects per treatment group

In general, AEs were infrequent and there were no clear differences among treatment groups. The most frequently reported all-causality AEs across treatment groups were upper respiratory tract infection, headache, diarrhea, and back pain (**Table 3**). The most frequently reported treatment-related AEs across all treatment groups were headache, fatigue, and constipation, none of which were judged by the investigator to be related to PF-04457845. The only commonly reported treatment-emergent AE that was also judged related to PF-04457845 was dizziness, which occurred in 1 participant. Treatment-related AEs were more commonly reported in the naproxen treatment group than in the PF-04457845 treatment group. The most common adverse events are presented in **Table 3**. There were no serious adverse events, or adverse events that caused functional un-blinding and no cannabinoid-type events.

3.4 <u>Proof of Concept (POC) Study with PF-04457845 in CUD:</u> We have completed conducting a preliminary study testing the safety and efficacy of PF-04457845. The study was conducted under IND#114,017. DSM-4 cannabis dependent participants with a clear previous episode of CWS were included in a randomized, double-blind, placebo-controlled study (**Figure 4**). After a screening period, participants were randomized to receive placebo or PF-04457845 (4mg). All participants were hospitalized for the 1st week on a locked inpatient research unit to achieve and maintain abstinence, and to precipitate CWS. The remaining 3-week treatment phase was conducted on an outpatient basis to assess relapse. The 4-week treatment phase was followed by 8 weeks of follow-up to assess safety.

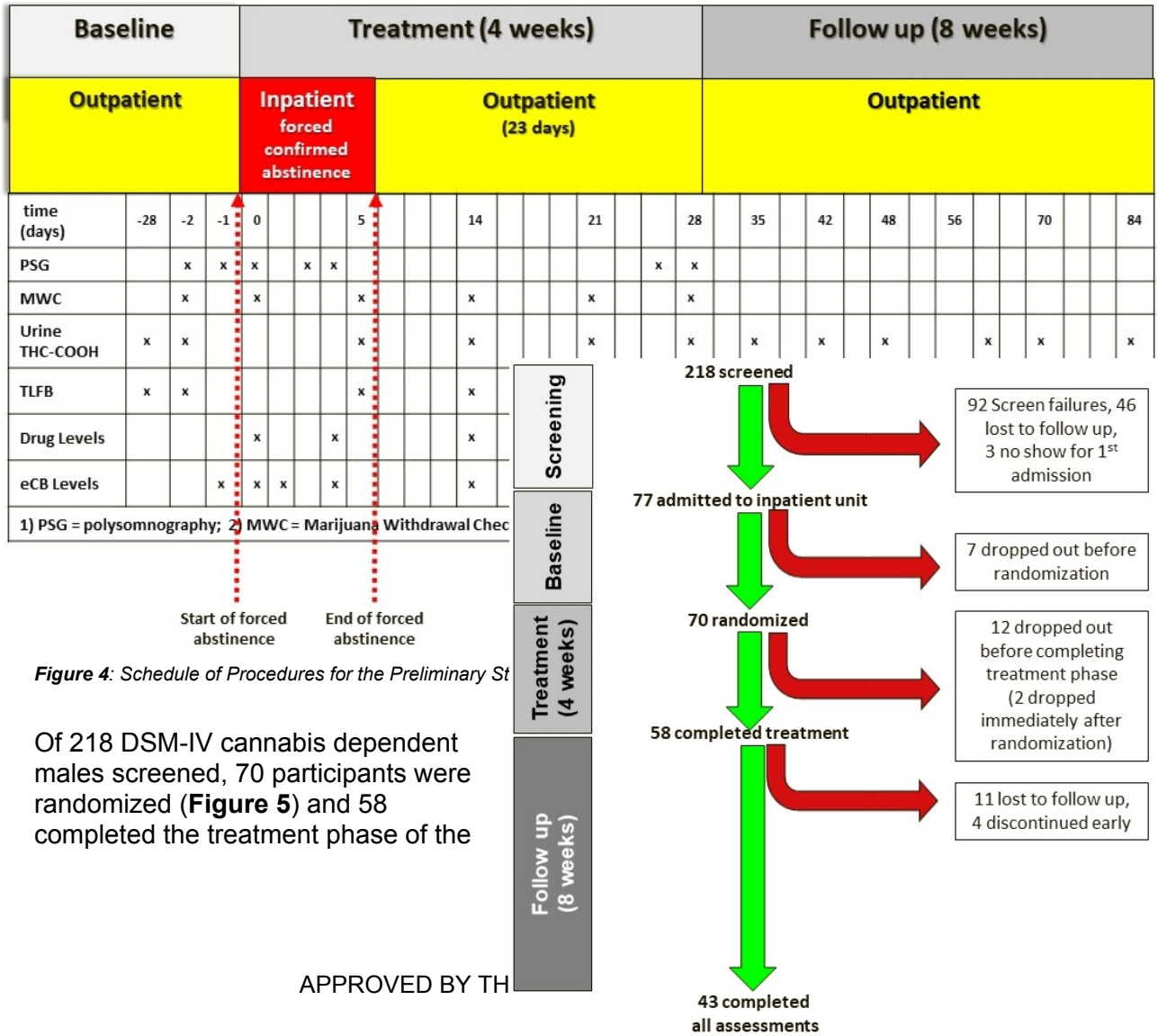


***Figure 4**: Schedule of Procedures for the Preliminary St*

Of 218 DSM-IV cannabis dependent males screened, 70 participants were randomized (**Figure 5**) and 58 completed the treatment phase of the

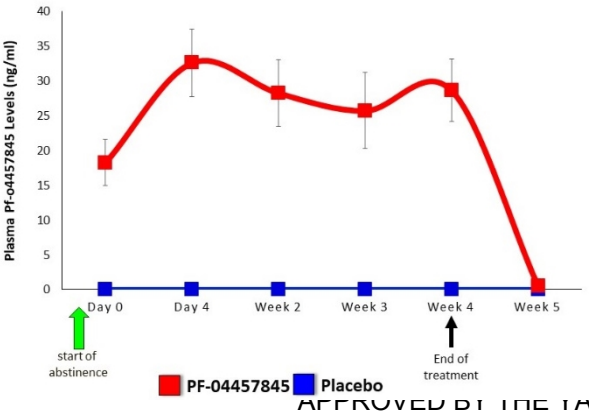
study. Participation of the last two participants who would have met the target of 60 completers was terminated shortly after learning of the outcome of the phase I *trial* of BIA 10-2474. Both groups were equivalent at baseline in terms of daily cannabis use captured by the 30-day TLFB (Wald $\chi^2(1)=0.003$, $p=0.959$) and urine THC-COOH levels (Wald $\chi^2(1)=0.004$, $p=0.947$). There were no significant differences in other demographic variables (**Table 4**).

Figure 5: *Consort Diagram for Preliminary Study*

Table 4: *Demographics for Preliminary Study*

		Placebo (n=24)	FAAH-I (n=46)	Statistic	p value
Age in years		27.46 (8.71)	28.46 (8.49)	t(68)=-0.46	0.65
Handedness	Right	79.17%	84.78%	$X^2(1)=0.35$	0.55
	Left	20.83%	15.22%		
Race	African American	50.00%	52.17%	$X^2(3)= 1.21$	0.75
	Caucasian	37.50%	39.13%		
	Native American	0%	2.17%		
	Mixed race	12.50%	6.52%		
Ethnicity	Hispanic	16.67%	15.22%	$X^2(1)=0.03$	0.87
	Non-Hispanic	83.33%	84.78%		
Education in years		12.73 (1.98)	12.79 (1.54)	t(68)=-0.15	0.88
Substance Use	Cannabis (joints/day)	3.84 (3.09)	3.59 (5.17)	t(68)=0.22	0.83
	Alcohol (drinks/day)	0.70 (0.72)	0.64(1.01)	t(67)=0.25	0.81
Tobacco (cigarettes/day)		1.47 (2.67)	2.44 (2.99)	t(67)=-1.34	0.19
FTND Total Score		1.39 (1.45)	2.06 (2.08)	t(43)=-1.07	0.29
Desire to quit	Low desire	33.33%	36.96%	$X^2(1)=0.90$	0.76
	High desire	66.67%	63.04%		

3.4.1 Pharmacokinetics: Plasma was sampled to assay levels of PF-04457845 by an independent laboratory (GVK Sciences) in a subset of participants using a proprietary method with permission from Pfizer. While PF-04457845 could not be detected in the placebo group, there were significantly higher levels in the PF-04457845 group across all timepoints except after the discontinuation of treatment (week 5) (**Figure 6**).



APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

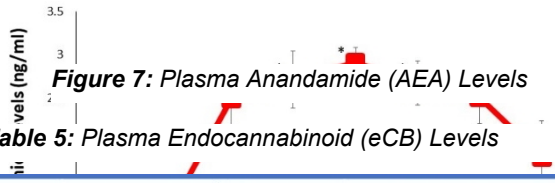


Figure 7: *Plasma Anandamide (AEA) Levels*

Table 5: *Plasma Endocannabinoid (eCB) Levels*

eCB	Time	Drug Condition		Statistical Comparison	
		Placebo (n= 4-7)	FAAH-I (n=7-12)	U	p_{Adj} value (FAAH-I>Placebo)
Anandamide (AEA)	Day -1 (baseline)	0.449 (0.130)	0.423 (0.146)	42	n.s.
	Day 0	0.450 (0.144)	1.150 (0.433)	79	0.008
	Day 2	0.270 (0.048)	2.361 (1.009)	46	0.024
	Day 4	0.342 (0.133)	2.695 (1.155)	48	0.018
	Week 2	0.386 (0.179)	2.907 (0.523)	45	0.007
	Week 3	0.325 (0.167)	2.637 (0.858)	36	0.015
	Week 4	0.400 (0.133)	2.555 (0.962)	32	0.016
	Week 5	0.476 (0.208)	1.999 (1.164)	27	n.s.
Palmitoylethanolamine (PEA)	Day -1 (baseline)	2.311 (0.505)	1.778 (0.605)	20	n.s.
	Day 0	2.351 (0.680)	3.954 (1.409)	72	0.050
	Day 2	1.914 (0.524)	5.345 (1.970)	47	0.035
	Day 4	2.300 (0.710)	5.564 (1.957)	45	0.039
	Week 2	2.212 (0.871)	5.917 (1.092)	45	0.008
	Week 3	2.060 (1.214)	5.718 (1.274)	35	0.036
	Week 4	2.012 (1.011)	5.541 (1.818)	37	0.044
	Week 5	1.882 (0.749)	4.134 (1.803)	30	n.s.
Oleoylethanolamine (OEA)	Day -1 (baseline)	2.324 (0.642)	1.758 (0.758)	21.5	n.s.
	Day 0	2.291 (0.876)	5.257 (1.991)	74	0.030
	Day 2	1.896 (0.334)	9.765 (3.817)	45	0.039
	Day 4	2.060 (0.538)	10.804 (4.173)	46	0.032
	Week 2	1.376 (0.639)	10.419 (2.379)	45	0.008
	Week 3	1.300 (0.762)	9.847 (3.317)	36	0.021
	Week 4	1.596 (0.640)	9.365 (3.382)	38	0.030
	Week 5	1.662 (0.677)	7.353 (4.163)	30	n.s.

3.4.2 *Target Engagement:* Levels of AEA that were expected to increase following treatment with PF-04457845 were assayed in a subset of participants by the laboratory of Alex Makriyannis at North Eastern University. Relative to the placebo group, plasma levels of AEA, PEA

Figure 6: *Plasma PF-04457845 Levels*

and OEA were higher in the PF-04457845 group on days 0, 2, and 4, and weeks 2, 3, and 4, but not at baseline (day -1) and after the discontinuation of treatment (week 5) (**Figure 7**, **Table 5**). These results demonstrate target engagement of PF-04457845 in CUD individuals.

Taken together, the levels of PF-04457845 and AEA provide confirmation of 1) adherence to treatment and 2) target specific effects of PF-04457845. Similarly, PF-04457845 also produced significant increases in plasma oleoylethanolamine (OEA) levels (**Table 5**).

3.4.3 *Adherence:* Adherence to study medication was visually confirmed to be at least 95% of higher as reported elsewhere (203). Concordance between expected and actual remaining study medication counted at weekly study visits was 87.69% and as noted above, participants assigned to active study medication had detectable plasma drug levels, and increases in serum endocannabinoid levels, while those assigned to placebo did not.

3.4.4 *Cannabis Withdrawal Inpatient:* As a reminder, only participants with a previous episode of CWS were included in the study, and all participants were hospitalized on the Clinical Neuroscience Research Unit to achieve and maintain abstinence. There were significant interaction effects between drug and time (Wald $\chi^2(4)=24.408$, $p<0.001$) and between drug, time, and desire to quit (Wald $\chi^2(4)=14.790$, $p=0.005$). Post hoc analyses revealed lower cannabis withdrawal scores in the FAAH-I vs. placebo-treated group on day 0 ($p_{Adj}=0.048$) and day1 ($p_{Adj}=0.035$), the first and second days of treatment. No other comparisons survived multiple comparisons correction.

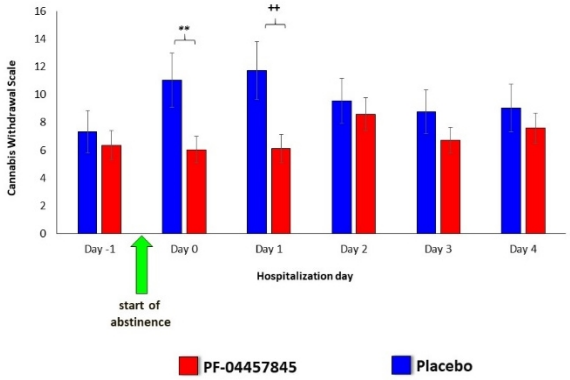


Figure 8: *Cannabis Withdrawal (Inpatient)*

3.4.5 *Cannabis Use:* At the end of treatment (4 weeks) there was a significant main effect of drug (Wald $\chi^2(1)=13.371$, $p<0.001$) such that the PF-04457845 treated group had lower cannabis use compared to the placebo group (**Figure 9**). Of note, mean cannabis use in the PF-04457845 treated group was below 1 joint/day at the end of the treatment. Furthermore, there

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

was a trend to significance for the main effect of desire to quit (Wald $\chi^2(1)=3.473$, $p=0.062$) which was driven by lower cannabis use in the group with high desire to quit compared to the group with low desire to quit.

3.4.6 Urinary THC-COOH Levels: At the end of treatment (week 4) There was a main effect of drug (Wald $\chi^2(1)=6.760$, $p=0.009$) on urinary THC-COOH levels that was driven by a reduction in urinary THC-COOH levels in the FAAH-I group compared to the placebo group (**Figure 10**). A significant drug x desire to quit interaction effect was observed (Wald $\chi^2(1)=4.380$, $p=0.036$). Exploratory analyses revealed that urinary THC-COOH levels correlated with self-reported cannabis use (TLFB) week 4 (rho=0.540, $p_{Adj}<0.001$).

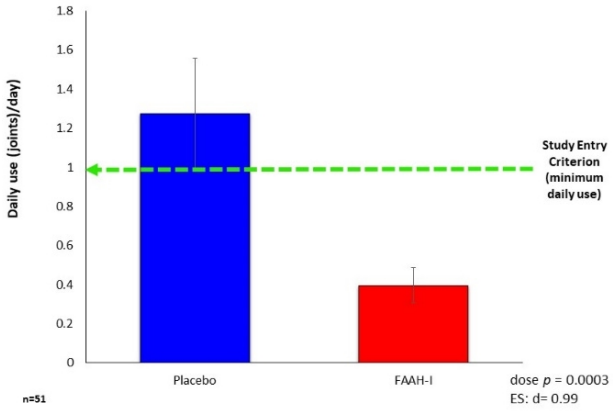


***Figure 9**: Daily Cannabis Use at the End of Treatment*

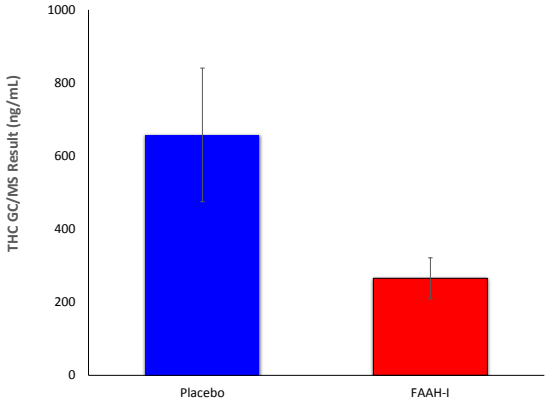


***Figure 10**: Urinary THC-COOH Levels at End of Treatment*

3.4.7 Feeling States: The drug by time interaction was significant for VAS depression (Wald $\chi^2(4)=13.328$, $p=0.01$); the PF-04457845 treated group had lower scores on day 0 (p =0.019) and day 1 (0.067) (**Table 6**). The drug by time interaction was significant for VAS anxious (Wald $\chi^2(4)=12.03$, $p=0.017$); the PF-04457845 treated group had lower scores on day 0 (p =0.052). The drug by time interaction was significant for VAS depression (Wald $\chi^2(4)=13.269$, $p=0.01$); the PF-04457845 treated group had lower scores on day 0 (p =0.012) and day 1 (0.011). There were no significant effects of interest on VAS irritable and hungry.

3.4.8 Polysomnography: For time in stage N1, a main effect of time (Wald χ^2 (4)=11.960, $p=0.018$) and a drug x time interaction was observed (Wald χ^2 (4)=10.676, $p=0.030$) (**Figure 12**). No

***Table 6:** Feeling States (Visual Analog Scale) During Acute Withdrawal*

easure	Effect	Wald χ^2 (df)	p value	Comparison	p value
Depressed	Drug	1.197 (1)	0.274	-	-
	Desire to Quit	1.854 (1)	0.173	-	-
	Time	25.274 (4)	0.000	Day 0 > Day 3	<0.001
				Day 0 > Day 4	0.025
				Day 1 > Day 3	0.011
				Day 1 > Day 4	0.019
				Day 2 > Day 3	0.012
				Day 2 > Day 4	0.039
	Drug x Desire to Quit	0.570 (1)	0.450	-	-
	Drug x Time	13.328 (4)	0.010	Day 0: Placebo > FAAH-I	0.019
				Day 1: Placebo > FAAH-I	0.067
	Desire to Quit x Time	4.312 (4)	0.365	-	-
	Drug x Desire to Quit x Time	1.715 (4)	0.788	-	-
Anxious	Drug	0.430	0.512	-	-
	Desire to Quit	0.315	0.575	-	-
	Time	13.543	0.009	Day 0 > Day 1	0.017
				Day 0 > Day 2	0.012
				Day 0 > Day 3	0.005
				Day 1 < Day 4	0.053
				Day 2 < Day 4	0.066
				Day 3 < Day 4	0.028
	Drug x Desire to Quit	0.150	0.698	-	-
	Drug x Time	12.030	0.017	Day 0: Placebo > FAAH-I	0.052
	Desire to Quit x Time	6.954	0.138	-	-
	Drug x Desire to Quit x Time	6.526	0.163	-	
Irritable	Drug	2.920	0.087	-	-
	Desire to Quit	0.006	0.936	-	-
	Time	4.216	0.378	-	-
	Drug x Desire to Quit	2.470	0.116	-	-
	Drug x Time	13.269	0.010	Day 0: Placebo > FAAH-I	0.012
				Day 1: Placebo > FAAH-I	0.011
	Desire to Quit x Time	1.775	0.777	-	-
	Drug x Desire to Quit x Time	6.341	0.175	-	-
Tired	Drug	3.237	0.072	-	-
	Desire to Quit	4.930	0.026	Low > High	0.026
	Time	2.691	0.611	-	-
	Drug x Desire to Quit	1.391	0.238	-	-
	Drug x Time	8.494	0.075	-	-
	Desire to Quit x Time	1.850	0.763	-	-
	Drug x Desire to Quit x Time	1.220	0.875	-	-
Hungry	Drug	2.231	0.135	-	-
	Desire to Quit	1.297	0.255	-	-
	Time	15.798	0.003	Day 0 < Day 1	0.096
				Day 1 > Day 2	0.002
				Day 1 > Day 4	0.024
				Day 2 < Day 3	0.085
				Day 3 > Day 4	0.020
	Drug x Desire to Quit	3.847	0.050	Low Desire: Placebo > FAAH-I	0.024
				Placebo: Low Desire > High Desire	0.049
	Drug x Time	1.962	0.743	-	-
	Desire to Quit x Time	6.358	0.174	-	-
	Drug x Desire to Quit x Time	4.807	0.308	-	-

pairwise differences survived correction for multiple comparisons. While no differences were observed for stage N2 (Figure 12), a significant drug x time interaction was observed for stage N3 (Wald $\chi^2(4)=10.084$, $p=0.039$). Pairwise comparisons revealed that the PF-04457845 group exhibited increased time in stage N3 on day 2 ($p_{Adj}=0.005$) (**Figure 11**). For time in REM, a significant main effect of time (Wald $\chi^2(4)=19.343$, $p=0.001$) and a trend towards a main effect of drug (Wald $\chi^2(4)= 3.032$, $p=0.082$) were observed. The latter was driven by a reduction in REM time in the PF-04457845 group compared to the placebo group. For secondary PSG measures (**Figure 13**), a main effect of time was observed for number of awakenings (Wald $\chi^2(4)=42.606$, $p<0.001$), sleep efficiency (Wald $\chi^2(4)= 15.512$, $p=0.004$), total sleep time (Wald $\chi^2(4)=15.512$, $p=0.004$), and wake time during sleep period (Wald $\chi^2(4)=9.806$, $p=0.044$). Finally, a main effect of drug (PF-04457845 >Placebo) was observed for latency to reach first REM period (Wald $\chi^2(1)=5.355$, $p=0.021$) (**Table 7**).

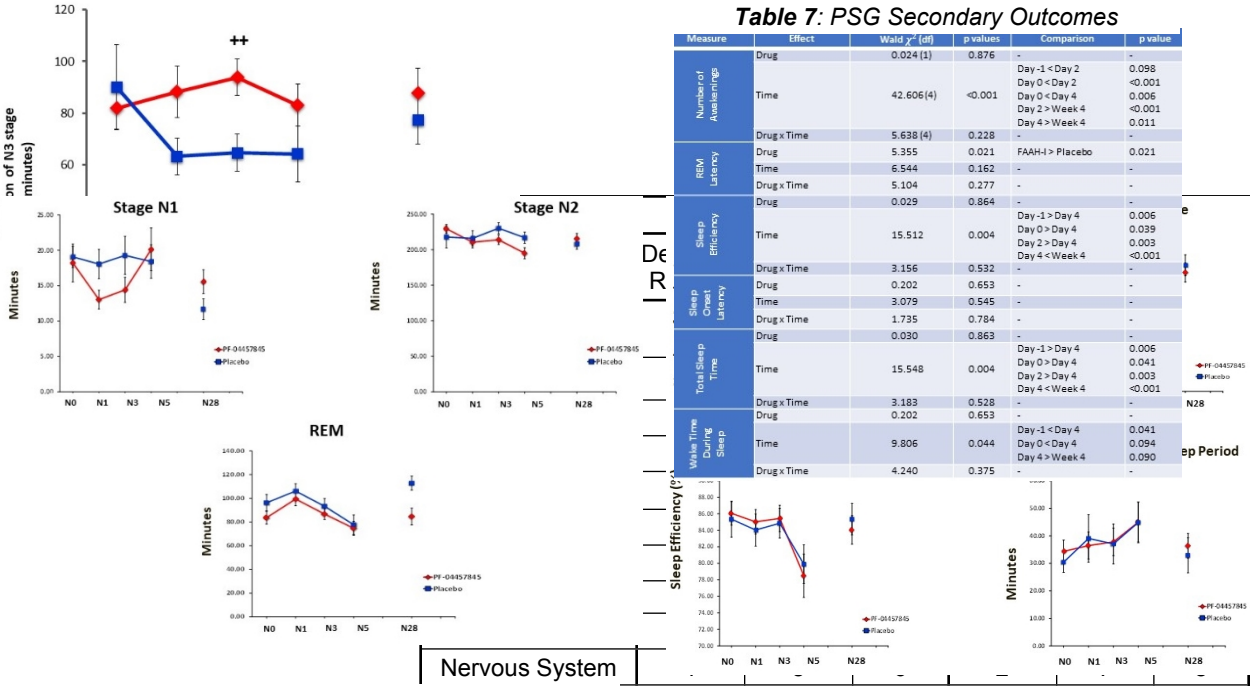


Figure 12: *Effects on Sleep N1, N2, and REM*

Table 7*: PSG Secondary Outcomes*

Measure	Effect	Wald χ^2 (df)	p values	Comparison	p value
Number of Awakenings	Drug	0.024 (1)	0.876	-	-
	Time	42.606 (4)	<0.001	Day -1 < Day 2	0.098
				Day 0 < Day 2	<0.001
				Day 0 < Day 4	0.006
				Day 2 > Week 4	<0.001
				Day 4 > Week 4	0.011
	Drug x Time	5.638 (4)	0.228	-	-
REM Latency	Drug	5.355	0.021	FAAH-I > Placebo	0.021
	Time	6.544	0.162	-	-
	Drug x Time	5.104	0.277	-	-
Sleep Efficiency	Drug	0.029	0.864	-	-
	Time	15.512	0.004	Day -1 > Day 4	0.006
				Day 0 > Day 4	0.039
				Day 2 > Day 4	0.003
				Day 4 < Week 4	<0.001
	Drug x Time	3.156	0.532	-	-
Sleep Onset Latency	Drug	0.202	0.653	-	-
	Time	3.079	0.545	-	-
	Drug x Time	1.735	0.784	-	-
Total Sleep Time	Drug	0.030	0.863	-	-
	Time	15.548	0.004	Day -1 > Day 4	0.006
				Day 0 > Day 4	0.041
				Day 2 > Day 4	0.003
				Day 4 < Week 4	<0.001
	Drug x Time	3.183	0.528	-	-
Wake Time During Sleep	Drug	0.202	0.653	-	-
	Time	9.806	0.044	Day -1 < Day 4	0.041
				Day 0 < Day 4	0.094
				Day 4 > Week 4	0.090
	Drug x Time	4.240	0.375	-	-

Figure 13: *Effects on Sleep Architecture*

Nervous System						
Respiratory	0	0	9	0	1	3
Skin and Subcutaneous	1	1	5	3	0	1

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

Vascular	0	0	1	0	0	1

***Table 8**: Adverse Events from Preliminary Study*

3.4.9 Safety and Tolerability of PF-04457845: Clinical laboratory tests for safety completed at screening, during inpatient stay (Day 0, Day 4), at all weekly appointments during treatment, and during follow up phase (Week 8). Participants monitored by inpatient nursing and research staff during the ~1 week long inpatient phase. Participants were evaluated by a study doctor at all outpatient visits. There were no serious adverse events associated with this trial. The rates of minor adverse events were no different between the 2 groups (**Table 8**). The DSMB met every 6 months and had no concerns nor recommendations.

3.4.10 Summary of Preliminary Study Results: The completed preliminary double-blind, randomized placebo-controlled study with PF-04457845 in DSM-4 cannabis dependent (CUD) participants demonstrated: 1) the capacity to recruit and retain cannabis use disorder participants; 2) the capacity to visually confirm study medication adherence, a critical prerequisite for interpreting clinical trials data, using a simple, inexpensive and novel approach; 3) biological confirmation of medication adherence (plasma PF-04457845 levels), 4) biological confirmation of target engagement (increased AEA levels), 4) a reduction in cannabis use, urinary THC-COOH, cannabis withdrawal, mood disturbances with PF-04457845 treatment, 5) a normalization of disturbances in stage N3 sleep measured by polysomnography (PSG) with PF-04457845, and 6) excellent tolerability and safety.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives:

4.1.1 Primary Objective: To determine whether 4 mg PF-04457845 once daily x 8 weeks is superior to placebo in reducing self-reported frequency of cannabis use.

4.1.2 Secondary and Exploratory Objectives:

1) To determine the safety and tolerability of 4 mg PF-04457845 QD x 8 weeks

2) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing cannabis use.

3) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing the problems associated with cannabis use.

4) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing sleep disturbances.

5) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in improving participant reported quality of life.

6) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing the severity of DSM-5 CUD.

7) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing cannabis withdrawal syndrome.

8) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing cannabis craving.

9) To explore whether genetic factors (e.g., polymorphism of the FAAH gene) influence the response to PF-04457845

10) To assess adherence to PF-04457845 over the 8 weeks of treatment.

11) To assess the effects of PF-04457845 compared with placebo on plasma endocannabinoid levels.

12) To evaluate the PD (plasma anandamide), and PK/PD relationships of PF-04457845.

13) To correlate changes in exposure to PF-04457845 and clinical response.

14) To correlate changes in plasma anandamide levels with clinical response to PF-04457845.

15) To identify potential biomarkers of disease activity and drug response in the serum, such as inflammatory mediators.

4.2 Endpoints:

There is no established endpoint for CUD in the literature. Furthermore, there is no US FDA approved drug treatment for CUD that could provide guidance on selection of an endpoint. Most previous studies have used some measure of cannabis exposure as an endpoint.

4.2.1 Primary Endpoint:

There are significant problems to accurately measuring the amount of cannabis exposure. Cannabis and cannabinoids may be used by smoking, vaping or per orally. Even within smoking, cannabis and cannabinoids may be smoked as joint, blunt, bowl, etc. There are no standard units of consumption: joints come in different shapes and sizes. The potency (THC content) and the THC:CBD ratio can vary considerably. Finally, urine toxicological estimation of exposure is also fraught with challenges, especially if abstinence is not the goal. Given these challenges to measuring amount of use, self-reported frequency of use has been chosen as an endpoint.

Specifically, the *change* from baseline to the last 4 weeks of the treatment phase in the average number of occasions per day of self-reported consumption of cannabis and cannabinoids captured using the daily TLFB data collected during CAROMA calls. A cannabis use occasion is defined as every time a participant initiates the use of cannabis. This will differ based on the method of use (see below). For example, if a participant uses blunts, or joints, every time he/she lights the joint, will be counted as one occasion. Baseline is defined as the last two weeks before the second screening visit; specifically, this is the TLFB capturing last week use done at the day -7 screening visit and the day of randomization.

Table 9: *Defining an Occasion of Cannabis Use*

Method of Use	**Definition of Occasion of Use**
Joint, blunt, roach, etc.	Every time a joint is lit and used = a new occasion
Bong	Every time a bong is prepared for use, and used

Bowl	Every time a bowl is packed and used = a new occasion

4.2.2 Secondary Endpoints:

1) To evaluate the safety and tolerability of 4 mg PF-04457845 QD x 8 weeks in cannabis use disorder patients as indexed by the % of participants who a) experience at least 1 treatment-emergent related and/or possibly related adverse event, b) meet the markedly abnormal criteria for safety laboratory tests at least once post-dose, or c) who meet the markedly abnormal criteria for vital sign measurements at least once post-dose.

2) To evaluate whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing cannabis use as measured by amount (grams) used per week (TLFB).

3) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing the severity of problems associated with cannabis use measured by the Psychiatric Research Interview for Substance and Mental Disorders (PRISM).

4) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing sleep disturbances measured by actigraphy.

4.2.3 Exploratory Endpoints:

1) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing cannabis withdrawal syndrome as measured by the visual analog scale for mood states (anxiety, depression, and irritability)

2) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing the problems associated with cannabis use measured by the Marijuana Problems Scale composite score.

3) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing cannabis withdrawal syndrome as measured by the Cannabis Withdrawal Scale.

4) To evaluate whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing cannabis use as measured by:
   a. average of creatinine corrected urinary THC-COOH levels.
   b. % creatinine corrected THC-COOH negative UDS during 8-week treatment phase.
   c. days of use per week (TLFB).
   d. $ spent per week (TLFB).
   e. the % of days of self-reported abstinence from cannabis during the 8-week treatment phase (TLFB).
   f. total duration of self-reported abstinence (days) from cannabis during the 8-week treatment phase (TLFB).

5) To assess adherence to PF-04457845 as indexed by:
   a. Visual confirmation (by video)
   b. PF-04457845 plasma concentrations, and
   c. Anandamide plasma concentrations.

6) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing cannabis craving as measured by the Marijuana Craving Questionnaire-Short Form total score.

7) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD is superior to placebo in reducing the number of symptoms reported per DSM-5 CUD.

8) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in improving participant-reported quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form version (Q-LES-Q-SF) total score and subscales.

9) Polymorphism of relevant genes (e.g., FAAH gene) will moderate the change in cannabis use with PF-04457845 treatment

10) Over 8 weeks plasma endocannabinoid levels will be higher with PF-04457845 compared with placebo.

11) To evaluate the PD (plasma anandamide), and PK/PD relationships of PF-04457845.

12) To correlate changes in exposure to PF-04457845 and clinical response.

13) To correlate changes in plasma anandamide levels with clinical response to PF-04457845.

14) Change in serum levels of soluble biomarkers, such as inflammatory mediators, and their relationship to participant characteristics and change in study assessments.

15) To determine whether over the 8 weeks of treatment 4 mg PF-04457845 QD weeks is superior to placebo in reducing sleep disturbances measured by:
    a. sleep report questionnaires,

16) To evaluate the safety and tolerability of 4 mg PF-04457845 QD x 8 weeks in cannabis use disorder patients:
    a. % of participants who meet the markedly abnormal criteria for safety electrocardiogram parameters at least once post-dose.
    b. % of participants with treatment-emergent suicidal ideation or suicidal behavior as measured using the Columbia-Suicide Severity Rating Scale (C-SSRS).

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

Table 10: *Primary and Secondary Objectives, Measures, and Endpoints*

	Objective/s	Instrument/s	Endpoint/s	Outcome/s
Primary	To determine whether PF-04457845 is superior to placebo in reducing self-reported frequency of cannabis use.	TLFB	Change from baseline in the average number of times per day of self-reported consumption of cannabis or a cannabis containing product.	Differences between groups in the change from baseline use (2 weeks prior to randomization) in the average number of times per day of self-reported consumption of cannabis or a cannabis containing product in the last 4 weeks of the treatment.
Secondary	To determine the safety and tolerability of 4 mg PF-04457845 QD x 8 weeks in cannabis use disorder patients.	Self-report	% of participants who experience at least 1 treatment-emergent adverse event.	% who self-reported AEs or exhibited clinically significant changes during 1) 8-week treatment phase (from the first dose until the last dose), and 2) the 4-week follow up phase (to assess any lingering post treatment safety issues)
		Laboratory parameters (hematology, chemistry, liver functions)	% of participants who meet the markedly abnormal criteria for safety laboratory tests at least once post-dose.	
		Systolic and diastolic blood pressure and heart rate	% of participants who meet the markedly abnormal criteria for vital sign measurements at least once post-dose.	
	To determine whether PF-04457845 QD weeks is superior to placebo in reducing cannabis use.	TLFB	Δ in amount (grams) used	Change from baseline (2 weeks prior to randomization) until the last dose
	To determine whether PF-04457845 is superior to placebo in reducing the problems associated with cannabis use.	Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	Δ in total score	
	To determine whether PF-04457845 is superior to placebo in reducing sleep disturbances.	Actigraphy	Δ in duration of sleep latency, total sleep, wake after sleep onset, sleep efficiency, and ambient light	
Exploratory	To determine the safety and tolerability of 4 mg PF-04457845 QD x 8 weeks in cannabis use disorder patients.	EKG	% of participants who meet the markedly abnormal criteria for safety electrocardiogram parameters at least once post-dose.	% who self-reported AEs or exhibited clinically significant changes during 1) 8-week treatment phase (from the first dose until the last dose), and 2) the 4-week follow up phase (to assess any lingering post treatment safety issues)
		Columbia Suicide Severity Rating Scale	% of participants with treatment-emergent suicidal ideation or suicidal behavior	
	To determine whether PF-04457845 QD weeks is superior to placebo in reducing cannabis use.	Urine	Δ in weekly average of creatinine corrected urinary THC-COOH levels	Change from baseline (2 weeks prior to randomization) until the last dose
			Δ in the % creatinine corrected THC-COOH negative UDS	
		TLFB	Δ in $ spent	
			Δ in # days of use	
			Δ in the % of days of self-reported abstinence from cannabis during the 8-week treatment phase	
			total duration of self-reported abstinence (days) from cannabis between	
	To determine whether PF-04457845 is superior to placebo in reducing the problems associated with cannabis use.	Marijuana Problem Scale	Δ in total score	
	To determine whether PF-04457845 QD is superior to placebo in reducing the severity of CUD.	DSM-5 CUD	Δ in severity	
	To determine whether PF-04457845 QD is superior to placebo in reducing cannabis withdrawal syndrome.	Cannabis Withdrawal Scale	Δ in total score	
		Visual analog scale (VAS) for mood states (anxiety, depression, etc)	Δ in total score	
	To determine whether PF-04457845 QD weeks is superior to placebo in improving participant-reported quality of life.	Quality of Life Enjoyment and Satisfaction Questionnaire-18 item version (Q-LES-Q-18)	Δ in total and subscale scores	
	To determine whether PF-04457845 QD is superior to placebo in reducing cannabis craving.	Marijuana Craving Questionnaire	Δ in total score	

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

	To determine whether PF-04457845 QD is superior to placebo in reducing cognitive deficits.	Cogstate Battery	Δ in composite score	
	To determine whether PF-04457845 is superior to placebo in reducing sleep disturbances.	Sleep report questionnaires	Δ in total score	
	To assess adherence to PF-04457845.	Visual confirmation (by video)	% of confirmed observations	Over 8 weeks
		PF-04457845 plasma concentrations	Difference in PF-04457845 plasma concentrations between placebo and PF-04457845 groups	Over the time period starting the first dose until the last dose
		Anandamide plasma concentrations	Difference in plasma anandamide concentrations between placebo and PF-04457845 groups	

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

5.0 STUDY DESIGN AND DESCRIPTION

5.1 Study Design: The efficacy, safety and tolerability of the Fatty Acid Amide Hydrolase (FAAH) Inhibitor PF-04457845 in adults with DSM-5 current Cannabis Use Disorder (CUD) will be evaluated in a 4-site (Columbia University, Johns Hopkins, Medical University of South Carolina and Yale University), randomized, double-blind, placebo-controlled, parallel-group, outpatient clinical trial comparing PF-04457845 (4mg) and placebo DSM-5 CUD individuals (**Table 1**). Participants will be randomized in a 1:1 ratio to either PF-04457845 or placebo using a random block sizes of 2 and 4, stratified by site and degree of cannabis use (CUD at the level of moderate (4-7 [of 11] symptoms) or severe (8-11 [of 11] symptoms)) based on DSM5 criteria. These variables were chosen because they are the most likely to strongly affect outcomes measures. The trial includes a 1) 2-week screening phase, 2) 8-week treatment phase (randomization to PF-04457845 or placebo) for, and 3) 4-week follow up phase (for safety especially because the effects of the drug take ~ 2 weeks to washout). The duration of the treatment phase was chosen because the available toxicity data that Pfizer has collected is up to 12 weeks in humans.

During the screening period, participants will be required to set a quit attempt date that falls within the first week of treatment after at least 2 days of taking study medication. Participants will receive motivational interviewing to facilitate a quit attempt and will be rewarded for a successful attempt.

***5.2 Study Population*:** Approximately 260 total participants (target of approximately 65 participants at each of the four participating sites based on competitive enrollment) of both genders and all ethnic/racial and socioeconomic backgrounds will be randomized for a total of 178 participants completing the study (approximately 45 subjects per site). All patients will meet DSM-5 criteria for cannabis use disorder. The complete inclusion and exclusion criteria is further described in Section 6.1 and Section 6.2. Final determination for eligibility will be made by each site's principal investigator.

5.3 Duration: Screening activities will be completed up to approximately 14 days (up to a maximum of 60 days) prior to randomization on the Week 1 visit. The total duration of this study (from signed consent to the last follow-up visit) will be approximately 14 weeks. The study is expected to last 3 years.

5.4 End of Study Definition: A participant is considered to have completed the study if he or she has completed the 8-week treatment phase of the trial.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

6.0 STUDY POPULATION

6.1 Inclusion Criteria: Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1) Ages 18-60 years, inclusive (age verified using one form of picture identification with date of birth).
2) Male or Female.
3) Individuals with DSM-V criteria for CUD of at least moderate severity (≥ 4 [of 11] symptoms).
4) Current cannabis consumption greater than or equal to 30 joints/month (approximately daily) over the past 3 months
5) Positive for urinary THC-COOH on two separate occasions during screening (> 50ng/ml).
6) Primary drug currently being used is cannabis.
7) Primary method of cannabis consumption (>80% of the time) is smoking cannabis.
8) Must express a willingness at screening to set a date within the first week of randomization to *attempt* to quit using cannabis.
9) Physically healthy i.e., no clinically unstable medical conditions at the discretion of the investigator.
10) Have given informed consent, and have capacity to consent and comply with study procedures.
11) Must be able to read English as per the judgment of the site investigators. Participants are required to be able to read because there are several self-administered measures that they must read, understand and provide written answers.
12) Must provide the name of at least 1 contact (preferably 2), who would assist study staff in locating them during the study period.
13) For women of childbearing potential (WOCBP) and men, willingness to practice birth control and to inform study staff immediately if either they (for women) or their partner (for men) becomes pregnant.
14) Must be willing to complete a number of study assessments and procedures remotely.

6.2 Exclusion Criteria: Participants presenting with any of the following exclusion criteria will be excluded from participation:

1) Clinically significant unstable medical disorders (as determined by the site investigator) that will increase potential risk or interfere with study participation e.g., ongoing seizure disorder, uncompensated congestive heart failure, uncontrolled severe diabetes, uncontrolled severe hypertension, etc.
2) Laboratory tests with clinically significant abnormalities (as determined by the site investigator)
3) Positive urine toxicology screen for another drug with clinical evidence of use disorder for that drug (with the exception of THC-COOH at screening).
4) Pregnancy by history and or laboratory confirmation (serum HCG).
5) Lactation.
6) Other DSM-5 substance use disorder in the past three months (excluding cannabis, nicotine, caffeine, and mild alcohol use disorder [≤ 3 criteria]).
7) Physiological dependence on another prescribed (e.g. benzodiazepine), not prescribed licit (e.g. alcohol or benzodiazepine) or illicit substance (e.g. opioid) requiring medical management, such as alcohol, opioids, or benzodiazepines, excluding caffeine, and nicotine.
8) Abstinence from cannabis for more than 1 week at the time of randomization.

9) Meeting DSM-5 criteria for current serious mental illness (e.g., major depression, bipolar disorder, schizophrenia, any psychotic illness, including substance-induced psychosis, and current substance-induced mood disorder.)
    a. Individuals who meet criteria for current major depression at a mild severity* may be included at the discretion of the site principal investigator.
    * Per the DSM-5, current major depression at a mild severity is defined as: “Few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.”(228)
10) Lifetime history of DSM-5 bipolar disorder or any psychotic disorder.
11) Meeting DSM-5 criteria for any psychiatric disorder that may, according to t he investigator's judgment, require initiation of a pharmacological or non-pharmacological intervention over the course of the study.
12) Taking psychotropic medication/s that could interfere with interpretation of the study results or interact with study medication. Includes but is not limited to opioid analgesics, sedative hypnotics, or other known CNS depressants, etc. Exceptions include preexisting treatment with sleep agents, antidepressants for preexisting stable insomnia or depression, respectively.
13) Current moderate risk for suicide as measured by the Columbia Suicide Severity Rating Scale (CSSRS) suicidal ideation (in the last month) score of greater than 2 and a history of recent (past 1 year) serious suicide attempt (lethality score of >2 on CSSRS).
14) Current or past history of significant violence (past 2 years).
15) Currently in a residential treatment setting in which substance use is monitored and restricted, since the restricted access to drugs could represent an important confounding variable.
16) Participants who, in the investigator's opinion, would be unable to comply with study procedures or assessments, or would be unacceptable study candidates (e.g., poses threat to staff).
17) Participation in a clinical trial and receipt of investigational drug(s) during past 30 days.
18) Known allergy to FAAH-inhibitors.
19) Primary method of cannabis consumption (>80% of the time) is using vaporized cannabis or ingesting edibles.
20) Co-medication with CYP3A inhibitor, CYP3A inducers, or P-glycoprotein substrates, within 48 hours or 5 half-lives prior to baseline, at the discretion of the site investigator.

6.3 <u>Concomitant Interventions:</u> Participants must be instructed to not take any medications, including over-the counter products, vitamins, or supplements during the study without first consulting with and getting the approval of the investigator.

Similarly, since specific behavioral treatments developed for cannabis dependence e.g., MET or CBT may increase abstinence (17, 123), and in doing so obscure the effects of a medication treatment, participants will be asked to refrain from starting any such treatment until after completing the trial. Participants always have the option of dropping out from the trial to purse these or other interventions.

6.3.1 <u>Pharmacokinetic interactions with PF-04457845</u>: In vitro studies using recombinant human cytochrome P450 (CYPs) enzymes suggest that CYP3A4 is the predominant isoform responsible for the oxidative metabolism of PF-04457845. Therefore, drugs that induce or inhibit CYP3A4 may reduce or increase PF-04457845 levels. While not absolutely contraindicated, treatment with the following drugs should be carefully evaluated. The following list provides some, but not all, of the drugs knows to induce or inhibit CYP3A4:

- Drugs that Induce CYP3A4 reduce PF-04457845 levels which may result in sub-therapeutic levels of PF-04457845. This includes: Carbamazepine, Dexamethasone, Ethosuximide, Glucocorticoids, Griseofulvin, Phenytoin, Primidone, Progesterone, Rifabutin, Rifampin, Nafcillin, Nelfinavir, Nevirapine, Oxcarbazepine, Phenobarbital, Phenylbutazone, Rofecoxib, St. John's Wart, Sulfadimidine, Sulfinpyrazone, and Troglitazone.
- Drugs that Inhibit CYP3A4 increase PF-04457845 levels which may result in above normal levels of PF-04457845. This includes: Amiodarone, Anastrozole, Azithromzcin, Cimetidine, Clarithromycin, Clotrimazole, Cyclosporine, Danazol, Delavirdine, Dexamethasone, Diethyldithiocarbamate, Diltiazem, Dirithyromycin, Disulfiram, Entacapone, Erythromycin, Ethinyl estradiol, Fluconazole, Fluoxetine, Fluvoxamine, Gestodene, Grapefruit juice, Indinavir, Isoniazid, Ketoconazole, Metronidazole, Mibefradil, Miconazole, Nefazodone, Nelfinavir, Nevirapine, Norfloxacin, Norfluoxetine, Omeprazole, Oxiconazole, Paroxetine, Propoxyphene, Quinidine, Quinine, Quinupristine and dalfopristin, Ranitidine, Ritonavir, Saquinavir, Sertindole, Sertraline, Troglitazone, Troleandomycin, Valproic acid.

6.3.2 Pharmacodynamic interactions with PF-04457845: Due to the mechanism of action as selective inhibitor of fatty acid amide hydrolase, pharmacodynamic drug interactions may be hypothesized for the following compounds or situations: metabolic diseases such as abdominal obesity and associated metabolic changes, and diabetes; β-amyloid-linked events; Huntington's disease; sedative use; and other compounds influencing the endocannabinoid system such as cannabinoid receptor ligands (rimonabant); use of Nonsteroidal Anti-inflammatory Drugs. As a result of the above hypothetical pharmacodynamic interactions special care may have to be taken when PF-04457845 is administered to patients with a background of metabolic diseases and use of sedatives and other CNS active compounds such as analgesics / anti-inflammatories. None of these are absolute contraindications. In the absence of pharmacodynamic studies, clinical judgement will need to be exercised to determine the risk:benefit of other drugs taken concomitantly with PF-04457845.

***6.4 Contraception*:** Participants will be provided with information on acceptable methods of contraception as part of the informed consent process, and will be required to use one of the below approved methods of contraception for the duration of the study. Participants will be asked to inform the study staff immediately if either they or their sexual partner has become pregnant while participating in the study. Participants will be asked to document their method of contraception and sign to acknowledge that they will continue to use contraception from signing of consent until two weeks after the last dose of study medication.

6.4.1 Male Participants: From signing of informed consent until 2 weeks after the last dose of study medication, non-sterilized male participants who are sexually active with a female partner of childbearing potential must agree to use barrier contraception (e.g. a condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

6.4.2 Female Participants: From signing of informed consent until 2 weeks after the last dose of study medication, female participants of childbearing potential (Women of Child Bearing Potential: WOCBP) who are sexually active with a non-sterilized male partner must use a highly effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

6.4.3 Methods of Contraception: Acceptable contraceptive methods for WOCBP participants include: double barrier contraception or a combination of a barrier contraception and a hormonal implant, injectable, combined oral contraceptive, or a male partner who has had a vasectomy; IUD or tubal ligation.

6.5 Pregnancy: If any participant is found to be pregnant during the study, participation in the treatment phase must be immediately terminated. The participant should stop taking the study medication and return any remaining study medication as soon as possible. If possible, the participant should complete the follow up phase which is to collect safety data. Furthermore, the investigator should make every effort to ensure that the participant has established follow up care with a medical provider (OBGYN). The pregnancy should be followed up by the site investigator to determine outcome (including spontaneous or voluntary termination), details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

6.6 Randomization Criteria: Participants who meet all inclusion and exclusion criteria will be randomized at the time of the Week 1 visit in a 1:1 ratio of PF-04457845 to placebo using random block sizes of 2 and 4, stratified by site and degree of cannabis use (CUD at the level of moderate (4-7 [of 11] symptoms) or severe (8-11 [of 11] symptoms)) based on DSM-5 criteria. These variables were chosen because they are the most likely to strongly affect outcomes measures. Random treatment assignment will be done using a centralized randomization process.

6.7 Enrollment:
Participants will be enrolled at each site by competitive enrollment (or at a rate of approximately 8 subjects per month or about 2 subjects per month per site) until up to approximately 260 participants have been enrolled, or until 8 weeks before the drug expiry date (**Figure 14**). The current batch of PF-04457845's expiration date is currently 10/31/2022.

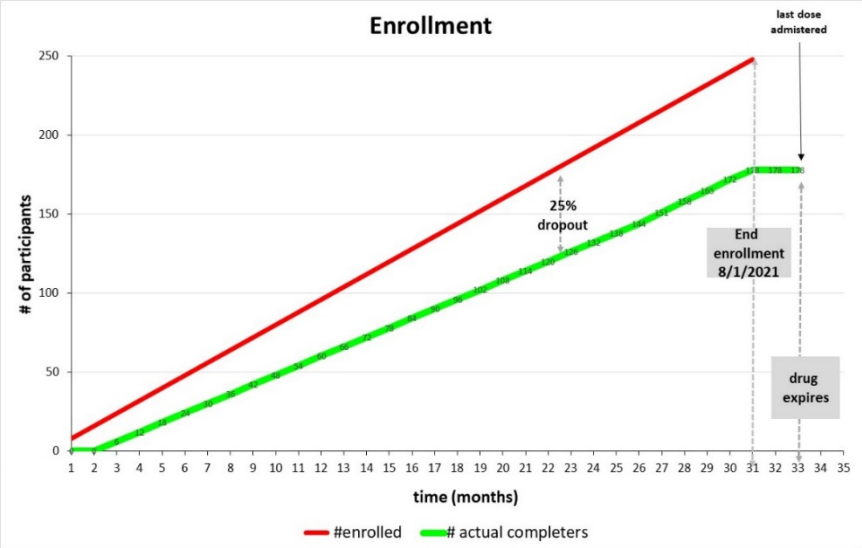


***Figure 14**: Participant Enrollment*

6.8 Enrollment by Race and Ethnicity: The sample recruited for this study needs to be composed of as close to70% men and 30% women as possible. Additionally, the sample will be composed of approximately 4% American Indian/Alaska Native, 6% Asian, 30% Black or African American, 50% White, and 9% greater than one race. Please refer to **Table 11** for planned inclusion enrollment broken down by ethnic categories. To ensure that these ethnic and racial divides are met, each site will submit to the Coordinating Center periodic enrollment reports (every 6 months). The Coordinating Center will then instruct each site on which ethnic categories still need to be met.

***Table 11**: Targeted Enrollment by Ethnic Categories*

Racial Categories	Not Hispanic or Latino	Hispanic or Latino	Total

	Female	Male	Unknown	Female	Male	Unknown	
American Indian or Alaska Native	1	6	0	0	0	0	7
Asian	2	13	0	0	0	0	15
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
Black or African American	24	42	0	2	17	0	85
White	35	80	0	3	11	0	129
More than One Race	6	6	0	5	7	0	24
Unknown	0	0	0	0	0	0	0
Total	68	147	0	10	35	0	260

6.9 Screen Failures: Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. If the participant is found to be ineligible at Screening, the investigator should complete the source document. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse events (SAE). Subject ID numbers assigned to participants who fail screening should not be reused.

The primary reason for screen failure should be recorded in the source document using one of the following categories:

- Adverse Event.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Important protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Other (specify reason).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened if the reason that they were excluded is no longer an issue (e.g., an underage participant who now falls within the permitted age range, or a participant who has stopped taking a prohibited medication). However, participants who were initially screen failures cannot be rescreened for this study more than twice. Rescreened participants should be assigned the same participant number as for the initial screening.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

7.0 STUDY INTERVENTION

7.1 Allocation to Treatment: Participants will be assigned a unique subject ID number that will be recorded in the randomization log. Then, prior to dosing, a randomization number will be allocated. This number will be retained throughout the study and will correspond to a treatment schedule determined by a randomization code. Participants will be made aware that there is a 50% chance that they will receive a placebo as a part of this research protocol.

All randomizations will be maintained centrally by the Coordinating Center, using the REDCap application. Participants will be randomized in a 1:1 manner. The randomizations will be stratified by site and severity of cannabis use (CUD at the level of moderate (4-7 [of 11] symptoms) or severe (8-11 [of 11] symptoms)) based on DSM-5 criteria.

7.2 Breaking the Blind: All study personnel will be blinded to the study treatment. To minimize the potential for bias, treatment randomization information will be kept confidential and will not be released to the investigator or investigator site personnel until after the study database has been locked.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. Blinding codes will only be broken in emergency situations for reasons of participant safety, where knowledge of treatment allocation ***is necessary*** to provide emergency care. Whenever possible, the investigator or co-investigator should consult with a member of the Coordinating Center prior to breaking the blind. When the blinding code is broken, the date, time, and reason the blind is broken must be fully documented in the source documents.

To preserve the blind, blood will be sampled for PF-04457845 assay from all participants regardless of whether they have been randomized to PF-04457845 or placebo.

7.3 Dose Selection: Given the FAAH inhibition mechanism and our understanding of the PK/PD relationship, if >95% inhibition of FAAH is not achieved, AEA levels are not reliably/robustly elevated. The minimum dose of PF-04457845 that produced >95% FAAH inhibition was 4 mg QD PF-04457845. PK at steady-state is dose-proportional. There are no major food effects on PF-04457845. Pharmacological washout takes 10 days after multiple dosing with 4mg due to a combination of the time it takes for drug clearance and FAAH activity recovery; the slow washout may offer the advantage of being less likely to result in withdrawal symptoms. The dose of 4mg PF-04457845 /day produces the maximal inhibition of FAAH, is safe as shown in the preliminary study, and furthermore, a higher dose does not afford any advantage.

7.4 Dose Administration: PF-04457845 (4mg) or matching placebo capsules will be taken by mouth at approximately the same time every morning. Exceptions about the time that the participant takes the study medication may be made at the discretion of the investigator if taking the study medication under observation (see below) conflicts with the participant's schedule (e.g., work). The study medication is not yet approved by the Food and Drug Administration for clinical use. This study will be conducted under an existing IND (#114,017). This will be explained to participants prior to signing the informed consent document.

7.5 Preparation/Handling/Storage/Accountability:

7.5.1 Acquisition and Accountability: To note, the study medication for this clinical trial was initially owned by SpringWorks Therapeutics, Inc. Ownership of the PF-04457845 study medication was transferred from SpringWorks to Jazz Pharmaceuticals as of October 2020.Upon receipt of the PF-04457845/placebo capsules from Jazz Pharmaceuticals, the site principal investigator and research pharmacist must verify the contents of the shipments against

the packing list. The verifier should ensure that the quantity is correct, and the study drug is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment If there are any discrepancies between the packing list versus the actual product received, the Coordinating Center must be contacted to resolve the issue with Jazz Pharmaceuticals. The packing list should be filed in the investigator's essential document file.

The investigator at each site must maintain 100% accountability for all drug received and dispensed during the site's participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if provided to the investigator
- Frequently verifying that the actual inventory matches the documented inventory
- Verifying that the log is completed with, at a minimum, the subject ID, name of investigator, date and amount dispensed, date and amount returned, lot number for each dose, and that all containers used are documented accurately on the log.
- Verifying that all required fields are completed accurately and legibly.

At the end of the study, each site will be provided with instructions as to the disposition of any unused investigational product. Drug supplies will be counted and reconciled at the site before being returned to the Coordinating Center. If Jazz Pharmaceuticals authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Jazz Pharmaceuticals. Prior to October 2020 the investigator must ensure that the materials are destroyed in compliance with any special instructions provided by SpringWorks.

7.5.2 Formulation and Packaging: PF-04457845 (4mg) and matching placebo capsules will be provided by Jazz Pharmaceuticals (prior to 2021 study medication was provided by SpringWorks Therapeutics). Weekly quantities of the capsules will be dispensed by the pharmacy in prescription bottles (10 capsules per bottle). Study medication will be dispensed to the participants at the in-person treatment phase study visits (Week 1, Week 3, Week 5, and Week 7 Visits), during which they will be provided with enough study medication to last until their next in-person treatment phase study visit (2 weeks of study medication).

7.5.3 Product Storage and Stability: Each site's research pharmacist will ensure that all investigational product is stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements. The PF-04457845 tablets have a recommended storage condition of 2-8 degrees Celsius. The clinical use period will be assigned based on the 5 degree Celsius stability data.

The site investigator must ensure that the Coordinating Center-supplied drug is used in accordance with the protocol and is dispensed only to participants enrolled in the study. To document appropriate use of Coordinating Centered supplied drug, the investigator must maintain records of all Coordinating Centered-supplied drug delivery to the site, site inventory, dispensation and use by each participant, and return to the Coordinating Center.

7.5.4 Chemistry, manufacturing and compounding (CMC): Chemistry manufacturing and compounding information is provided in the IND for PF-04457845, IND#114,017, and can also be found in the Investigator's Brochure for PF-04457845.

7.6 Study Intervention Adherence:

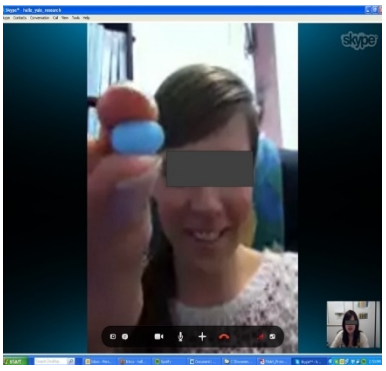


Figure 15: *Cellphone Assisted Remote Observation of Medication Adherence (CAROMA)*

7.6.1 *Study Medication Adherence using the Cell Phone Assisted Remote Observation of Adherence (CAROMA)*: Adherence to study medication will be confirmed using the CAROMA method as described elsewhere (203). Every morning 5 days per week (Monday-Friday), research staff will video-call participants to visually observe them swallow the study medication using a standardized protocol (**Figure 15**). Every morning, within a time period pre-determined by agreement, participants will be called on the cell phone and will be observed removing study medication from the packaging and swallowing the medication with water or juice. For privacy, participants will be first asked to ensure that nobody else is in the room. Participants will be asked to have water or juice handy. Participants will then be instructed to 1) hold the study capsule up to the camera, 2) show research staff that the medication is on their tongue, and 3) then hold the camera up to their mouth for a mouth check after swallowing. The research assistant will log visual confirmation of compliance. Participants will receive additional compensation for CAROMA visits, and for returning the smartphone when they complete the study, which is outlined in the economic considerations section below. If participants fail to complete the CAROMA visit, it will be assumed to be an event of nonadherence and payment will be forfeited. Please refer to Appendix H for detailed instructions on the CAROMA visit.

Participants will be provided with a cellphone that has the hardware, software, and service necessary to transmit high quality video. Prior to randomization, each participant will receive training on how to use the cell phones and also trained on the CAROMA compliance protocol. For this, each participant will be placed in one clinic office with the phone. A research staff member will video call the participant from another location in the clinic and will observe the participant consuming one M&M candy (or similar) with a glass of water. All participants will need to have at least one successful training session prior to randomization.

The CAROMA video calls **will not be recorded.** Immediately following each call, research staff will document visual confirmation of the participant taking his/her study medication, the time that the medication was taken.

7.6.2 *Plasma PF-04457845 Levels*: Adherence will also be confirmed later by measuring PF-04457845 levels in plasma from blood sampled at Week 1, Week 5, and Week 9 study visits.

7.6.3 Plasma Anandamide Levels: Adherence will also be confirmed later by measuring anandamide levels in plasma from blood sampled at Week 1, Week 5, and Week 9 study visits.

7.6.4 Weekly Pill Counts: At each in-person visit (Week 3, Week 5, Week 7, and Week 9), research staff will reconcile the number of capsules actually returned with the number that were expected to be returned. Virtual pill counts will also be conducted via video call at each remote study visit (Week 2, Week 4, Week 6, and Week 8) to reconcile the number of remaining capsules the participant has in their possession with the expected number of remaining capsules.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

8.0 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention: Discontinuation from PF-04457845 does not mean discontinuation from the study. Attempts will be made to complete the remaining study procedures as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Every attempt should be made to collect the data that would be collected at a termination visit (Week 9 Visit) as listed in **1.5 Schedule *of Procedures:*** ***Table 2***. If the participant is prematurely withdrawn from the treatment phase, he/she may be entered into the 4-week follow up phase.

***8.2 Participant Discontinuation/Withdrawal from the Study*:** Participants are free to withdraw from participation in the study at any time upon request. The investigator may discontinue a participant's study participation at any time during the study if the participant meets the study termination criteria. In addition, a participant may discontinue his or her participation without giving a reason at any time during the study.

8.2.1 Criteria for Discontinuation or Withdrawal of a Participant: The primary reason for discontinuation or withdrawal of the participant from the study or study drug should be recorded using the following categories.

1) *Adverse Event*: The participant has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.
2) *Important Protocol Deviation*: The discovery post-randomization that the participant failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the participant's health.
3) *Lost to Follow-Up*: The participant did not return to the study site and multiple attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented.
4) *Voluntary Withdrawal*: The participant wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded. Please note: all attempts should be made to determine the underlying reason for the withdrawal and where possible, the primary underlying reason should be recorded.
5) *Pregnancy*: The participant is found to be pregnant. Note: if the participant is found to be pregnant, the participant must be withdrawn immediately.
6) *Nonadherence with Study Drug during Treatment Phase*: based on the assessment of the investigator an out-of-adherence participant may be withdrawn from the study.

8.3 Lost to Follow-Up: A participant will be considered lost to follow up if he/she fails to complete 2 scheduled consecutive weekly visits or 10 consecutive days of missed study medication (~20% of nonadherence) during the treatment phase and is unable to be contacted by the study site staff. The following actions must be taken if a participant fails to return to the clinic or is non-contactable for the remote study visits:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should all be documented in the participants study file.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow up.

8.4 <u>Trial Stopping Rules</u>*:* The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information about the safety of PF-04457845 that alters the risk to benefit ratio in a significantly negative manner.
- If the planned interim analysis reveals a worsening of cannabis use in the PF-04457845 treatment group
- **For three or more serious adverse events, related to the study, from the same cause.** SAE is defined as something that:
  1. is life-threatening
  2. results in in-patient hospitalization or prolongation of existing hospitalization
  3. results in persistent or significant disability or incapacity
  4. results in a congenital anomaly or birth defect OR
  5. results in death
  6. based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
  7. adversely affects the risk/benefit ratio of the study

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected. For each procedure, participants are to be assessed by the same investigator or site personnel whenever possible. Please refer to **1.5 Schedule *of Procedures:***

Table 2 for a detailed schedule of study procedures.

9.1 Recruitment: Participants will be recruited from the community with advertising (print, radio, television, online [Craigslist, Facebook, Instagram], and subway) or by clinical referrals. The advertisements ask *"Is Marijuana or Cannabis a Problem for You? If so, you may qualify for a free and confidential research treatment study."* This study will also be registered on *clinicaltrials.gov*, an online listing of clinical trials that is available to the public, which also will serve as a recruitment source. The advertisements for this study are located in Appendix B.

Interested participants will be informed of the study and will first be screened on the phone to initially determine eligibility (see phone screen in Appendix C). If participants pass the initial screening for the study, they will then be invited for a full evaluation to assess eligibility based on the inclusion and exclusion criteria. Information collected during the phone screen will only be used in the event that the participant continues to participate in the study. For those found ineligible, the information collected during the phone screen will be kept with the permission of the participant for the duration of the study to ensure that participants are not phone screened on multiple occasions. After determining initial eligibility, research staff will provide a brief description of the research and the participant will present to the clinic for the screening procedure.

9.2 Informed Consent Procedures: The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential participants. Participants will be required to read the informed consent form and the investigator or her/his designee will additionally describe the risks and discomforts. The consent process may be completed remotely or in person. As part of the consenting process, one form of picture identification with date of birth will be copied and kept on file to verify the participant meets age inclusion requirements. Once all screening procedures have been collected, research staff as well as the principal investigator will review all relevant information and determine, based on the inclusion and exclusion criteria, if the participant will continue with the remaining study procedures.

To ensure that the study participant understands the study, the participant will be asked questions about the study procedures and the risks associated with participation. Participants will be asked to pass a study questionnaire to document their understanding of the study. This consent questionnaire is located in Appendix D. If any concern arises that the study participant did not fully understand the study, the principal investigator (PI) or her/his designee may decide that the participant is not suitable for participation. If the participant is still interested after all questions have been answered, the PI will ask the participant to sign the informed consent form. Any participant who appears incapable of providing informed consent will be excluded.

9.3 Contact/Informant: As a requirement for entry into this study, participants will need to identify an individual who is can serve as a contact and as a collateral source of information. Or two people could serve in these roles. A family member or a significant other/spouse is preferred. The participant will need to sign a hospital approved release of information to permit the study team to contact the individual. The contact/informant could be contacted to locate the participant during the study. The contact/informant will also be contacted to provide collateral

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

information that will be used to determine the participant's eligibility (Appendix F). Furthermore, the contact/informant may help corroborate information provided by the participant which in turn will enhance the reliability of the information, as described elsewhere (204).

9.4 Subject ID Number Assignment: A unique subject ID number will be assigned to each participant at the time that informed consent is obtained/explained, and this is the subject id number that will be used throughout the study. Subject ID numbers will be maintained by the Coordinating Center. Each subject ID number will be composed of the ID for the site where the participant was screened and then sequential numbering. The subject ID's for each site are as follows:

- *Columbia University:* CU### (i.e. CU001, CU002, CU003…)
- *John Hopkins University:* JH### (i.e. JH001, JH002, JH003...)
- *Medical University of South Carolina:* SC### (i.e. SC001, SC002, SC003...)
- *Yale University:* YU### (i.e. YU001, YU002, YU003...)

9.5 Screening: Participants will be evaluated at the study site to confirm that they meet the participant selection criteria for the study. The participant's identity obtained at screening will be verified with one form of picture identification. Screening will be spread across approximately 2 weeks (up to a maximum of 60 days) and will be divided into both remote and in-person screening sessions.

Upon completion of the phone screen, participants who seem to meet the general criteria of the study will be invited to complete the virtual portion of screening. Prior to the first virtual session, interested participants will be mailed a packet of information. This packet will include the following: a urine toxicology quick dip cup, urine pregnancy test for WOCBP, and an evening/morning sleep questionnaire. Participants who are unable to complete the informed consent electronically will also be mailed a blank consent form and supplement to consent questionnaire. Participants who do not have access to a computer will also be mailed the following self-report assessments: VAS Marijuana Ladder, Marijuana Problems Scale, and Pittsburg Sleep Quality Index.

9.5.1 Remote Screening Visits: The first portion of screening will be conducted remotely. In order to standardize the remote screening process, the virtual screening sessions will be broken into a minimum of two sessions over the course of one week (+/- 3 days) that are no longer than 2 hours each. Prior to beginning each remote visit, research staff will confirm that the study participant is in an area where they have privacy and will be undisturbed. During the virtual screening process, the following procedures will be completed:

1) Obtain written informed consent (must be completed first).
2) Have participant complete the Supplement to Consent questionnaire.
3) Collect demographics.

Safety:

4) Obtain complete medical and psychiatric history.
5) Obtain complete history of all prescription or nonprescription medications, dietary and herbal supplements within the past 6 months.
6) Administer the Structured Clinical Interview for DSM-5, RV
7) Administer the Columbia Suicide Severity Rating Scale (C-SSRS)
8) Have participant provide a urine sample for drug testing via a urine toxicology quick dip cup. Participant will be asked to hold the quick dip cup results up to the screen for research staff to visually assess the test results.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

9) Have WOCBP participants complete a pregnancy test. Participant will be asked to hold the test up to the screen so that research staff can visually see the test result.
10) An initial check-in visit will be completed with a licensed clinician (MD, RN, APRN, PA).

Cannabis and Other Drug Outcomes:

11) Obtain history of drug, alcohol, and tobacco use with the following assessments:
    i. Scale for Assessment of Lifetime Cannabis Use (SALCU) to capture first use, heaviest use, lifetime use, and past 30-day use.
    ii. Modified timeline follow-back approach to estimate last 30-day cannabis use.
    iii. Timeline follow-back approach to estimate last 30-day alcohol and tobacco use.
12) Have the participant complete the following assessments via an electronic survey. Of note, if the participant does not have access to a computer then these self-report assessments will be mailed to the participant prior to the virtual screening visit and the coordinating center should be notified.
    i. VAS Marijuana Ladder.
    ii. Marijuana Problems Scale.
    iii. Evening/Morning Sleep Questionnaire.
    iv. Pittsburgh Sleep Index.
13) Record the participant's desire to quit.
14) PRISM lifetime, last 12 months and last 30 days.
15) Motivational Interviewing, if the participant has access to a computer. If the participant does not have access to a computer then this will be completed during the face to face screening visit.

9.5.2 In Person Screening Visit: All participants who seem to be eligible for the study after completion of the virtual screening visits will be invited to come in for an in-person screening visit. During this visit, the following procedures will be completed in person:

Safety:

1) Obtain informant/contact information and have participant sign release of information to obtain permission to contact informant/contact.
2) Collect blood for hematology, clinical chemistry, LFTs, and DNA. Label and store blood sample for DNA extraction.
3) Collect urine to test for:
    i. Urinalysis (including creatinine)
    ii. Presence of drugs of abuse via urine toxicology quick dip cup
    iii. Quantitative analysis for cannabinoids (THC-COOH)
    iv. Urine pregnancy test for WOCBP
4) Alcohol breath test may be conducted at the discretion of the investigator.
5) Record vital signs (sitting blood pressure, heart rate and temperature).
6) Record height and weight.
7) Complete physical and neurological examination, as well as a check-in visit with a licensed clinician.
8) Record standard 12-lead electrocardiogram (ECG).

Cannabis and Other Drug Outcomes:

8) Modified timeline follow-back approach to estimate last week cannabis use (capture days since the date that the initial 30 day TLFB was conducted at virtual screening).
9) Nicotine dependence will be evaluated using the Fagerstrom Test for Nicotine Dependence.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

10) Timeline follow-back approach to estimate last 7-day alcohol and tobacco use.
11) VAS Marijuana Ladder.
12) Marijuana Problems Scale.
13) Marijuana Craving Scale.
14) Evening/Morning Sleep Questionnaire.
15) Pittsburg Sleep Quality Index.
16) Marijuana Withdrawal Checklist.
17) Desire to Quit.
18) VAS mood states.
19) Start actigraphy. A charged actigraph will placed around the wrist of the participant's non-dominant hand.
20) Motivational Interviewing, only if the participant was unable to complete this during the virtual screening sessions.
21) Quit date: During screening participants will counseled to attempt a quit date that will fall sometime within the first week of treatment (Quit Week). The participants will be asked to sign a commitment to quit document (Appendix G) that includes the following statement: "*I agree that I will attempt to quit using cannabis or cannabis based products during the first week of the treatment phase of the study, and if successful I could receive $50*."

In extenuating circumstances, or at the convenience of the research participant, the completion of some screening procedures may deviate from the above schedule and may be completed at the other screening visit or at an alternately scheduled time prior to randomization. However, the following screening procedures must be completed prior to all other screening procedures: obtain written informed consent (must be completed first), have participant complete the Supplement to Consent questionnaire, obtain informant/contact information and have participant sign release of information to obtain permission to contact informant/contact, and collect demographics information.

9.5.3 Motivational Interviewing: Participants will receive motivational interviewing by a trained rater during the screening period leading up to the quit date (does not need to be a licensed clinician). The motivational interviewing will be conducted via completion of the eCheckup To Go program, created by San Diego State University. The rater will facilitate the completion of this program with the participant and will then review the results generated by this program with the participant. All participants who have access to a computer will be asked to complete the motivational interviewing during the virtual screening session. Research staff will remain on the video call with the participant throughout the completion of the motivational interviewing to answer any questions that the participant may have. When the participant attends the in person screening visit they will be given a hard copy of their motivational interviewing results to the participant to take home. In the event that a participant is unable to complete the motivational interviewing remotely (i.e. if they don't have access to a computer), it may be completed during the in person screening session.

9.5.4 Setting a Quit Date: During screening participants will counseled to attempt a quit date to fall sometime within the first week of treatment, at least two days after taking the study medication (Quit Week). The participants will be asked to sign a commitment to quit document (Appendix G) that includes the following statement: "*I agree that I will attempt to quit using cannabis or cannabis based products during the first week of the treatment phase of the study, and if successful I could receive $50*."

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

9.5.5 Adherence (CAROMA training): Participants will be provided with a cellphone with the hardware, software and service necessary to transmit high quality video. Prior to randomization, the participant will be trained how to use the phone and also trained on the adherence protocol. For this, the participant will be placed in one clinic office with the phone. A research staff member will video call the participant from another location in the research clinic and observe the participant consuming one placebo capsule or M&M candy with a glass of water. All participants will need to have at least one successful training session prior to randomization. This cellphone will be used for completion of the CAROMA calls and for completion of the study procedures/visits that are conducted remotely. Participants will return the phone to research staff at the End of Study visit.

9.6 Treatment Phase Study Visits (Week 1 – Week 8):

9.6.1 Week #1 (Quit week): At the week 1 visit, prior to randomization, the inclusion and exclusion criteria should be re-reviewed. Confirm with the participant that they will make an attempt to quit using marijuana, and their previously agreed upon quit date. Please note, the quit date should be at least two days after the subject has started taking the study medication. Therefore, the quit date will fall between day 3 and day 7.

9.6.2 In-Person Treatment Phase Study Visits (Week 1, Week 3, Week 5, and Week 7 Visits) Procedures: During the treatment phase of the study, Week 1, Week 3, Week 5, and Week 7 study visits will be conducted both in-person and remotely. It is preferable that the remote portion of these study visits are completed prior to the in-person portion of the visit, and that both portions of the visit are completed on the same day (+/- 1). At these visits, the following study procedures will be completed (***1.5 Schedule of Procedures:***

Remote Portion of Visit: Safety Procedures:

1) Review of medical and psychiatric history, including a review of all prescription or nonprescription medications, dietary and herbal supplements the participant is taking.
2) Administer the Columbia Suicide Severity Rating Scale (C-SSRS).

Remote Portion of Visit: Cannabis and Other Drug Outcomes:

3) 7-Day Timeline Follow Back Approach for Nicotine/Tobacco.
4) 7-Day Timeline Follow Back Approach for Alcohol.
5) 7-Day Modified Timeline Follow Back Approach for Cannabis: to verify the information on the participant's marijuana use that has been previously captured during the daily CAROMA calls, including the assigned dollar value.
6) The participant's desire to quit will be captured.
7) PRISM (Week 5 only)

Self-Report Assessments for Remote Portion of Visit: Participants will be instructed to complete each of the below questionnaires via an electronic survey (using the REDCap platform). These questionnaires are to be completed while the participant is on their virtual call with research staff to ensure that the questionnaires are being completed on the day of the study visit and that research staff is available to answer any questions and confirm that all questions have been answered. In the event that the participant does not have access to a computer and it is not feasible to complete these assessments electronically, a packet of blank questionnaires will be given to the participant at the end of each in-person study visit, that they will then complete during the remote portion of the next in-person visit. The participant will then return these completed assessments to research staff at their next in-

person visit. The coordinating center should be notified if these self-report assessments cannot be completed electronically.

8) Marijuana Problems Scale (administered at Week 1 only).
9) Marijuana Withdrawal Checklist.
10) Marijuana Craving Scale.
11) Fagerstrom Test of Nicotine Dependence (administered at Week 1 only).
12) VAS Marijuana Ladder.
13) Pittsburg Sleep Quality Index
14) Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Week 1 only)

In-Person Safety Visit Procedures:

1) Record vital signs (sitting blood pressure, heart rate and temperature) and weight.
2) Alcohol breath test may be done at the discretion of the investigator based on clinical suspicion.
3) Obtain blood and urine samples (hematology, clinical chemistry, LFTs) and urine samples (urinalysis) for safety laboratory tests (Week 1, Week 5, and Week 7 only).
4) Obtain urine sample for on site drug testing via a urine toxicology quick dip cup and for quantitative urine toxicology.
5) Blood drawn for PF-04457845 assay and serum endocannabinoid levels at the week 1 and week 5 visits only.
6) Collect urine for on-site urine drug testing and quantitative urine toxicology.
7) Administer urine pregnancy test for WOCBP
8) Ask participant about any adverse events. May be initially assessed remotely if the remote portion of the study visit occurs prior to the in-person portion of the study visit.
9) Pill counts will be performed for all medication dispensed since the last in-person study visit (2 weeks of medication).
10) Medication will be dispensed for the following two weeks (so the participant will have enough study medication until their next in-person study visit).
11) A check-in visit will be completed with a licensed clinician (MD, RN, APRN, PA). The Week 1 and Week 3 check-in visit should be completed in-person. Of note, the MD check-in visits must be completed last so that the MD has all of the necessary information to evaluate the participant.

In-Person Miscellaneous Outcomes:

12) Download actigraphy data, charge actigraph, and return to participant.
13) CogState Battery (Week 1 only).
14) VAS Mood States
15) Evening Morning Sleep Questionnaire

Of note, prior to the participant leaving each in-person visit research staff will provide them with a quick dip urine toxicology cup to complete during the following week's remote visit and a pregnancy test for WOCBP to complete during the next week's remote visit. They will also be provided with a hard copy of the VAS Mood States and Evening Morning Sleep Questionnaires. In the event that the participant does not have access to a computer, they will also be provided with a packet of the blank self-report assessments to be completed during the following week's remote visit.

9.6.3 Remote Treatment Phase Study Visits (Week 2, Week, 4, Week 6, and Week 8) Procedures: The Week 2, Week 4, Week 6, and Week 8 study visits will be conducted remotely, utilizing the same method as the daily CAROMA calls (video call using the clinic provided cell phone). Prior to beginning each remote visit, research staff will confirm that study participant is

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

in an area where they have privacy and will be undisturbed. During each remote study visit, the following procedures will be completed (***1.5 Schedule of Procedures:***

Safety:

1) Review of medical and psychiatric history, including a review of all prescription or nonprescription medications, dietary and herbal supplements the participant is taking. Research staff will review this information with the participant, and will relay the updated information to the licensed clinician prior to the remote MD check-in visit.
2) Urine pregnancy test for WOCBP. At each in-person study visit, all WOCBP participants will be given a pregnancy test to take home for the following week's remote visit. During the remote visit, participants will be asked to put the phone down, take the pregnancy test, and then hold the pregnancy test up to the screen, so that research staff can visually see the results of the test.
3) Urine drug testing via the quick dip urine toxicology cup. At each in-person study visit, all participants will be given a quick dip urine toxicology cup to take home for the following week's remote visit. During the remote visit, participants will be asked to put the phone down, give a urine sample into the test cup, and then hold the test cup up to the screen, so that research staff can visually see the results of the urine toxicology quick dip.
4) Administer the Columbia Suicide Severity Rating Scale (C-SSRS). Any information obtained by research staff should be relayed to the licensed clinician prior to the remote MD check in visit.
5) Ask participant about any adverse events. Any information obtained by research staff should be relayed to the licensed clinician prior to the remote MD check in visit.
6) A check-in visit will be completed with a licensed clinician (MD, RN, APRN, PA), remotely. Research staff will assist in the coordination of this visit by arranging a time on the day of the remote study visit for the licensed clinician and research participant to have a video call.

Cannabis and other Drug Outcomes:

7) 7-Day Timeline Follow Back Approach for Nicotine/Tobacco.
8) 7-Day Timeline Follow Back Approach for Alcohol.
9) 7-Day Modified Timeline Follow Back Approach for Cannabis: to verify the information on the participant's marijuana use that has been previously captured during the daily CAROMA calls, including the assigned dollar value.
10) The participant's desire to quit will be captured.
11) Participants will be asked to confirm that they have received their study medication for the following week. A virtual pill count will be performed by the participant opening the current week's study medication bottle, pouring the remaining medication into their hand, and holding their phone up to their hand so that research staff can visually see how much study medication remains.

Self-Report Assessments: Participants will be instructed to complete each of the below questionnaires via an electronic survey (using the REDCap platform). These questionnaires are to be completed while the participant is on their video call with research staff to ensure that the questionnaires are being completed on the day of the study visit and that research staff is available to answer any questions and confirm that all questions have been answered. In the event that the participant does not have access to a computer and it is not feasible to complete these assessments electronically, a packet of blank questionnaires will be given to the participant at the end of each in-person study visit, that they will then complete during the remote portion of the next in-person visit. The participant will then return these completed

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

assessments to research staff at their next in-person visit. The coordinating center should be notified if these self-report assessments cannot be completed electronically.

12) Marijuana Withdrawal Checklist.
13) Marijuana Craving Scale.
14) Fagerstrom Test of Nicotine Dependence (week 4, and week 8 visits only).
15) VAS Mood States (paper copy of questionnaire provided to participant to complete).
16) VAS Marijuana Ladder.
17) Evening Morning Sleep Questionnaire (paper copy of questionnaire provided to participant to complete).
18) Pittsburg Sleep Quality Index

Should there be any perceived safety concerns, the participant may be asked to come into the clinic during the week of the remote study visit. For example, if unscheduled clinical labs need to be obtained as a result of a previous abnormal value, the participant will be asked to come into the clinical to complete only the blood draw, and all other procedures will be completed remotely.

9.6.4 Adherence to Study Medication: Approximately every morning, within a time period predetermined by agreement, participants will be called on the cell phone and will be observed removing study medication from the packaging and swallowing the medication with water or juice. The research assistant will log visual confirmation of adherence. A brief time line follow back assessment of cannabis and other drug use will be conducted. The entire process takes less than 5 minutes to complete.

9.6.5 Contingency Management: Participants will be asked about their use of cannabis or cannabinoid products daily on the CAROMA call. A successful “quit” attempt is defined as 1) an intentional (not lack of availability), 2) reduction (by 50% or more) in 3) the # of occasions of cannabis use in a day, 4) lasting a day (24 hours) or more, 5) compared to the average daily # of occasions of cannabis use captured by the last week screening TLFB for cannabis. Participants who have a successful quit attempt before the week 2 study visit will be eligible to receive $50.

9.7 Follow-Up Phase Study Visits (Week 9 – Week 12): Upon completion of the 8-week treatment phase, participants will complete weekly follow up visits for four weeks primarily for safety purposes given that the effects of the study medication may take up to two weeks to wash out.

9.7.1 Week 9 In-Person Study Visit: The week 9 visit will serve as the end of treatment visit. This is an in-person study visit. The following procedures will be completed at this visit:

Remote Portion of Visit: Safety Procedures:

1) Review of medical and psychiatric history, including a review of all prescription or nonprescription medications, dietary and herbal supplements the participant is taking.
2) Administer the Columbia Suicide Severity Rating Scale (C-SSRS).

Remote Portion of Visit: Cannabis and Other Drug Outcomes:

3) 7-Day Timeline Follow Back Approach for Nicotine/Tobacco.
4) 7-Day Timeline Follow Back Approach for Alcohol.
5) 7-Day Modified Timeline Follow Back Approach for Cannabis: to verify the information on the participant’s marijuana use that has been previously captured during the daily CAROMA calls, including the assigned dollar value.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

6) The participant's desire to quit will be captured.
7) PRISM

Self-Report Assessments for Remote Portion of Visit: Participants will be instructed to complete each of the below questionnaires via an electronic survey (using the REDCap platform). These questionnaires are to be completed while the participant is on their virtual call with research staff to ensure that the questionnaires are being completed on the day of the study visit and that research staff is available to answer any questions and confirm that all questions have been answered. In the event that the participant does not have access to a computer and it is not feasible to complete these assessments electronically, a packet of blank questionnaires will be given to the participant at the end of each in-person study visit, that they will then complete during the remote portion of the next in-person visit. The participant will then return these completed assessments to research staff at their next in-person visit. The coordinating center should be notified if these self-report assessments cannot be completed electronically.

8) Marijuana Problems Scale.
9) Marijuana Withdrawal Checklist.
10) Marijuana Craving Scale.
11) VAS Marijuana Ladder.
12) Pittsburg Sleep Quality Index
13) Quality of Life Enjoyment and Satisfaction Questionnaire Short Form

In-Person Safety Visit Procedures:

1) Complete physical and neurological examination (this counts for check in with licensed clinician).
2) Record vital signs (sitting blood pressure, heart rate and temperature).
3) Alcohol breath test may be done at the discretion of the investigator based on clinical suspicion.
4) Record height and weight.
5) Obtain blood (hematology, clinical chemistry, LFTs) and urine samples (urinalysis) for safety laboratory tests.
6) Obtain urine sample for on site drug testing via a urine toxicology quick dip cup and for quantitative urine toxicology.
7) Blood drawn for PF-04457845 assay and serum endocannabinoid levels.
8) Administer urine pregnancy test for WOCBP
9) Record standard 12-lead electrocardiogram (ECG).
10) Ask participant about any adverse events. May be initially assessed remotely if the remote portion of the study visit occurs prior to the in-person portion of the study visit.
11) Pill counts will be performed for all medication dispensed since the last in-person study visit (2 weeks of medication).

In-Person Miscellaneous Outcomes:

12) Download actigraphy data, charge actigraph, and return to participant.
13) CogState Battery.
14) VAS Mood States
15) Evening Morning Sleep Questionnaire

9.7.2 Week 10 – Week 12 Remote Study Visits: At the Week 10, Week 11, and Week 12 follow up visits, safety data will be collected on the participant remotely. The following procedures will be completed for each participant:

1) A check-in visit will be completed with a licensed clinician (MD, RN, APRN, PA). Research staff will assist in the coordination of this visit by arranging a time on the day of the remote study visit for the licensed clinician and research participant to have a video call.
2) Review of medical and psychiatric history, including a review of all prescription or nonprescription medications, dietary and herbal supplements the participant is taking. Research staff will review this information with the participant, and will relay the updated information to the licensed clinician prior to the remote MD check-in visit.
3) Urine pregnancy test for WOCBP. At the Week 9 in-person study visit, all WOCBP participants will be provided with urine pregnancy tests to be completed remotely during the Week 10, Week 11, and Week 12 virtual study visits. During the remote visit, participants will be asked complete the pregnancy test and then hold the test up to the screen, so that research staff can visually see the results of the test.
4) Ask participant about any adverse events.
5) Administer the Columbia Suicide Severity Rating Scale (C-SSRS).
6) 7-Day Timeline Follow Back data will be collected for cannabis, alcohol, and nicotine/tobacco.
7) Marijuana Problems Scale (Week 11 only). Participants will be instructed to complete this assessment via an electronic survey (using the REDCap platform). This self-report assessment will be completed while the participant is on their virtual call with research staff. In the event that the participant does not have access to a computer or it is not feasible to complete electronically, a paper assessment will be given to the participant at the Week 9 visit which will then be returned at the End of Study Visit.

9.7.3 End of Study In-Person Visit: At the end of week 12 (~day 85), a visit will be conducted that will mark the end of the study. This visit will be completed both in-person and remotely. It is preferable that the remote portion of these study visits are completed prior to the in-person portion of the visit, and that both are completed on the same day (+/- 1).The following procedures will be completed at this visit.

Remote Portion of Visit: Safety Procedures:

1) Review of medical and psychiatric history, including a review of all prescription or nonprescription medications, dietary and herbal supplements the participant is taking.
2) Administer the Columbia Suicide Severity Rating Scale (C-SSRS).

Remote Portion of Visit: Cannabis and Other Drug Outcomes:

3) 7-Day Timeline Follow Back Approach for Nicotine/Tobacco.
4) 7-Day Timeline Follow Back Approach for Alcohol.
5) 7-Day Modified Timeline Follow Back Approach for Cannabis: to verify the information on the participant's marijuana use that has been previously captured during the daily CAROMA calls, including the assigned dollar value.
6) The participant's desire to quit will be captured.

Self-Report Assessments for Remote Portion of Visit: Participants will be instructed to complete each of the below questionnaires via an electronic survey (using the REDCap platform). These questionnaires are to be completed while the participant is on their virtual call with research staff to ensure that the questionnaires are being completed on the day of the study visit and that research staff is available to answer any questions and confirm that all questions have been answered. In the event that the participant does not have access to a computer and it is not feasible to complete these assessments electronically, a packet of blank questionnaires will be given to the participant at the end of each in-person study visit,

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

that they will then complete during the remote portion of the next in-person visit. The participant will then return these completed assessments to research staff at their next in-person visit. The coordinating center should be notified if these self-report assessments cannot be completed electronically.

7) Marijuana Problems Scale.
8) Marijuana Withdrawal Checklist.
9) Marijuana Craving Scale.
10) VAS Marijuana Ladder.
11) Pittsburg Sleep Quality Index

In-Person Safety Visit Procedures:

16) A check-in visit will be completed with a licensed clinician (MD, RN, APRN, PA).
17) Record vital signs (sitting blood pressure, heart rate and temperature).
18) Alcohol breath test may be done at the discretion of the investigator based on clinical suspicion.
19) Record height and weight.
20) Obtain blood (hematology, clinical chemistry, LFTs) and urine samples (urinalysis) for safety laboratory tests.
21) Obtain urine sample for on site drug testing via a urine toxicology quick dip cup and for quantitative urine toxicology.
22) Blood drawn for PF-04457845 assay and serum endocannabinoid levels.
23) Administer urine pregnancy test for WOCBP
24) Ask participant about any adverse events. May be initially assessed remotely if the remote portion of the study visit occurs prior to the in-person portion of the study visit.

In-Person Miscellaneous Outcomes:

25) Download actigraphy data.
26) VAS Mood States
27) Evening Morning Sleep Questionnaire

***9.8 Participant Reimbursement*:** All participants will be compensated for their participation in various study procedures. Please refer to **Table 12** for the full breakdown of participant payment. In addition, participants will receive escalating payments contingent on attending their appointments and completing study related procedures. Participants will be repeatedly told before the study and reminded once enrolled in the study that the contingency management payments are not linked to abstinence from cannabis. Participants will be compensated for the remote study visits at the next subsequent in-person visit.

Table 12: *Participant Payments*

STUDY VISITS	REGULAR PAYMENTS	ADHERENCE PAYMENTS	TOTAL
Screening	$50	$0	$50
Week 1	$40	$0	$40
Successful quit attempt	$50	$0	$50
Week 2	$20	$20	$40
Week 3	$25	$25	$50
Week 4	$30	$35	$65
Week 5	$35	$50	$85
Week 6	$40	$70	$110

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

Week 7	$45	$95	$140
Week 8	$50	$125	$175
Week 9	$55	$160	$215
Week 10	$60	$0	$60
Week 11	$65	$0	$65
Week 12	$70	$0	$70
End of study	$75	$0	$75
Payment for returning phone	$50	$0	$50
Total	$760	$580	**$1,340**

9.*9* ***Early Termination Study Visit:*** If a participant decides to withdraw from the study after randomization or is terminated by the site principal investigator for any reason after randomization, an early termination study visit will be conducted to close out the participant from the study. At this visit the participant will be instructed to return all unused study medication. The Week 9 procedures will be attempted at an early termination visit, which will be conducted per Section 9.7.1, both in person and remotely.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

10.0 ASSESSMENTS:

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. When a protocol-required test cannot be performed, study staff will be instructed to document the reason for the missed test and any corrective and preventative actions which s/he has taken to ensure that required processes are adhered to as soon as possible. Any protocol deviations should be documented in the study log.

10.1 Blood: Total blood sampling volume for the individual participants is approximately 420 mL over approximately 14 weeks of the study. The actual times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by the Coordinating Center, provided the total volume taken during the study does not exceed 450 mL (safety, PF-04457845 levels, endocannabinoid levels).

10.2 Safety:

10.2.1 Laboratory Tests: The following safety laboratory tests will be performed at the following study visits: Screening, Week 1, Week, 5, Week 7, Week 9, and End of Study Visit (end of Week 12). They are conducted periodically throughout the duration of the study to monitor electrolyte and liver/kidney function. Additional laboratory results may be generated on the samples (without additional blood volume drawn) as a result of the method of analysis, the type of analyzers used, or as derived or calculated values; if such results are available, they may also be reported. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Hematology: Hemoglobin, Hematocrit, RBC Count, MCV, MCHC, RDW, MCH, MPV, Platelet Count, WBC Count, Total Neutrophils (Abs), Eosinophils (Abs), Monocytes (Abs), Basophils (Abs), Lymphocytes (Abs); Collected using one 10cc Lavender-top Tube (tube contains EDTA as an anticoagulant).

Chemistry: BUN and Creatinine, BUN/Creatinine Ratio, Glucose, Calcium, Sodium, Potassium, Chloride, Total CO2, AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, Urine acid, Albumin, Total protein, HDL, LDL, Cholesterol; Collected using one 10 cc Tiger-top Tube (tube does not contain an anticoagulant but does contain a clot activator and serum separator gel).

Urinalysis: Color, Appearance, Specific Gravity, pH, Glucose, Protein, Blood, Ketones, Nitrites, Leukocyte esterase, Bilirubin, Urobilinogen, Bacteria, Casts, Crystals, Yeast, Amorphous Sediment, Epithelial Cells, WBC, RBC; Collected using one 10cc urinalysis preservative tube (tube includes a preservative of chlorhexidine, ethylparaben, and sodium propionate).

On-Site Urine Drug Testing: At every study visit, participants will be tested using a urine drug quick dip. A 12-panel all-in-one drug test cup with a built-in temperature strip (CLIA waived) should be used for these quick dip urine drug tests. The minimum requirement for drug testing includes:

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

1. Amphetamines (Detection Period: 1-2 days; Cutoff Level: 1000 ng/mL)
2. Barbiturates (Detection Period: 1-4 days; Cutoff Level: 200 ng/mL)
3. Buprenorphine (Detection Period: 1-3 days; Cutoff Level: 10 ng/mL)
4. Benzodiazepines (Detection Period: 1-2 days; Cutoff Level: 200 ng/mL)
5. Cocaine (Detection Period: 2-4 days; Cutoff Level: 300 ng/mL)
6. THC-COOH (Detection Period: up to 5+ days; Cutoff Level: 50 ng/mL)
7. Methamphetamines (Detection Period: 2-4 days; Cutoff Level: 500 ng/mL)
8. Methylenedioxymethamphetamine (Detection Period: 2-4 days; Cutoff Level: 1000 ng/mL)
9. Methadone (Detection Period: 1-3 days; Cutoff Level: 300 ng/mL)
10. Opiates (Detection Period: 2-3 days; Cutoff Level: 300 ng/mL)
11. Oxycodone (Detection Period: 1-3 days; Cutoff Level: 100 ng/mL)
12. Phencyclidine (Detection Period: 7-14 days; Cutoff Level: 25 ng/mL)

If during the in-person visits a sample tests positive for any drug (other than THC) on site, a sample will be sent to the laboratory for confirmation.
Participants may undergo random urine drug testing at the discretion of the investigator. Spot urine drug testing conducted prior to dosing must be positive for cannabinoids for participants to receive study medication.

On Site Urine and Serum Pregnancy Test: Urine HCG testing should first be performed using a urine pregnancy spot kit. If the result yields a positive result, then a serum HCG test will be sent out for confirmation. If the result yields a positive result during one of the remote study visits the participant will be asked to come in to the clinic to provide a blood sample and study medication will be suspended. For the serum HCG test, a blood serum sample will be collected using one 10 cc Tiger-top Tube (tube does not contain an anticoagulant but does contain a clot activator and serum separator gel).

Quantitative Urine Cannabinoids Toxicology: Urine samples will be collected at each of the in-person visits as specified in the Schedule of Procedures (***1.5 Schedule of Procedures: Table 2***). At each in-person visit, a urine sample will be obtained from the participant, pipetted into one 1.5 mL cryovial tube (urine sample should be filled up to the top line of the tube), and will be stored in a -80 degree Celsius freezer until the sample is ready for shipment. Samples will be shipped in batches, on dry ice, directly to the lab of Dr. Tom Cooper at the Nathan Kline Institute: 140 Old Orangeburg Road Orangeburg, NY 10962. The Coordinating Center will instruct each individual site on when to ship these samples to Dr. Cooper, at intervals of approximately 6 months. Levels of THC-COOH the principal inactive metabolite of cannabis will be assayed by the lab of Tom Cooper at the Nathan Kline Institute in 6 month batches using a GCMS method (205). Assays have intra- and inter-assay RSD% of 10% at 1 ng/ml with 0.5 ng/ml as the lower limit of detection. Creatinine corrected THC-COOH levels will be reported.

10.2.2 Vital Signs: Blood pressure, pulse rate, oral temperature, height and body weight will be measured periodically and recorded, as specified in ***1.5 Schedule of Procedures: Table 2***, the Study Procedures Table. Sitting blood pressure will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after at least 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring BP

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

A participant should have weight and height measured while wearing indoor clothing and with shoes off. The standard for collecting height is inches without decimal places and for weight it is pounds with one decimal place. BMI will be calculated for each participant through the Table listed in Appendix I.

10.2.3 Physical Examinations: Completed physical and neurological examinations will be conducted at screening and at the end of the treatment phase or early termination visit. Physical examinations will be conducted by a physician, trained physician assistant, or nurse practitioner, as designated by the site principal investigator.

10.2.4 Electrocardiogram (ECG): ECGs should be collected after the participant has rested quietly for at least 10 minutes in a supine position. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure, and pulse rate.

A standard 12-lead ECG will be recorded. A qualified individual appointed by the site investigator will make comparisons to baseline measurements. If interpreted as abnormal, the local investigator will assess the findings as either abnormal clinically significant, or abnormal not clinically significant. The interpretation of the ECG will be recorded in the source documents. ECG traces recorded on thermal paper will be photocopied to avoid degradation of the trace over time.

10.3 Pharmacokinetics:

10.3.1 PF-04457845 Levels: Blood will be sampled for PF-04457845 levels as specified in the Schedule of Procedures (***1.5 Schedule of Procedures:*** ***Table 2***). Given that adherence will be confirmed visually, the PF-04457845 levels will be assayed in only a random sampling of approximately 1/3 of participants from each site to confirm adherence, as specified by the Coordinating Center. Assays will be conducted by laboratory of Alex Makriyannis at Northeastern University using a proprietary assay with existing permission from SpringWorks and Jazz Pharmaceuticals. The serum sample to be analyzed for PF-04457845 levels should be collected in one 4 cc lavender top tube (tube containing K2-EDTA). Blood samples should be collected as close to approximately 1 hour after the participant has taken their daily dose of study medication (PF-04457845/placebo). The time at which the blood sample has been drawn at should be documented, along with the time that the study medication was taken that day. The sample should then be centrifuged at approximately 1700g for about 10 minutes at 4 degrees Celsius, pipetted into appropriately labeled 1.5 mL screw capped polypropylene tubes (1 mL of serum sample per tube; 2 polypropylene tubes), and then stored in a -80 degree Celsius freezer within 1 hour of collection. Samples will be stored on site until they are to be sent directly to WuXi by each site, at the end of the study.

Shipment of Pharmacokinetic Samples*:* Each site will store blood samples to be assayed for PF-04457845 levels on site in a -80 degree Celsius freezer. Samples will be stored on site, and will be shipped on dry ice directly to the lab of Dr. Makriyannis at Northeastern University, in batches of at least 50 samples. The Coordinating Center will instruct each individual site on which random sampling of participants should be shipped.

10.3.2 Plasma Anandamide Levels: Blood will be sampled for plasma anandamide and other

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

endocannabinoid levels as specified in the Schedule of Procedures (***1.5 Schedule of Procedures:***

Shipment of Plasma Anandamide Samples*:* Each site will store blood samples to be assayed for anandamide levels on site at -80 degree Celsius. Samples will be shipped on dry ice directly to the lab of Dr. Makriyannis at Northeastern University, approximately every 6 months.

10.3.3 DNA: A single nucleotide polymorphism (SNP) in the gene encoding for FAAH - C385A variance was reported to be significantly associated with changes in withdrawal after abstinence, and happiness after smoking cannabis (206-208). Recently, 3 specific CUD risk alleles were reported for the first time in a Yale-led study by Gelernter et al., 216 (209). These included rs143244591 in novel antisense transcript RP11-206M11.7; rs146091982 in the solute carrier family 35 member G1 gene (SLC35G1); and rs77378271 in the CUB and Sushi multiple domains 1 gene (CSMD1). These and other genes will be studied in an exploratory manner to examine for genetic moderators of response to PF-04457845. DNA will be sent to the laboratory of Dr. Gelernter at Yale.

One 10cc PAXgene Blood DNA tube (sterile vacutainer plastic tube with hemogard closure and K3 EDTA additive) should be collected for DNA analysis for all participants at the screening visit and appropriately labeled. Each sample should be frozen first at -20 degrees Celsius for 24 hours, and then transferred to a -80 degree Celsius freezer, in the original 10cc tube that it was collected in.

DNA will be extracted from whole blood samples using the salting out method implemented in the PaxGene (PreAnalytix Inc.) DNA extraction systems. DNA samples are aliquoted into 96 PCR plates at a concentration of 10ng/µl. These working PCR plates are stored at -20ºC until their use for genotyping. Stock DNA samples are stored at -80ºC. The PCR reactions are prepared either manually or using the TECAN GENESIS pipetting robots. To minimize possibility for cross contamination, one TECAN robot is dedicated to pre-PCR and another to post-PCR use. PCR will be conducted using MJR PTC-200 (96 or 384 wells), MJR PTC-225 Tetrad (4x384 wells) or ABI GeneAmp 9700 cyclers (384 wells). We will use the TaqMan method for SNP genotyping, which is in routine use in this laboratory. In the TaqMan method, a primer is allowed to hybridize on top of the SNP site. In the presence of a mismatch between the primer and the variant base, the affinity of the primer to the template is less than in the case of a perfect match. PCR primers hybridized adjacent to the SNP site are then allowed to be elongated. In the presence of a mismatch, the hybridization primer is displaced. If the hybridization primer is not displaced, it emits fluorescence, which is detected by the PCR machine. SNP assays will be ordered from Applied Biosystems Inc.,s (ABI) Assay-on-Demand collection or they will be custom designed and ordered from ABI,s Assay-by-Design service. An ABI 7900 HT real time PCR machine, located at the Yale-VA Laboratory of Psychiatric Genetics, will be used to analyze TaqMan SNP assays. Variants of the cannabinoid receptor gene and other relevant genes will be studied.

Shipment of DNA Samples*:* Each site will store samples at -80 degrees Celsius. Samples will be sent in large batches (every 6 months) directly to the laboratory of Dr. Joel Gelernter at Yale University.

10.4 Demographics, Medical History, and Medication History Procedure: At the screening visits, extensive demographic information will be collected including date of birth or age, sex, ethnicity, race as described by the participant, smoking status, reproductive status, alcohol consumption, and caffeine consumption of the participant.

10.4.1 Documentation of Concomitant Medication: Concomitant medication is any drug given in

addition to the study drug. These may be prescribed by a physician or obtained by the participant over the counter. Concomitant medication is not provided by the Coordinating Center. At each study visit, participants will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medications including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the source documents. Permitted concomitant medications will be left to the direction of the site principal investigator. When in doubt the site investigator should contact the overall medical monitor or the study principal investigator to discuss.

10.4.2 Documentation of Concurrent Medical Conditions: Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening, according the judgment of the investigator. The condition (i.e., diagnosis) should be described.

Participants with stable, chronic, nonemergent, well-controlled conditions may be permitted to participate at the discretion of the site investigator. Conditions that will be excluded: 1) serious or acute conditions e.g., appendicitis, 2) conditions that require frequent and significant medical interventions e.g., sickle cell crisis, 3) conditions that interfere with the primary outcome of interest e.g., alcohol or nicotine withdrawal, intoxication or dependence, etc. When in doubt the site investigator should contact the overall medical monitor or the PI to discuss.

10.4.3 Documentation of Concurrent Psychiatric Conditions: Concurrent psychiatric conditions are those significant ongoing psychiatric conditions that are present at the signing of informed consent. Any concurrent psychiatric conditions should be well documented at screening. Participants with stable, chronic, nonemergent, well-controlled psychiatric conditions may be permitted to participate at the discretion of the site investigator e.g., anxiety disorder. Conditions that will be excluded: serious, acute conditions e.g., acutely suicidality, or conditions that require frequent and significant medical interventions e.g., bipolar disorders, conditions that interfere with the primary outcome of interest e.g., alcohol or nicotine withdrawal, intoxication or dependence, etc. When in doubt the site investigator should contact the overall medical monitor or the PI to discuss.

Disallowed psychiatric problems include: a) Schizophrenia Spectrum and other Psychotic disorder in lifetime (current or past), b) Bipolar or related disorder in lifetime (current or past), and c) current Major Depressive Disorder.

10.5 Structured Clinical Interview for DSM-5: to diagnose any significant psychiatric disorders (210).

10.6 Psychiatric Research Interview for Substance and Mental Disorders (PRISM): is a semi-structured diagnostic interview designed to deal with the problems of psychiatric diagnosis when participants drink heavily or use drugs. This interview will help differentiate between primary disorders, substance-induced disorders, and the effects of intoxication and withdrawal.

For training and quality control purposes, the PRISM interviews will be audio recorded. The interviewees' Subject ID number and the study visit week that the interview is being conducted at will be stated at the beginning of the recording. The participants name will not be included in the recording. Participants will be asked at screening if they are willing to consent to the audio recording being conducted. If the participant does not consent to this, the PRISM interview will still be conducted, but will not be audio recorded. The audio recordings will be transferred to Dr. Hasin at Columbia University for training and quality control purposes via each site's IRB approved method of data transfer.

***10.7 Fagerstrom Test for Nicotine Dependence (FTND)*:** will be used to estimate nicotine dependence (211).

10.8 Scale for Assessment of Lifetime Cannabis Use (SALCU): this scale developed and being refined at our laboratory that examines estimates first use, heaviest use, lifetime use, frequency, amount, type and preferred method. Cannabis use is estimated with by assigned $ value and weight with the help of a prop (see adjacent figure) that displays both joints of increasing sizes and the increasing amounts of oregano (as a proxy of cannabis) that have been carefully weighed. The prop (**Figure 16**) helps participant more accurately estimate the amount of and frequency of cannabis used.

***10.9 Timeline Follow-Back (TLFB)*:** This approach will be used to estimate cannabis use (212) at baseline, and periodically throughout the study. Some TLFB data will be captured in face-to-face visits, while some will be captured during the CAROMA calls. Last 30 day, last week and last day use will be captured at different times. Frequency, quantity, and assigned-dollar value will be captured. The # of exposures within the defined time period i.e., week will be summed is the outcome of interest. Only for cannabis, a prop (**Figure 16**) will be used to facilitate accurate estimation of amount used. The same approach will be used to assess alcohol and tobacco use.

Figure 16: *Prop to Estimate Cannabis Use*

10.10 Marijuana Withdrawal Checklist: A withdrawal discomfort score (summary score) will be computed by summing the 10 most frequently reported items of the Marijuana Withdrawal Checklist (213) reported in previous studies will be used to track withdrawal symptoms. Each item of the marijuana withdrawal checklist is rated on a 4-point scale (none, mild, moderate, severe).

10.11 Marijuana Craving Questionnaire-Short Form (MCQ-12): consists of 12 statements about the respondent's feelings and thoughts about smoking cannabis as he/she is completing the questionnaire (i.e., right now) (214, 215).

10.12 Marijuana Contemplation Ladder: Participants are asked to rate where they are re:changing their use of marijuana (216) with a score of 1 ("*I enjoy using marijuana and have decided I'll never change it. I have no interest in changing the way I use marijuana*") to a score of 10 ("*I have changed my marijuana use and will never go back to the way I used marijuana before*").

10.13 Desire to Quit: Participants will be asked to rate their desire to quit using marijuana. *Please rate how interested you are right now to quit or reduce your use of cannabis or cannabinoid products.* Participants will be asked to respond to that question by selecting one of the following responses: 0 = I'm not really interested; 1 = I'm somewhat interested; 2 = I'm seriously interested.

10.14 Visual Analog Scale for Mood States: Participants will be asked to rate 12 feeling states including "anxious", "depressed", "irritable", "tired", "hungry", and "energetic" by scoring

the perceived intensity of these feeling states at that moment on a 100mm line (0= not at all, 100=extremely). This is a simple, quick and replicable method to capture information about mood states. Additionally, the Marijuana Ladder (216), a visual analog measure, will be used to assess a cannabis user's stage of change.

***10.15 <u>Systematic Assessment for Treatment Emergent Events (SAFTEE)</u>*:** (217-219) Safety and adverse events will be captured using the SAFTEE's general and specific inquiry forms, which take ~ 20 minutes to administer.

10.16 <u>24-Hour Actigraphy:</u> Throughout the study, participants will wear a wrist actigraph [wgt3x-bt Monitor (Actigraphcorp®)] with technology that has been developed for sleep-wake assessment and allows access to raw accelerometer data (Figure 17) (http://actigraphcorp.com/actigraph-wgt3x-bt/). Wrist actigraphy has been validated and used successful in healthy, clinical, and substance-using populations (220-224). The wrist actigraph is a comfortable wristwatch-like device that measures arm accelerations and hence is a proxy for activity. Ambient light is also measured to assist in determining sleep onset/wake times. It is tamper-proof and water-resistant, and will be worn ~24-hrs/day during the course of the study (removed only for swimming, bathing, and other fully submerged activities) on the participant's non-dominant wrist. The wgt3x-bt is well-suited for a clinical trial, as it maintains 25 straight days of battery life before the need to recharge, and it can collect and store 180 total days of data before the need to upload. The use of the actigraph will begin during the baseline/lead-in period so that participants become accustomed to wearing it, using it as directed, and to collect baseline sleep/activity data. 24-Hour actigraphy will be used to assess sleep-wake, activity levels, and circadian phase during the lead-in and treatment phase, where it will be compared to self-reported data. The actigraphy outcome measures will include *sleep latency, total sleep time, wake after sleep onset, sleep efficiency,* and *ambient light*. Analysis of sleep-related actigraphy data will performed with ActiLife+Sleep feature package (Figure 18), which is ActiGraph's premier actigraphy data analysis software platform (http://actigraphcorp.com/actilife/). The software is fully customizable, and raw data can be exported for analysis via 3rd party software platforms if required.

Figure 17: Wrist Actigraph WGT3X-BT Monitor

Figure 18: ActiLife + Sleep Software Screen Shot

Each participant will be fitted with the actigraph. The serial number of the watch will be recorded to be linked to the subject ID. At every study visit, data will be downloaded and the device will be charged before being returned to the participant.

***10.17 <u>Subjective Sleep Measures</u>*:**

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

10.17.1 Sleep Disorders Questionnaire: This questionnaire (202) is administered during screening to discriminate between 4 types of sleep disorders – sleep apnea, narcolepsy, psychiatric sleep disorders, and periodic limb movement disorder. This questionnaire will be used in establishing participant eligibility for participation.

10.17.2 Pittsburg Sleep Quality Index (PSQI): This self-administered questionnaire queries normal sleep patterns and sleep problems (203). This will be given to participants at Screening, Week 1, Week 5, Week 9, and Week 12 (***1.5 Schedule of Procedures:***
Table 2). Higher scores indicate poor sleep and PSQI at screening will be analyzed as a covariate in the main outcome measures.

10.17.3 Clinician Administered Evening/Morning Sleep Questionnaire: Participant will be asked about the quality and quantity of their sleep, as well as how well-rested and alert they feel in the morning and at the end of the day (204). Instead of asking participants to fill out this questionnaire on their own, the same questions will be asked when participants are contacted everyday as part of the CAROMA procedure. In addition, participants note their sleep-wake schedule and timing of when medication was taken, as well as their daily intake of caffeinated beverages, nicotine, alcohol, and any other drugs or medications. The questionnaire will be given to participants at every clinic visit (***1.5 Schedule of Procedures:***
Table 2) to report on the night before and the morning of the visit. This questionnaire is the primary instrument for assessing subjective sleep quality, sleep-wake cycle outside of the sleep laboratory, and retrospective, subjective measurement of alertness. Subjectively reported sleep quality, alertness, and sleep schedule data from the Evening/Morning Sleep Questionnaire are secondary outcome measures in this study.

10.18 Rater Qualification and Certification Process: To ensure collection of quality data from scales administered by raters, raters assigned to this study will be required to fulfill qualification and/or training requirements. The process for qualifying and training raters will be described in manuals provided by rater training and assessment vendors. Furthermore, the study will include additional steps related to monitoring the quality of rater activity, which will be described in the manuals provided by these vendors.

All raters will be required to successfully fulfill the full scope of rater training requirements for any scale they will be administering prior to rating any participants in this study. The sites will be responsible for ensuring that they have qualified raters who can conduct assessments in the study prior to enrollment of study participants.

Raters will be required to complete and submit experience details and curriculum vitae (if applicable) to the rater vendor in a timely manner. Once the rater's experience level is reviewed and deemed adequate, then study-assigned raters will be approved to participate in the rater certification process.

11.0 RISK/BENEFIT ASSESSMENT

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

11.1 Known Potential Risks: The risks from this study include: 1) effects of PF-04457845, 2) cannabis withdrawal syndrome, 3) blood drawing, and 4) behavioral and cognitive testing.

11.1.1 PF-04457845: The full investigator brochure contains detailed safety information about PF-0445784. Presented below is a synopsis of the safety, pharmacokinetics, and pharmacodynamics of PF-04457845.

Animals Studies: PF-04457845 has potent and long lasting antinociceptive effects in rats with oral administration. At 1 mg/kg displays PF-04457845 in vivo efficacy for over 24 hours with concomitant FAAH inhibition, and elevation of brain and plasma anandamide, *N*-palmitoyl ethanolamine (PEA) and *N*-oleoyl ethanoamine (OEA). Furthermore, unlike direct CB1 R agonists even at high doses PF-04457845 does not have effects on motility, catalepsy, or body temperature, which are the classic central nervous system effects of CB1R agonists.

Humans Phase 1 Studies: Randomized, double-blind, placebo-controlled phase 1 studies have been conducted in healthy male participants (n=64), aged 21 to 55 to characterize the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of single and multiple oral doses of PF-04457845 in healthy participants. Dose regimens included single doses from 0.1 to 40mg and multiple doses from 0.5 to 8mg once daily (QD) for 14 days. Blood and urine were collected for PK analysis.

Pharmacokinetics: With single doses, absorption of PF-04457845 is rapid, and concentrations peak (Cmax) within an average of 2 hours post dose. Elimination of PF-04457845 is multi-phasic, with a half-life (t1/2) ranging from 12-23 hours. With multiple dosing steady-state plasma concentrations were attained by Day 7. An approximate 2-3 fold accumulation in exposure was observed between days 1 and 14. PK at steady-state appeared dose-proportional. There are no major food effects on PF-04457845. Urine excretion of PF-04457845 as intact parent was negligible. PK is commensurate with QD dosing. Phase 1 safety: Several phase 1 studies have been conducted. Safety assessments including adverse events monitoring, physical examinations, 12-lead ECGs, vital signs (blood pressure, pulse rate and body temperature) and laboratory safety tests were conducted at intervals throughout all studies. Continuous cardiac monitoring, via telemetry was conducted up to 8 hours post-dose in the SRD study and up to 4 hours post-dose on Day 1, 7 and 14 of the MRD study. All observed or reported AEs were recorded for all participants and AEs were classified as mild, moderate or severe and their relationship to study drug was assessed by the investigator. As illustrated (**Figure 19**) the drug and its effects persist for up to 2 weeks after last dose; this is the reason for the 4-week safety follow-up.

Pharmacodynamics: Peripheral FAAH activity was measured ex vivo in blood leukocytes. Plasma concentrations of anandamide, PEA, OEA and *N*-linoleoylethanolamide (LEA) were measured as pharmacodynamic biomarkers. PEA, OEA and LEA have anti-inflammatory, sleep inducing and appetite inducing effects. Inhibition of FAAH activity and elevation of a number of fatty acids has been demonstrated with single and multiple doses. Pharmacological washout takes 10 days after multiple dosing with 4mg due to a combination of the time it takes for the drug to clear and the time that it takes for FAAH activity to recover. This slow pharmacological washout may offer the advantage of being less likely to result in withdrawal symptoms.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

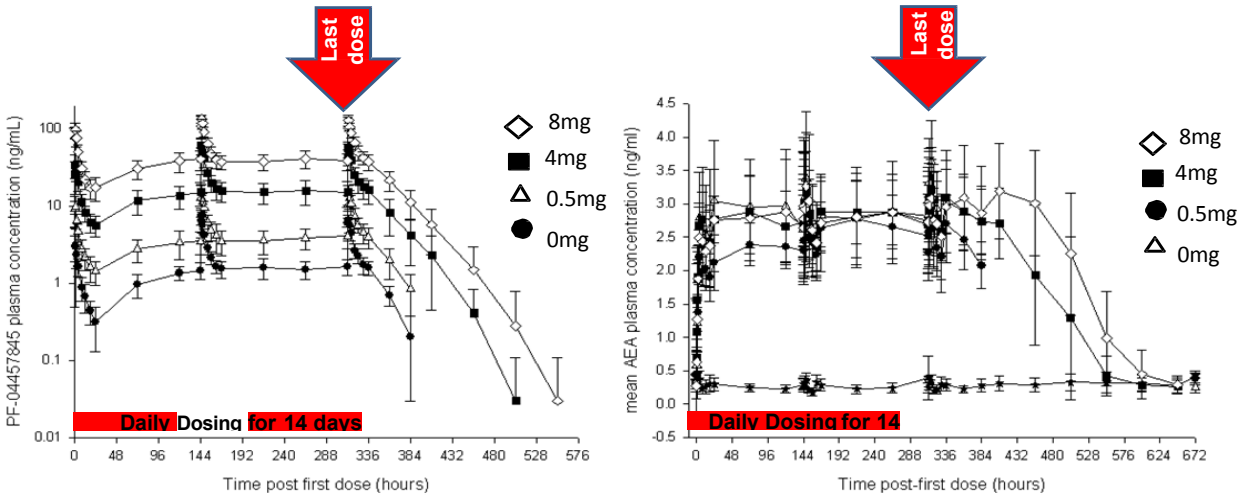


Figure 19:*a) Pharmacokinetics of repeated PF-04457845 administration in healthy human subjects. b) Pharmacodynamics of repeated PF-04457845 administration in healthy human subjects.*

PF-04457845 has undergone extensive testing in animals. All the necessary toxicology testing was completed to permit FDA approved phase 1 and 2 studies. PF-04457845 was evaluated in a 7-day rat dose range inding study where higher doses were explored to define the maximum tolerated dose.

The preclinical safety strategy included 4-week definitive toxicity studies in male and female rats and dogs, standard genetic toxicology assessments, and safety pharmacology studies including CNS and pulmonary evaluations in rats as well as cardiovascular evaluation in dogs) to support clinical development through Phase 1 and 2 clinical trials. PF-04457845 has met or surpassed all of the safety requirements to support nomination as a clinical candidate. These include the *in vitro* dofetilide binding, hERG patch-clamp assays, the panel of CEREP selectivity assays, the BioLum Ames, the *in vitro* micronucleus assay, rat cardiovascular safety study and 4- week definitive toxicity studies in 2 species (rats and dogs).

Table 13: *Summary of Safety Profile for PF-04457845*

Assay	Result
Biolum Ames	Negative
Micronucleus Test	Negative
Dofetilide Binding	Ki = 3.41 μM
hERG (IKr) Assay	IC_{50} = 4.7 μM
Affinity for other receptors, transporters and enzymes (Ki in parenthesis)	CB1 (14 μM), CB2 (5.1 μM), 5HT2A (1.6 μM) and Cl channel (3 μM)
Evaluation of cardiovascular effects in oral PF-04457845 in rats	No effect on heart rate or blood pressure up to 426-fold projected human Cmax (ss)
7-Day rat *in vivo* toleration	No adverse effects at 820-fold and 608-fold the projected human efficacious Cmax (ss) and AUC (0-24 hr), respectively

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

Cognitive safety data: PF-04457845 was not associated with changes in cognitive function in healthy adults when given over 14 days (**Figure 20**). The cognitive effects of PF-04457845 were investigated in study B0541002 by CogState Ltd. The study was a phase 1, double-blind (Coordinating Center open), randomized, placebo-controlled, parallel group, oral multiple-dose trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-04457845 in healthy volunteers. The CogState test battery consisted of a series of computerized tasks that assessed a range of cognitive functions. Cognitive functions assessed included psychomotor function, visual attention, learning, executive function, and delayed recall, as well as a global measure of cognition across domains (i.e., composite). Each test administration was completed in approximately 15 minutes. Participants were assessed 15 times (including 2 practice sessions at screening). Across a wide dose range, including the dose proposed in this study, given over 14 days PF-04457845 was not associated with changes in cognitive function in healthy adults when given over 14 days.

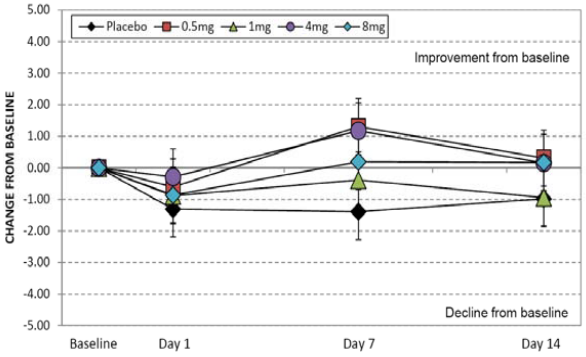


Figure 20: *Effects of 5 doses of PF-04457845 on cognitive test performance over time in healthy individuals. Composite score performance remained within plus or minus one standard deviation unit across the study period.*

Phase 2A (Osteoarthritis): Pfizer conducted a phase 2a randomized, double-blinded, double-dummy, placebo- and active-controlled, 2-way cross-over, flare-enriched multi-center clinical trial to examine the pain relief produced by 2 weeks of daily oral administration of PF-04457845 in patients with osteoarthritis of the knee. PF-04457845 was well tolerated in patients with OA, with a safety profile that was indistinguishable from placebo. The study was conducted in 5 centers in Canada, Sweden, and the United States of America and randomized 76 participants. During the study, no participant died or had a Serious Adverse Event (SAE). No participant was permanently withdrawn due to an Adverse Event (AE). A total of 136 AEs (all causalities) were reported in 51%, 58%, and 51% of participants treated with PF-04457845, naproxen, and placebo, respectively. There were no clinically significant trends or clinically significant abnormalities in clinical laboratory tests, vital signs measurements, or ECG findings. Most AEs were mild in severity; 31 AEs were moderate, and 2 AEs were severe (nightmare and headache in the placebo treatment group).

Table 14: *Treatment Emergent Adverse Events Reported in a ≥5% of Subjects in Any Treatment Group - All Causality/Treatment-Related*

	Number (%) of Subjects					
	PF-04457845 N = 37		Naproxen N = 36		Placebo N = 70	
MedDRA (v13.0) Preferred Term	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Upper respiratory tract infection	6 (16.2)	0	3 (8.3)	0	6 (8.6)	0
Headache	1 (2.7)	0	2 (5.6)	1 (2.8)	10 (14.3)	3 (4.3)
Diarrhea	1 (2.7)	0	2 (5.6)	0	3 (4.3)	1 (1.4)
Back pain	2 (5.4)	0	2 (5.6)	0	2 (2.9)	0
Fatigue	0	0	1 (2.8)	1 (2.8)	4 (5.7)	3 (4.3)
Dizziness	2 (5.4)	1 (2.7)	2 (5.6)	1 (2.8)	1 (1.4)	0
Constipation	1 (2.7)	0	3 (8.3)	3 (8.3)	0	0
Dyspepsia	0	0	3 (8.3)	2 (5.6)	0	0

Includes data up to 14 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
This table includes data up to 14 days after the last dose of study drug.
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, v = version, N = number of subjects per treatment group

In general,

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

AEs were infrequent and there were no clear differences among treatment groups. The most frequently reported all-causality AEs across treatment groups were upper respiratory tract infection, headache, diarrhea, and back pain (**Table 14**).

The most frequently reported treatment-related AEs across all treatment groups were headache, fatigue, and constipation, none of which were judged by the investigator to be related to PF-04457845. The only commonly reported treatment-emergent AE that was also judged related to PF-04457845 was dizziness, which occurred in 1 participant. Treatment-related AEs were more commonly reported in the naproxen treatment group than in the PF-04457845 treatment group. The most common adverse events are presented in **Table 14**. There were no serious adverse events, or adverse events that caused functional un-blinding and no cannabinoid-type events.

Phase 2A (Cannabis Use Disorder): Details of the study design are provided (earlier). Of 218 DSM-IV cannabis dependent males screened, 70 participants were randomized (**Figure 5**) and 58 completed the treatment phase of the study. Participation of the last two participants who would have met the target of 60 completers was terminated shortly after learning of the outcome of the phase I *trial* of BIA 10-2474 (see below).

Clinical laboratory tests for safety completed at screening, during inpatient stay (Day 0, Day 4), at all weekly appointments during treatment, and during follow up phase (Week 8). Participants monitored by inpatient nursing and research staff during the ~1 week long inpatient phase. Participants were evaluated by a study doctor at all outpatient visits. There were no serious adverse events associated with this trial. The rates of minor adverse events were no different between the 2 groups (**Table 8**). The DSMB met every 6 months and had no concerns nor recommendations.

Premature discontinuation of the Proof of Concept (POC) Trial: On 1/18/2016, we halted our POC trial voluntarily after learning about the neurological SAEs that occurred during Biotrial's FAAH Inhibitor study (BIA 10-2474) in France. At the time, there was very limited information available about the structure of the drug, its pharmacodynamics, or the doses that were being tested, and whether BIA 10-2474 shared any similarities with PF-04457845 and other FAAH-Inhibitors in development. Because of this, we halted our trial out of an abundance of caution. Two participants were participating in the inpatient treatment portion of the study at that time, so the principal investigator discontinued their participation the same day. The two participants were examined and provided with information about the SAEs that occurred in the other clinical trial, and given the opportunity to ask questions. In addition to putting our trial on hold, we notified our IRB and DSMB within 24 hours of learning of these events. In February 2016, the FDA put all trials using FAAH inhibitors on a full clinical hold while the events related to BIA 10-2474 were investigated.

As more information became available, it became clear that these SAEs were likely a result of *off*-target effects, rather than due to FAAH Inhibition. None of the participants that have completed the trial here at Yale have had similar side effects. Similarly, other pharmaceutical companies that manufacture FAAH inhibitors such as Merck, Johnson & Johnson, Sanofi, and Vernalis have not observed neurological side effects similar to BIA 10-2474 in any of their trials. In September 2016, the FDA completed their review of the events at Biotrial in France and removed the full clinical hold on FAAH inhibitors in the US. They released this statement before removing the hold:

"*The U.S. Food and Drug Administration, with information received from the European Medicines Agency (EMA) and the French national medicines agency (ANSM), has completed a comprehensive review of safety information relevant to the investigational new drug BIA 10-2474 and the potential implications for related drugs under investigation in the U.S. The Agency has found, based on the available information, that BIA 10-2474 exhibits a unique toxicity that*

does not extend to other drugs in the class, called fatty acid amide hydrolase (FAAH) inhibitors. There are no clinical trials with BIA 10-2474 underway in the U.S. The first phase 1 clinical trial of BIA 10-2474 was conducted in France in January, 2016, and resulted in the death of one enrolled participant and hospitalization of 5 others. Four of these 5 participants experienced neurological injury. Based on these findings, the FDA is working with Coordinating Centers to establish the appropriate path forward for FAAH inhibitors under investigation in the U.S. We are also working to ensure healthy participants, patients, and investigators participating in FAAH inhibitor clinical trials are fully informed of the risks and potential benefits of these experimental therapies."

Phase 2A (PTSD): Of the 80 participants screened for this study, 27 participants have completed all three test days. This study was designed to study whether the administration of PF-04457845 will facilitate extinction learning in healthy control participants and participants with a diagnosis of PTSD. Comprised of three test days, the first day has two phases: *habituation*, during which the participants are familiarized with the testing apparatus and conditioned stimuli, and *acquisition*, in which the positive conditioned stimulus is paired with the unconditioned stimulus, an electric shock delivered by a Biopac 150. The second day has two phases: *drug administration*, in which PF-04457845 or placebo will be administered prior to the extinction learning phase, FAAH inhibition occurs and endocannabinoid levels rise, and *extinction learning*, in which the association learned in the acquisition phase is weakened or eliminated. The third day has one phase; *extinction recall*, in which participants will be assigned to extinction recall, which has different environmental cues. Single doses of PF-0445784 were well-tolerated. There were no serious adverse events associated with this study.

11.1.2 Cannabis Withdrawal Symptoms: The typical withdrawal symptoms in humans include: cannabis craving, anger, aggression, appetite change, weight loss, irritability, anxiety, restlessness, altered sleep, strange dreams and physical discomfort (39, 40, 99, 225). Less common symptoms include: chills, depressed mood, stomach pain and sweating. Most symptoms appear within 1 day of abstinence, peak within 2–3 days, and resolve within 1–2 weeks. Two studies evaluated symptom time course for at least four weeks (45 days and 28 days, respectively). Both studies observed prominent withdrawal symptoms during the initial two to three weeks of abstinence, some of which persisted through the entire study period (63, 70). The findings of these studies suggest that withdrawal symptoms may persist longer than 4 weeks. Characteristic of a true withdrawal syndrome, abstinence symptoms occur with blind discontinuation and resolve with CB1R agonist re- administration. Finally, the administration of cannabis or THC attenuates withdrawal symptoms.

These symptoms that people experience when they stop smoking marijuana are uncomfortable but not life threatening. The marijuana withdrawal symptoms will be monitored closely. If intolerable, participants will be able to withdraw from further study participation.

11.1.3 Phlebotomy: Bruising, infection and thrombosis can occur during phlebotomy. These risks can be minimized by having these procedures performed by experienced personnel using good clinical technique. Participants will have no more than 3 oz. of blood drawn over the entire study period. These amounts are well within the Red Cross blood standards.

11.1.4 Behavioral/Cognitive Testing: Some participants may experience the behavioral as boring or frustrating. Trained research staff will work closely with participants and if necessary provide them with breaks.

11.2 Known Potential Benefits: Study participation may facilitate a reduction of cannabis use for study participants. Group data collected from this study will also inform the development of

this drug for the treatment of CUD, for which there are no currently approved pharmacological treatments.

11.3 Assessment of Potential Risks and Benefits: Cannabis is the most widely used illicit substance worldwide. In 2009, cannabis was the illicit drug with the highest rate of past year dependence or abuse; there were more treatment admissions for cannabis in the US than for any other drug including cocaine or heroin. There are no approved pharmacological treatments for CUD and as stated in the FOA: *"the development of safe and effective medications to treat these disorders is an urgent public health need."* Furthermore, in keeping with the expectation stated in the FOA the proposed study represents a collaboration with the pharmaceutical industry.

In the completed phase 2A study, PF-04457845 reduced cannabis withdrawal, reduced self-reported cannabis use, reduced urinary levels of THC-COOH and restored stage 3 sleep deficits in cannabis dependent individuals with an excellent tolerability and safety profile. For the proposed study, the potential risks to participants appear low. Furthermore, the study entails no financial or social risk to the participant.

FAAH inhibitors are a new chemical entity. There are very few FAAH-inhibitors that are available for use in humans, and none are available commercially. The proposed study has the potential to yield important knowledge towards continued development of this treatment approach for an unmet need. Therefore, the proposed study has a favorable risk/benefit profile.

11.4 Mitigation of Risk:

11.4.1 Screening: For the proposed study, participants will be carefully screened to exclude participants with any significant medical or psychiatric problems. The screening process is rigorous and includes a structured clinical interview for DSM, a psychiatric and medical evaluation by a psychiatrist, laboratory tests, EKG, etc. An outside informant specified by the participant will be contacted to confirm the history. This process should screen out unsuitable participants.

11.4.2 Effects of PF-04457845: Once enrolled into the study, participants will be seen weekly by a clinician. Furthermore, participants will also be contacted almost daily as part of CAORMA and this will provide additional information re: tolerability. The research assistant making the CAROMA call will pass along to the Investigator or her/his designee any tolerability or safety issues discovered on the CAROMA call. Laboratory testing will also be conducted during the study to detect any clinically significant changes. At study visits, formal assessment for AEs (discussed below) will also be done. These overlapping mechanisms to monitor participants for safety should greatly minimize the risk to participants.

11.4.3 Phlebotomy and IV Placement: Bruising, infection and thrombosis can occur when phlebotomy is performed. These risks are minimized by having these procedures performed by experienced personnel using good clinical technique. Participants who have recently donated blood will need to wait for eight weeks before participating in the study. Sterile procedures will be followed to minimize the likelihood of infection.

11.4.4 Cannabis Withdrawal: Most symptoms appear within one day of abstinence, peak within two to three days, and resolve within one to two weeks. Research staff will be available to provide support and reduce anxiety.

11.4.5 Resumption of cannabis use in cannabis dependent participants who achieve abstinence: At the end of the study, interested participants will be offered information to

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

substance use treatment programs in their area.

12.0 ADVERSE EVENT REPORTING

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

The site principal investigator will be responsible for monitoring the data and assuring protocol adherence. At a minimum of every six months (including when re-approval of the protocol is sought), each site should notify the Coordinating Center of all adverse events. The Coordinating Center will then conduct safety reviews across all sites participating in the study. During the review process, the study principal investigator and coordinating physician investigator (responsible for medical oversight) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the study principal investigator or institutional review boards overseeing the study have the authority to stop or suspend the study or require modifications.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Coordinating Center. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the Coordinating Center concurs with that assessment.

As part of ongoing safety reviews conducted by the Coordinating Center, any non-serious adverse event that is determined by the Coordinating Center to be serious will be reported by the Coordinating Center as a SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

12.1 Reporting Period: For SAEs, the active reporting period begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, through the last follow up visit (end of study visit). Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported.

12.2 Capturing Adverse Events: Safety and adverse events will be captured using the Systematic Assessment for Treatment Emergent Events (SAFTEE) general and specific inquiry forms, which take approximately 20 minutes to administer. Collection of adverse events will commence from the time the participant signs the informed consent to participate in the study and will continue until the last safety follow up visit. At each study visit, the investigator will

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Participants may report AEs occurring at any other time during the study. All participants experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented, whether or not the investigator concludes that the event is related to the drug treatment. 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.
The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Pattern of AE (Frequency).
4. Intensity.
5. Investigator’s opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the participant. The event does not generally interfere with usual activities of daily living.
- Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: An AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention, and are usually potentially life-threatening or incapacitating. The term “severe” does not necessarily equate to “serious”.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with participant’s usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

Action Concerning the Study Drug: For every adverse event, the action taken concerning the study drug will be documented on the source document.

- Drug withdrawn: a study drug is stopped due to the particular AE.
- Dose not changed: the particular AE did not require stopping a study drug.
- Unknown: only use if it has not been possible to determine what action has been taken.
- Not Applicable: study drug was stopped for a reason other than the particular AE (the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE)
- Dose Interrupted: the dose was interrupted due to the particular AE.

***12.3 <u>Assigning Causality of Adverse Events</u>*:** Causality to study procedures should be determined for all adverse events. The degree of certainty about causality will be graded using

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Coordinating Center If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable. Adverse events will be monitored for each participant participating in the study and attributed to the study procedures / design by the study principal investigator (Deepak Cyril D'Souza) according to the following categories:

- Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
- Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
- Possible: Adverse event may be related to investigational procedures(s)/agent(s).
- Unlikely: Adverse event is likely not to be related to the investigational

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

procedures(s)/agent(s).
- Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

***12.4 Adverse Event Outcome**:* For every adverse event, the outcome must be documented in the source document as one of the following.
- Recovered/resolved – participant returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or Baseline; the participant died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the participant died from another cause with the particular AE state remaining "not recovered/not resolved".
- Resolved with sequelae – the participant recovered from an acute AE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

The overall principal investigator will conduct a review of all adverse events upon completion of every study participant. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

12.5 Pre-Existing Conditions: Pre-existing conditions, present at the time of signing informed consent, are considered to be concurrent medical conditions and should not be recorded as adverse events. All pre-existing conditions and their severity need to be documented at the time of the screening visit. If the participant experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an adverse event. Investigators should ensure that the event term recorded captures the change in the condition.

12.6 Worsening of Adverse Events: If the participant experiences a worsening or complication of an AE after the first administration of study drug or any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

12.7 Serious Adverse Events: An SAE is defined as any untoward medical occurrence that at any dose:
1. Results in death.
2. Is life threatening.
    - The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

6. Is an important medical event that a) may require intervention to prevent items 1 through 5 above, or b) may expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization

Each adverse event is to be assessed to determine if it meets the criteria for a serious adverse event. An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the HIC or HSC is necessary.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.8 Follow-up of Serious Adverse Events: If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and notify the Coordinating Center within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested. All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

12.9 Serious Adverse Event Reporting Requirements: If an SAE occurs, the Coordinating Center is to be notified within 24 hours of investigator awareness of the event, using a standard reporting form (e.g. local institutional SAE form, CIOMS, MedWatch 3500a, or similar), regardless of the suspected causal relationship between the SAE and the study drug. In particular, if the SAE is fatal or life-threatening, notification to must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study participant initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE. The Coordinating Center will submit any SAE report to Jazz Pharmaceuticals via email (AEReporting@Jazzpharma.com) on behalf of the investigator within 1 business day after it was received at the Coordinating Center.

For all SAEs, the investigator is obligated to pursue and provide information to the Coordinating Center in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE source document. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to the Coordinating Center.

12.10 Pregnancy Reporting Requirements: In the case of a pregnancy in a female participant or a female partner of a male participant, the site must notify the Coordinating Center within 24 hours of awareness. The Coordinating Center will report to Jazz Pharmaceuticals via email

(AEReporting@jazzpharma.com) using the Jazz Pregnancy Query Form within 1 business day after receiving notification from the site. The Pregnancy Query Form must be further completed and sent to Jazz Pharmaceuticals via email (AEReporting@jazzpharma.com) as additional details of the pregnancy become available, and at the time that the outcome of the pregnancy is known. The pregnancy should be followed up to determine outcome (including spontaneous or voluntary termination), details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

While pregnancy itself is not considered an AE or SAE, any pregnancy complications or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. An abnormal pregnancy outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy, etc.) are considered SAEs and will be reported as such.

12.11 Safety Reporting to Investigators, IRBs, and Regulatory Authorities: The Coordinating Center will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs, as applicable. All SAEs will be reported to NIDA within 72 hours of the principal investigator becoming aware of the event. The Coordinating Center will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with local regulations.

The primary responsibility for monitoring data and safety will lie with the principal investigator (Deepak Cyril D'Souza), along with the site investigators and the research team. Each local investigator will meet with the research team at least once per week to discuss the safety of the study. The study principal investigator (Deepak Cyril D'Souza) will conduct a review of all adverse events upon completion of every study participant. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

As recommended the Serious Adverse Event Reporting and Tracking System (SAETRSII) will be used when reporting to NIDA.

- Actions of the Yale Human Investigations Committee will be reported to NIDA within 10 days of receipt of such correspondence from the Yale HIC.
- Changes or major amendments to the protocol will also be reported to the NIDA SO and PO for their approval prior to implementation.

13.0 UNANTICIPATED PROBLEMS

13.1 Definition of Unanticipated Problems: The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

13.2 Unanticipated Problem Reporting: The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study Coordinating Center within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study Coordinating Center within 5 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 days of the IRB's receipt of the report of the problem from the investigator.]

14.0 STATISTICAL METHODS

All data obtained during the course of the study will be uploaded to an electronic database created by the Yale Center for Analytical Sciences (YCAS). Baseline and demographic data will be summarized for all treatment groups, and summary statistics will be provided by treatment group for the primary and all secondary outcomes. Treatment compliance measures and retention in treatment will be calculated by group and time and presented in tabular form. The full analysis set will be based on the modified Intent-To-Treat (ITT) principle, consisting of all participants who receive at least one dose of randomized study medication, and have a baseline and at least one post-baseline measurement. The per-protocol population will include all participants in the full analysis set but without any major protocol violations. Analyses of the per-protocol population will be considered secondary. The data will first be scanned for potential outliers. All outliers will be double-checked prior to analysis and as necessary, sensitivity analyses without outliers will be performed. Descriptive statistics (mean, standard deviation, range, frequency) will be computed for each variable first and presented in tabular form. Continuous variables will be checked for normality using normal probability plots and Kolmogorov-Smirnov tests. In case of non-normal distribution, transformations will be applied or non-parametric tests (226) will be used as necessary. A significance cutoff of 0.05 will be used to test the primary hypothesis whereas analyses of secondary outcomes will be adjusted using the Bonferroni-Holm procedure. Effect sizes and associated 95% confidence intervals will be calculated for the primary and all secondary outcomes in order to inform the design of future studies. All analyses will be performed in the latest version of SAS software.

14.1 Sample Size Determination: Since there are no published studies on the effect of FAAH inhibitors on cannabis use reduction in humans, we estimated the expected size of the effect of PF-04457845 on cannabis use based on a subsample of participants from the completed Phase 2A study. In the phase 2A study we forced everyone into abstinence by hospitalizing them for one week. The proposed study design is different: participants are neither hospitalized nor forced into abstinence, which is more ecologically valid and consistent with most treatments for CUD being outpatient. Therefore, to estimate the expected size of the effect of PF-04457845 on cannabis use, we selected a subsample of participants from the preliminary study whose use of cannabis during the first week *after* being hospitalized continued to be high enough to meet the met the inclusion criteria of the original study of using >1 joint/day. Analyses revealed that the effect size of the difference in cannabis use by the end of the study was medium-small (d=0.42). To detect such an effect size with 80% power, we require a sample size of 178 participants assuming two-sided alpha = 0.05. Based on the completed study, and the experience of the 3 other sites a ~25% dropout rate is expected and therefore, 237 participants will need to be studied to obtain complete data in 178 participants.

14.2 Efficacy Analysis:

14.2.1 Primary Outcome: To test the efficacy of PF-04457845 treatment on cannabis use the group (placebo vs. active) differences in change from baseline use in the average number of times per day of self-reported consumption of cannabis or a cannabis containing product will be tested using ANCOVA with treatment group as the main predictor of interest and stratification variables (site [4 sites] and degree of cannabis exposure [medium and high] = 8 strata) as additional factors in the model. Multiple imputation of outcome data will be performed using PROC MI in SAS using regression imputation with baseline average number of times per day, treatment and baseline participant-level characteristics (age, sex, cannabis use, tobacco use, alcohol use) as predictors in the imputation model. Significantly higher change from baseline in the active group compared to the placebo group at 0.05 significance level will be considered

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

supportive of our hypothesis. In addition to statistical testing, we will present least square mean estimates with 95% confidence limits for change from baseline by treatment group. We will also present estimates of treatment effects by site and baseline degree of cannabis exposure (high user or medium user) and evaluate whether treatment effects vary significantly by stratification factor (this assessment will be secondary to the primary evaluation of average treatment effects across strata). Other secondary and sensitivity analyses of the primary outcome include: (1) mixed model analysis with average number of times per day of self-reported consumption of cannabis or a cannabis containing product as the outcome, treatment group (active vs. placebo), site (4 levels), degree of cannabis exposure (medium, high) as between-participant factors, and time (baseline, first four weeks of the treatment period, last four weeks of the treatment period) as a within-participant factor; (2) tipping point analysis to assess sensitivity of conclusions to assumptions about missing data; (3) analyses of the per-protocol sample. In the mixed model analysis all available data on individuals will be used and the best fitting variance-covariance structure (among compound symmetry, compound symmetry heterogeneous, autoregressive of first order (AR(1)), autoregressive heterogeneous (ARH(1)), and unstructured) will be selected using Schwarz's Bayesian Criterion (BIC). Post-hoc analyses will provide information about treatment effect across the different time points, and the potential influence of the data collection site and baseline degree of cannabis exposure on the outcome trajectories. Additional exploratory analyses will be conducted to assess the effect of gender, desire to quit, lifetime cannabis use, tobacco use, alcohol use, and other drug use on the outcomes by including them into the models. Mixed models use all available data and are unaffected by data missing at random. Sensitivity analyses under missing not at random assumptions will also be performed.

14.2.2 Secondary Outcomes: The same analytic strategy will be followed for secondary outcomes compared to the primary outcome. Primary analyses will be based on ANCOVA with multiple imputation on the modified intent-to-treat sample, secondary analyses will include mixed models, tipping point analyses and analyses of the per protocol sample. The emphasis will be on effect estimation. Testing in the primary analyses will be adjusted using the Bonferroni-Holm method. For each eCB, plasma levels will be assessed by fitting a mixed effects model with treatment, time, site, and the interaction terms as fixed effects, and tobacco use as covariate. Exploratory analyses will be conducted to assess the effect of variables such as gender and use of other substances on endocannabinoids. Since we expect floor effects for the blood levels of PF-04457845 in the placebo condition, PF-04457845 blood level will be assessed by using non-parametric models (226, 227) with treatment, time, site, and the interaction terms as factors.

14.3 Safety Analysis: The review and summary of safety will be performed on the modified intent-to-treat sample. Events or abnormalities will be searched from the time of the first dose until 5 half-lives after the last dose. Clinical laboratory data will be summarized quantitatively using descriptive statistics such as changes from baseline summarized by mean, standard deviation, median, minimum and maximum, and summarized qualitatively by tabulating clinical abnormalities. Vital signs, BMI, weight will be summarized using descriptive statistics. Group differences in the percentage of participants who report AEs or exhibit clinically significant changes during 1) 8-week treatment phase (from the first dose until the last dose), and 2) the 4-week follow up phase (to assess any lingering post treatment safety issues) will be summarized in tabular form and presented. Data permitting, exploratory analyses may be performed to evaluate the statistical significance of between-group differences (e.g. using Fisher's exact tests for adverse events, t-tests or non-parametric equivalent for changes in continuous measures) and evaluation of the effects of duration of drug exposure or drug dose on any adverse events (e.g. using exact logistic regression) and laboratory measures (e.g. using mixed effects models).

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

15.0 DATA HANDLING AND RECORDKEEPING

15.1 Case Report Forms: As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs should not be made available in any form to third parties, without written permission from the Coordinating Center. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts. In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

The Coordinating Center will supply study sites with access to CRFs. The Coordinating Center will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Coordinating Center and regulatory authorities. CRFs must be completed in English.

15.2 Data Entry: Each site will be responsible for entering data into the electronic data base. After completion of the data entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the Coordinating Center and will need to be answered by the site.

Corrections will be recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. The principal investigator must review both the paper and electronic CRFs for completeness and accuracy. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After all data for a participant has been entered electronically, the data will be locked. Any change of, modification of, or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs. The principal investigator must review the data change for completeness and accuracy, and must e-sign and date the electronic eCRFs.

15.3 Record Retention: The investigator will have to agree to keep all study-specific documents, the identification log of all participating participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, participant authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of all paper CRFs and query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities or from the Coordinating Center or designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility.

All study records should be retained by the investigator according to local regulations, or

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

as specified by the study principal investigator, whichever is longer.

15.4 Genetic Samples: Results of genetic tests will not be available to the participant, nor will we add them to medical records. (If a participant wants to know their risk for genetic diseases, we will refer them to a genetic counselor.) Additionally, the biological materials collected will be identified by code number rather than by name to maintain confidentiality. These procedures should prevent any confidential information from becoming known to anyone other than the scientists and research staff involved in this study. We believe that the chance of this information becoming known to others in such a way that it would be harmful to study participants is small.

All samples will be identified by a code number and will never been coded with any PHI. Once samples have been sent to be analyzed, the individuals working at the laboratory will not have access to the link between the names and the code numbers. This link between the names and code numbers will be held by the investigator for seven years after the research has been completed after which time the link will be destroyed and the data will be kept for an indefinite amount of time.

In the event that the materials collected for this project are shared or distributed for future research, they will first be stripped of any identifying information before distribution. Any material will only be shared in the event that another investigator provides a written request for the materials. In this request, the inquiring investigator must provide a hypothesis and specific aims that are deemed as appropriate by this investigator. Furthermore, the inquiring investigator must ensure this investigator that the same protections will be afforded to the genetic information and that the requesting investigator adhere to appropriate confidentiality guidelines. It is only then that materials will be shared or distributed.

15.5 Publication and Data Sharing: This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (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.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the study principal investigator.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

16.0 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Study Site Monitoring Visits: Monitoring visits to the study site will be conducted periodically during the study by the Yale Center for Clinical Investigation (YCCI) or similar organization to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the Coordinating Center or designee and by the IRB.

All aspects of the study and its documentation will be reviewed by the Coordinating Center or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, participant medical records, informed consent documentation, documentation of participant authorization to use personal health information (if separate from the informed consent forms), and eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

16.2 Data Monitoring: A data monitoring plan will be developed to assess the data in an ongoing manner over the course of the study to ensure validity and integrity of key study endpoint data.

16.3 Protocol Deviations: Should it become necessary to deviate from the protocol in order to eliminate an immediate hazard to study participants or some other unexpected circumstances arises, the investigator should consult with the Coordinating Center or designee and if necessary the IRB to determine the appropriate course of action.
The site should document all protocol deviations in the participant's source documents. In the event of an important protocol deviation, the site should notify the Coordinating Center or designee (and IRB as required). Important deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment. Important protocol deviations will be reviewed at regular intervals by the Coordinating Center and designee.

16.4 Quality Assurance Audits and Regulatory Agency Inspections: The study site also may be participant to quality assurance audits by the Coordinating Center or designees. In this circumstance, the Coordinating Center -designated auditor e.g., YCCI will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where study drug is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including: the Food and Drug Administration (FDA), the National Institute of Drug Abuse (NIDA). If the study site is contacted for an inspection by a regulatory body, the Coordinating Center should be notified immediately.

***16.5 Data Monitoring Committee*:** This study does not include endpoints related to assessing mortality or major adverse health outcomes, and the study population is not at expected risk of serious safety events. The NIDA data and safety monitoring board (DSMB) that is independent of the study and project teams will periodically review unblinded safety data during conduct of the study to complement the routine safety monitoring approach for drugs at this stage of development. The NIDA DSMB will meet at least semiannually, but may meet more frequently if deemed necessary, to assess safety and efficacy data. The NIDA DSMB will provide its input to the Coordinating Center. A report of the NIDA DSMB meetings will be prepared and circulated to the IRBs and NIDA.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

16.6 Study Discontinuation and Closure:

16.6.1 Criteria for Premature Termination or Suspension of the Study: The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

16.6.2 Criteria for Premature Termination or Suspension of Study Sites: A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

16.6.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites: In the event that the Coordinating Center, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the overall principal investigator; the procedure will be followed by the investigational site during the course of termination or study suspension. The principal investigator will promptly inform study participants, the institutional review board, and Coordinating Center, and will provide the reason(s) for termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

17.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Participants (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008). Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix J.

17.1 IRB Approval: It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB should be retained in the Investigator File. Copies of IRB approvals should be forwarded to the Coordinating Center. The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB and the Coordinating Center in writing immediately after the implementation.

The Coordinating Center or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the local IRB for approval. The IRB's written approval of the protocol and participant informed consent must be obtained and submitted to the Coordinating Center or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The Coordinating Center or designee will ship drug/notify site once the Coordinating Center or designee has confirmed the adequacy of site regulatory documentation.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Coordinating Center or designee.

17.2 Participant Information, Informed Consent, and Participant Authorization: All parties will ensure protection of participant personal data and will not include participant names on any Coordinating Center forms, reports, publications, or in any other disclosures, except where required by laws. Participant names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by the Coordinating Center in order to de-identify trial participants. In case of data transfer, the Coordinating Center will maintain high standards of confidentiality and protection of participant personal data.

The Coordinating Center will provide the protocol and consent form that sites can use to submit to their IRB. Any substantive changes made to the consent form or protocol provided by the Coordinating Center will need approval prior to submission to the local IRB. The investigator or her/his designee must ensure that each study participant, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or her/his designee, will obtain written informed consent from each participant before any study-specific activity is performed. Copies of the

signed informed consent form, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant. The site investigator will retain the original of each participant's signed consent document.

All revised informed consent forms must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised informed consent form.

Participants who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. The Coordinating Center is to be notified when consent has been withdrawn.

17.3 Participant Confidentiality: The Coordinating Center and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the Coordinating Center's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Coordinating Center requires the investigator to permit the monitor or the Coordinating Center's designee, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Coordinating Center's designated auditors, and the appropriate IRBs to review the participant's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process.

Copies of any participant source documents that are provided to the Coordinating Center must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's eCRF).

There is a risk of loss of confidentiality in this study. All participant information will be kept confidential and only members of the investigative team with appropriate IRB/HIC and HIPAA training will have access to the study data. Data will be maintained and secured in locked file cabinets or password protected electronic media. A numbering code will be used to assign a unique identifier to each participant.

For the Cellphone Assisted Remote Observation of Medication Adherence (CAROMA) procedures, participants will be called and observed taking study medications. The CAROMA procedure is not recorded, broadcast, nor will the likeness of the participants be used for anything other than what has been specified. The potential for loss of confidentiality is if someone taps the phone while a call is being made, but this risk is no different from someone tapping into a phone (audio) conversation between the participant and the research team. The phones used for this practice will be encrypted by sites' Information Technology Service so that loss of confidentiality is minimized. CAROMA was set up with input from Yale ITS in order to conform to Yale's policies.

17.4 Publication and Disclosure: The investigator is obliged to provide the Coordinating Center with complete test results and all data derived by the investigator from the study. During and after the study, only the Coordinating Center may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly

accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Coordinating Center. The Coordinating Center may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail. The investigator needs to obtain a prior written approval from the Coordinating Center to publish any information from the study externally such as to a professional association.

17.5 Clinical Trials Registration: In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the Coordinating Center (Yale University) will register this study on clinicaltrials.gov and will maintain the record at a minimum of every 6 months. All sites will be referred to in this record.

17.6 Future Use of Stored Specimens and Data: Data collected for this study will be analyzed and stored at the Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the FAAH-Inhibitor Phase 2A Study Data Repository, for use by other researchers including those outside of the study. Permission to transmit data to the FAAH-Inhibitor Phase 2A Study Data will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the FAAH-Inhibitor Phase 2A Study Biosample Repository with the same goal as the sharing of data with the FAAH-Inhibitor Phase 2A Study Data Repository. These samples could be used to research the causes of cannabis use disorder and related conditions, its complications and other conditions for which individuals with cannabis use disorder are at increased risk, and to improve treatment. The FAAH-Inhibitor Phase 2A Study Biosample Repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.
When the study is completed, access to study data and/or samples will be provided through the FAAH-Inhibitor Phase 2A Study Data Repository.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

18.0 ABBREVIATIONS:

2-AG: 2-arachidonoylglycerol
ABHD6: 2-arachidonoylglycerol hydrolase
AE: Adverse Event
AEA: Anandamide
CAROMA: Cell Phone Assisted Remote Observation of Adherence
CB1R: Cannabinoid Receptor
CBD: Cannabidiol
CBT: Cognitive Behavioral Treatment
CFR: Code of Federal Regulations
CM: Contingency Management
CNS: Central Nervous System
CONSORT: Consolidated Standards of Reporting Trials
C-SSRS: Columbia Suicide Severity Rating Scale
CUD: Cannabis use disorder
CWS: Cannabinoid Withdrawal Syndrome
DSMB: Data Safety Monitoring Board
eCB: Endocannabinoid System
ECG: Electrocardiogram
FAAH: Fatty Acid Amide Hydrolase Inhibitor
FDA: Food Drug Administration
FTND: Fagerstrom test for Nicotine Dependence
IND: Investigational New Drug
IRB: Institutional Review Board
LEA: N-linoleoylethanolamine
MAG-L: Monoacylglycerol lipase
MCQ-12: Marijuana Craving Questionnaire-Short Form
MET: Motivational Enhancement
MI: Motivational Interviewing
NIH: National Institute of Health
OEA: N-oleoyl ethanolamine
PD: Pharmacodynamics
PD: Plasma Anandamide
PEA: N-palmitoyl ethanolamine
PK: Pharmacokinetics
POC: Proof of Concept
PRISM: Psychiatric Research Interview for Substance and Mental Disorders
PSG: Polysomnography
QD: Once Daily
Q-LES-Q-18: Quality of Life Enjoyment and Satisfaction Questionnaire
SAE: Serious Adverse Event
SAFTEE: Systematic Assessment for Treatment Emergent Events
SALCU: Scale for Assessment of Lifetime Cannabis Use
THC: delta-9-tetrahydrocannabinol
TLFB: Timeline Follow Back
US: United States
VAS: Visual Analog Scale
WOCBP: Women of Childbearing Potential
YCAS: Yale Center for Analytical Studies
YCCI: Yale Center for Clinical Investigation

19.0 PROTOCOL AMENDMENT HISTORY:

Version	Date	Description of Change	Brief Rationale

20.0 REFERENCES

1. SAMHSA (2015): National Survey on Drug Use and Health: National Findings. In: Studies OoA, editor. Rockville, MD.: Substance Abuse and Mental Health Services Administration.
2. UNODC (2006): World Drug Report. In: on UNO, Crime Da, editors. *[online]* http://wwwunodcorg/unodc/ *en/world_drug_report_2006html (2006)*.
3. Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, et al. (2015): Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA psychiatry*. 72:1235-1242.
4. Grucza RA, Agrawal A, Krauss MJ, Cavazos-Rehg PA, Bierut LJ (2016): Recent Trends in the Prevalence of Marijuana Use and Associated Disorders in the United States. *JAMA psychiatry*. 73:300-301.
5. Johnston LD, O'Malley PM, Miech RA, Bachman HG, Schulenberg JE (2016): Monitoring the Future national results on drug use, 1975-2015. Overview, key findings on adolescent drug use. . Ann Arbor: Institute for Social Research, The University of Michigan.
6. Chen X, Yu B, Lasopa SO, Cottler LB (2016): Current patterns of marijuana use initiation by age among US adolescents and emerging adults: implications for intervention. *The American journal of drug and alcohol abuse*.1-10.
7. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R (2016): National Estimates of Marijuana Use and Related Indicators - National Survey on Drug Use and Health, United States, 2002-2014. *MMWR Surveill Summ*. 65:1-28.
8. Hasin DS, Wall M, Keyes KM, Cerda M, Schulenberg J, O'Malley PM, et al. (2015): Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys. *The lancet Psychiatry*. 2:601-608.
9. Albertson TE, Chenoweth JA, Colby DK, Sutter ME (2016): The Changing Drug Culture: Medical and Recreational Marijuana. *FP essentials*. 441:11-17.
10. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC (2016): Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. *Biological psychiatry*.
11. Spaderna M, Addy PH, D'Souza DC (2013): Spicing things up: synthetic cannabinoids. *Psychopharmacology*. 228:525-540.
12. Fattore L (2016): Synthetic Cannabinoids-Further Evidence Supporting the Relationship Between Cannabinoids and Psychosis. *Biological psychiatry*. 79:539-548.
13. Gonzalez S, Cebeira M, Fernandez-Ruiz J (2005): Cannabinoid tolerance and dependence: a review of studies in laboratory animals. *Pharmacol Biochem Behav*. 81:300-318.
14. Compton DR, Dewey WL, Martin BR (1990): Cannabis dependence and tolerance production. *Adv Alcohol Subst Abuse*. 9:129-147.
15. Jones RT, Benowitz NL, Herning RI (1981): Clinical relevance of cannabis tolerance and dependence. *J Clin Pharmacol*. 21:143S-152S.
16. Hollister LE (1978): Cannabis and the development of tolerance. *Adv Biosci*. 22-23:585-589.
17. Budney AJ, Roffman R, Stephens RS, Walker D (2007): Marijuana dependence and its treatment. *Addiction science & clinical practice*. 4:4-16.
18. Budney AJ, Moore BA (2002): Development and consequences of cannabis dependence. *J Clin Pharmacol*. 42:28S-33S.
19. Clapper JR, Mangieri RA, Piomelli D (2009): The endocannabinoid system as a target for the treatment of cannabis dependence. *Neuropharmacology*. 56 Suppl 1:235-243.
20. (APA) APA (2013): *Substance-related and addictive disorders.*
21. Gruber AJ, Pope HG, Hudson JI, Yurgelun-Todd D (2003): Attributes of long-term heavy cannabis users: a case-control study. *Psychological medicine*. 33:1415-1422.

22. Stephens RS, Babor TF, Kadden R, Miller M (2002): The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction*. 97 Suppl 1:109-124.
23. Broyd SJ, van Hell HH, Beale C, Yucel M, Solowij N (2015): Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review. *Biological psychiatry*.
24. Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJ, Parsons LH (2016): Keep off the grass? Cannabis, cognition and addiction. *Nat Rev Neurosci*. 17:293-306.
25. Crean RD, Crane NA, Mason BJ (2011): An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med*. 5:1-8.
26. Ranganathan M, D'Souza D (2006): The Acute Effects of Cannabinoids on Memory in Humans: A review. *Psychopharmacology*.
27. Rogeberg O, Elvik R (2016): The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction*. 111:1348-1359.
28. Asbridge M, Hayden JA, Cartwright JL (2012): Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *Bmj*. 344:e536.
29. Radhakrishnan R, Addy PH, Sewell RA, Skosnik PD, Ranganthan M, D'Souza DC (2012): Cannabis, Cannabinoids, and the Association with Psychosis. . In: Madras B, Kuhar MJ, editors. *The Effects of Drug Abuse on the Human Nervous System*: Neuroscience-Net, LLC. .
30. Radhakrishnan R, Wilkinson ST, D'Souza DC (2014): Gone to Pot - A Review of the Association between Cannabis and Psychosis. *Frontiers in psychiatry*. 5:54.
31. Ranganathan M, Skosnik PD, D'Souza DC (2016): Marijuana and Madness: Associations Between Cannabinoids and Psychosis. *Biological psychiatry*. 79:511-513.
32. Davis GP, Compton MT, Wang S, Levin FR, Blanco C (2013): Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Schizophrenia research*. 151:197-202.
33. Lev-Ran S, Imtiaz S, Taylor BJ, Shield KD, Rehm J, Le Foll B (2012): Gender differences in health-related quality of life among cannabis users: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and alcohol dependence*. 123:190-200.
34. Stinson FS, Ruan WJ, Pickering R, Grant BF (2006): Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. *Psychological medicine*. 36:1447-1460.
35. NSDUH (2013): Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration.
36. Lopez-Quintero C, Hasin DS, de Los Cobos JP, Pines A, Wang S, Grant BF, et al. (2011): Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction*. 106:657-669.
37. Lopez-Quintero C, Perez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, et al. (2011): Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and alcohol dependence*. 115:120-130.
38. SAMHSA (2010): Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings Rockville, MD.: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Substance Abuse and Mental Health Services Administration Office of Applied Studies.
39. TEDS. (2007): Treatment Episode Data Set (TEDS). High-lights. National Admissions to Substance Abuse Treatment Services, DASIS Series. In: Substance Abuse and Mental Health Services Administration, Studies. OoA, editors. Rockville, MD.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

40. SAMHSA (2006): Treatment Episode Data Set (TEDS):Highlights - 2005. National Admissions to Substance Abuse Treatment Services.
41. Hall W, Degenhardt L (2009): Adverse health effects of non-medical cannabis use. *Lancet*. 374:1383-1391.
42. Hall W (2009): The adverse health effects of cannabis use: what are they, and what are their implications for policy? *The International journal on drug policy*. 20:458-466.
43. Pope HG, Jr., Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D (2001): Neuropsychological performance in long-term cannabis users. *Archives of general psychiatry*. 58:909-915.
44. Pope HG, Jr., Gruber AJ, Yurgelun-Todd D (1995): The residual neuropsychological effects of cannabis: the current status of research. *Drug & Alcohol Dependence*. 38:25-34.
45. Pope HG, Jr., Yurgelun-Todd D (1996): The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 275:521-527.
46. Lundqvist T (2005): Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav*. 81:319-330.
47. Solowij N, Battisti R (2008): The Chronic Effects of Cannabis on Memory in Humans: A Review. *Current Drug Abuse Reviews*. 1:81-98.
48. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL (2002): Dose-related neurocognitive effects of marijuana use. *Neurology*. 59:1337-1343.
49. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. (2007): Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 370:319-328.
50. Chan GC, Hinds TR, Impey S, Storm DR (1998): Hippocampal neurotoxicity of Delta9-tetrahydrocannabinol. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 18:5322-5332.
51. Landfield PW, Cadwallader LB, Vinsant S (1988): Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. *Brain research*. 443:47-62.
52. Landfield PW (1987): Delta-9-tetrahydrocannabinol-dependent alterations in brain structure. *NIDA Res Monogr*. 78:143-157.
53. Lawston J, Borella A, Robinson JK, Whitaker-Azmitia PM (2000): Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. *Brain research*. 877:407-410.
54. Scallet AC (1991): Neurotoxicology of cannabis and THC: a review of chronic exposure studies in animals. *Pharmacol Biochem Behav*. 40:671-676.
55. Matochik JA, Eldreth DA, Cadet JL, Bolla KI (2005): Altered brain tissue composition in heavy marijuana users. *Drug and alcohol dependence*. 77:23-30.
56. Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007): Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol*. 29:141-152.
57. SAMHSA (2014): Treatment Episode Data Set (TEDS): 2002-2012. National Admissions to Substance Abuse Treatment Services. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality.
58. Mechoulam R, Parker LA (2013): The endocannabinoid system and the brain. *Annu Rev Psychol*. 64:21-47.
59. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, et al. (2010): International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev*. 62:588-631.

60. Marrs WR, Blankman JL, Horne EA, Thomazeau A, Lin YH, Coy J, et al. (2010): The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. *Nature neuroscience*. 13:951-957.
61. D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Cooper T, et al. (2008): Blunted Psychotomimetic and Amnestic Effects of Delta-9-Tetrahydrocannabinol in Frequent Users of Cannabis. *Neuropsychopharmacology*.
62. Ranganathan M, Braley G, Pittman B, Cooper T, Perry E, Krystal J, et al. (2008): The effects of cannabinoids on serum cortisol and prolactin in humans. *Psychopharmacology*.
63. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR (2009): Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol*. 23:266-277.
64. Jones RT, Benowitz NL, Herning RI (1981): Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology*. 21:143S-152S.
65. Jones RT, Benowitz N, Bachman J (1976): Clinical studies of cannabis tolerance and dependence. *Annals of the New York Academy of Sciences*. 282:221-239.
66. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999): Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 141:385-394.
67. Fan F, Compton DR, Ward S, Melvin L, Martin BR (1994): Development of cross-tolerance between delta 9-tetrahydrocannabinol, CP 55,940 and WIN 55,212. *J Pharmacol Exp Ther*. 271:1383-1390.
68. De Vry J, Jentzsch KR, Kuhl E, Eckel G (2004): Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development. *Behav Pharmacol*. 15:1-12.
69. Hampson RE, Simeral JD, Kelly EJ, Deadwyler SA (2003): Tolerance to the memory disruptive effects of cannabinoids involves adaptation by hippocampal neurons. *Hippocampus*. 13:543-556.
70. de Miguel R, Romero J, Munoz RM, Garcia-Gil L, Gonzalez S, Villanua MA, et al. (1998): Effects of cannabinoids on prolactin and gonadotrophin secretion: involvement of changes in hypothalamic gamma-aminobutyric acid (GABA) inputs. *Biochem Pharmacol*. 56:1331-1338.
71. Sim-Selley LJ (2003): Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. *Crit Rev Neurobiol*. 15:91-119.
72. Martin BR, Sim-Selley LJ, Selley DE (2004): Signaling pathways involved in the development of cannabinoid tolerance. *Trends Pharmacol Sci*. 25:325-330.
73. Rodriguez de Fonseca F, Gorriti MA, Fernandez-Ruiz JJ, Palomo T, Ramos JA (1994): Downregulation of rat brain cannabinoid binding sites after chronic delta 9-tetrahydrocannabinol treatment. *Pharmacol Biochem Behav*. 47:33-40.
74. Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Vogt LJ, Sim-Selley LJ (1999): Chronic delta9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. *Journal of neurochemistry*. 73:2447-2459.
75. Oviedo A, Glowa J, Herkenham M (1993): Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain research*. 616:293-302.
76. Sim-Selley LJ, Schechter NS, Rorrer WK, Dalton GD, Hernandez J, Martin BR, et al. (2006): Prolonged recovery rate of CB1 receptor adaptation after cessation of long-term cannabinoid administration. *Mol Pharmacol*. 70:986-996.
77. McKinney DL, Cassidy MP, Collier LM, Martin BR, Wiley JL, Selley DE, et al. (2008): Dose-related differences in the regional pattern of cannabinoid receptor adaptation and in vivo tolerance development to delta9-tetrahydrocannabinol. *J Pharmacol Exp Ther*. 324:664-673.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

78. Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ (1997): Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain research Molecular brain research*. 46:100-108.
79. Sim LJ, Hampson RE, Deadwyler SA, Childers SR (1996): Effects of chronic treatment with delta9-tetrahydrocannabinol on cannabinoid-stimulated [35S]GTPgammaS autoradiography in rat brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 16:8057-8066.
80. D'Souza DC, Cortes-Briones JA, Ranganathan M, Thurnauer H, Creatura G, Surti T, et al. (2016): Rapid Changes in CB1 Receptor Availability in Cannabis Dependent Males after Abstinence from Cannabis. *Biological psychiatry : cognitive neuroscience and neuroimaging*. 1:60-67.
81. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, et al. (2012): Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular psychiatry*. 17:642-649.
82. Ceccarini J, Kuepper R, Kemels D, van Os J, Henquet C, Van Laere K (2013): [F]MK-9470 PET measurement of cannabinoid CB receptor availability in chronic cannabis users. *Addiction biology*.
83. Boileau I, Mansouri E, Williams B, Le Foll B, Rusjan P, Mizrahi R, et al. (2016): Fatty Acid Amide Hydrolase Binding in Brain of Cannabis Users: Imaging With the Novel Radiotracer [11C]CURB. *Biological psychiatry*. 80:691-701.
84. Di Marzo V, Berrendero F, Bisogno T, Gonzalez S, Cavaliere P, Romero J, et al. (2000): Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of delta9-tetrahydrocannabinol-tolerant rats. *Journal of neurochemistry*. 74:1627-1635.
85. Morgan CJ, Page E, Schaefer C, Chatten K, Manocha A, Gulati S, et al. (2013): Cerebrospinal fluid anandamide levels, cannabis use and psychotic-like symptoms. *Br J Psychiatry*. 202:381-382.
86. Lichtman AH, Martin BR (2002): Marijuana withdrawal syndrome in the animal model. *J Clin Pharmacol*. 42:20S-27S.
87. Aceto MD, Scates SM, Martin BB (2001): Spontaneous and precipitated withdrawal with a synthetic cannabinoid, WIN 55212-2. *European Journal of Pharmacology*. 416:75-81.
88. Aceto MD, Scates SM, Lowe JA, Martin BR (1996): Dependence on delta 9-tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. *J Pharmacol Exp Ther*. 278:1290-1295.
89. Beardsley PM, Balster RL, Harris LS (1986): Dependence on tetrahydrocannabinol in rhesus monkeys. *J Pharmacol Exp Ther*. 239:311-319.
90. Tsou K, Patrick SL, Walker JM (1995): Physical withdrawal in rats tolerant to delta 9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *Eur J Pharmacol*. 280:R13-15.
91. Rodriguez de Fonseca F, Carrera MR, Navarro M, Koob GF, Weiss F (1997): Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science*. 276:2050-2054.
92. Budney AJ, Hughes JR, Moore BA, Vandrey R (2004): Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*. 161:1967-1977.
93. Budney AJ, Moore BA, Vandrey RG, Hughes JR (2003): The time course and significance of cannabis withdrawal. *Journal of Abnormal Psychology*. 112:393-402.
94. Haney M (2005): The marijuana withdrawal syndrome: diagnosis and treatment. *Curr Psychiatry Rep*. 7:360-366.
95. Murillo-Rodriguez E (2008): The role of the CB1 receptor in the regulation of sleep. *Prog Neuropsychopharmacol Biol Psychiatry*. 32:1420-1427.

96. Pava MJ, den Hartog CR, Blanco-Centurion C, Shiromani PJ, Woodward JJ (2014): Endocannabinoid modulation of cortical up-states and NREM sleep. *PloS one*. 9:e88672.
97. Kouri EM, Pope HG, Jr. (2000): Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol*. 8:483-492.
98. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, et al. (2006): Cannabis withdrawal among non-treatment-seeking adult cannabis users. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 15:8-14.
99. Jones RT, Benowitz N, Bachman J (1976): Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci*. 282:221-239.
100. Budney AJ, Hughes JR, Moore BA, Novy PL (2001): Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Archives of general psychiatry*. 58:917-924.
101. Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, et al. (2004): Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 29:158-170.
102. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B (2007): Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug and alcohol dependence*. 86:22-29.
103. Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z (2008): Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. *J Subst Abuse Treat*. 35:362-368.
104. Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, et al. (2010): Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend*. 111:120-127.
105. Roehrs T, Papineau K, Rosenthal L, Roth T (1999): Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. *Neuropsychopharmacology*. 20:279-286.
106. Bishop C, Roehrs T, Rosenthal L, Roth T (1997): Alerting effects of methylphenidate under basal and sleep-deprived conditions. *Exp Clin Psychopharmacol*. 5:344-352.
107. Roehrs T, Papineau K, Rosenthal L, Roth T (1999): Sleepiness and the reinforcing and subjective effects of methylphenidate. *Exp Clin Psychopharmacol*. 7:145-150.
108. Roehrs T, Johanson CE, Meixner R, Turner L, Roth T (2004): Reinforcing and subjective effects of methylphenidate: dose and time in bed. *Exp Clin Psychopharmacol*. 12:180-189.
109. Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT (2006): Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: Evidence for occult insomnia. *Drug and alcohol dependence*. 82:238-249.
110. Angarita GA, Emadi N, Hodges S, Morgan PT (2016): Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. *Addiction science & clinical practice*. 11:9.
111. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, et al. (2008): Sleep disturbance in heavy marijuana users. *Sleep*. 31:901-908.
112. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR, et al. (2010): Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med*. 11:882-889.
113. Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM (2011): Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend*.
114. Freemon FR (1972): Effects of marihuana on sleeping states. *JAMA*. 220:1364-1365.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

115. Freemon FR (1982): The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug and alcohol dependence*. 10:345-353.
116. Feinberg I, Jones R, Walker JM, Cavness C, March J (1975): Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther*. 17:458-466.
117. Schierenbeck T, Riemann D, Berger M, Hornyak M (2008): Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev*. 12:381-389.
118. Feinberg I, Jones R, Walker J, Cavness C, Floyd T (1976): Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther*. 19:782-794.
119. Adams PM, Barratt ES (1975): Effect of chronic marijuana administration of stages of primate sleep-wakefulness. *Biological psychiatry*. 10:315-322.
120. Pivik RT, Zarcone V, Dement WC, Hollister LE (1972): Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clin Pharmacol Ther*. 13:426-435.
121. Budney AJ, Hughes JR (2006): The cannabis withdrawal syndrome. *Current opinion in psychiatry*. 19:233-238.
122. Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, et al. (2010): Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug and alcohol dependence*. 111:120-127.
123. Denis C, Lavie E, Fatseas M, Auriacombe M (2006): Psychotherapeutic interventions for cannabis abuse and/or dependence in outpatient settings. *The Cochrane database of systematic reviews*. 3:CD005336.
124. Copeland J, Swift W, Roffman R, Stephens R (2001): A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. *J Subst Abuse Treat*. 21:55-64; discussion 65-56.
125. Dennis M, Godley SH, Diamond G, Tims FM, Babor T, Donaldson J, et al. (2004): The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. *J Subst Abuse Treat*. 27:197-213.
126. MTPRG (2004): Marijuana Treatment Project Research Group, Brief treatments for cannabis dependence: findings from a randomized multisite trial. *J Consult Clin Psychol*. 72:455-466.
127. Stephens RS, Roffman RA, Curtin L (2000): Comparison of extended versus brief treatments for marijuana use. *J Consult Clin Psychol*. 68:898-908.
128. Budney AJ, Moore BA, Rocha HL, Higgins ST (2006): Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *J Consult Clin Psychol*. 74:307-316.
129. Kadden RM, Litt MD, Kabela-Cormier E, Petry NM (2007): Abstinence rates following behavioral treatments for marijuana dependence. *Addict Behav*. 32:1220-1236.
130. Anggadiredja K, Yamaguchi T, Tanaka H, Shoyama Y, Watanabe S, Yamamoto T (2003): Prostaglandin E2 attenuates SR141716A-precipitated withdrawal in tetrahydrocannabinol-dependent mice. *Brain Res*. 966:47-53.
131. Verberne AJ, Taylor DA, Fennessy MR (1981): Attenuation of delta 9-tetrahydrocannabinol-induced withdrawal-like behaviour by delta 9-tetrahydrocannabinol. *Psychopharmacology*. 73:97-98.
132. Lichtman AH, Sheikh SM, Loh HH, Martin BR (2001): Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. *J Pharmacol Exp Ther*. 298:1007-1014.
133. Cui SS, Bowen RC, Gu GB, Hannesson DK, Yu PH, Zhang X (2001): Prevention of cannabinoid withdrawal syndrome by lithium: involvement of oxytocinergic neuronal activation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 21:9867-9876.

134. Balter RE, Cooper ZD, Haney M (2014): Novel Pharmacologic Approaches to Treating Cannabis Use Disorder. *Curr Addict Rep*. 1:137-143.
135. Gorelick DA (2016): Pharmacological Treatment of Cannabis-Related Disorders: A Narrative Review. *Current pharmaceutical design*. 22:6409-6419.
136. Marshall K, Gowing L, Ali R, Le Foll B (2014): Pharmacotherapies for cannabis dependence. *The Cochrane database of systematic reviews*.CD008940.
137. Sherman BJ, McRae-Clark AL (2016): Treatment of Cannabis Use Disorder: Current Science and Future Outlook. *Pharmacotherapy*. 36:511-535.
138. Walther L, Gantner A, Heinz A, Majic T (2016): Evidence-based Treatment Options in Cannabis Dependency. *Deutsches Arzteblatt international*. 113:653-659.
139. Weinstein AM, Gorelick DA (2011): Pharmacological Treatment of Cannabis Dependence. *Current pharmaceutical design*.
140. Levin FR, Kleber HD (2008): Use of dronabinol for cannabis dependence: two case reports and review. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 17:161-164.
141. Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV (2011): Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend*.
142. Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. (2014): Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA psychiatry*. 71:281-291.
143. Trigo JM, Soliman A, Staios G, Quilty L, Fischer B, George TP, et al. (2016): Sativex Associated With Behavioral-Relapse Prevention Strategy as Treatment for Cannabis Dependence: A Case Series. *J Addict Med*. 10:274-279.
144. Huestis MA, Boyd SJ, Heishman SJ, Preston KL, Bonnet D, Le Fur G, et al. (2007): Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. *Psychopharmacology (Berl)*. 194:505-515.
145. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, et al. (2001): Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Archives of General Psychiatry*. 58:322-328.
146. Haney M, Ward AS, Comer SD, Hart CL, Foltin RW, Fischman MW (2001): Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology*. 155:171-179.
147. Haney M, Hart CL, Ward AS, Foltin RW (2003): Nefazodone decreases anxiety during marijuana withdrawal in humans. *Psychopharmacology*. 165:157-165.
148. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR (2009): A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 18:53-64.
149. Findling RL, Pagano ME, McNamara NK, Stansbrey RJ, Faber JE, Lingler J, et al. (2009): The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 3:11.
150. Weinstein AM, Miller H, Bluvstein I, Rapoport E, Schreiber S, Bar-Hamburger R, et al. (2014): Treatment of cannabis dependence using escitalopram in combination with cognitive-behavior therapy: a double-blind placebo-controlled study. *The American journal of drug and alcohol abuse*. 40:16-22.
151. Levin FR, Mariani J, Brooks DJ, Pavlicova M, Nunes EV, Agosti V, et al. (2013): A randomized double-blind, placebo-controlled trial of venlafaxine-extended release for co-occurring cannabis dependence and depressive disorders. *Addiction*. 108:1084-1094.

152. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW (2008): Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 197:157-168.
153. Nanjayya SB, Shivappa M, Chand PK, Murthy P, Benegal V (2010): Baclofen in cannabis dependence syndrome. *Biological psychiatry*. 68:e9-10.
154. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, et al. (2010): Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 211:233-244.
155. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, Wahlquist AE, Simpson SA, et al. (2009): A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug and alcohol dependence*. 105:132-138.
156. McRae AL, Brady KT, Carter RE (2006): Buspirone for treatment of marijuana dependence: a pilot study. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 15:404.
157. McRae-Clark AL, Baker NL, Gray KM, Killeen TK, Wagner AM, Brady KT, et al. (2015): Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial. *Drug and alcohol dependence*. 156:29-37.
158. McRae-Clark AL, Baker NL, Gray KM, Killeen T, Hartwell KJ, Simonian SJ (2016): Vilazodone for cannabis dependence: A randomized, controlled pilot trial. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 25:69-75.
159. Winstock AR, Lea T, Copeland J (2009): Lithium carbonate in the management of cannabis withdrawal in humans: an open-label study. *J Psychopharmacol*. 23:84-93.
160. Levin FR, McDowell D, Evans SM, Nunes E, Akerele E, Donovan S, et al. (2004): Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 13:21-32.
161. Morley KC, Haber PS, Morgan ML, Samara F (2012): Pericyazine in the treatment of cannabis dependence in general practice: a naturalistic pilot trial. *Subst Abuse Rehabil*. 3:43-47.
162. Geoffroy PA, Rolland B, Guardia D, Warembourg F, Cottencin O (2012): Use of aripiprazole in treatment of cannabis dependence in a patient presenting with Borderline Personality Disorder. *The Journal of neuropsychiatry and clinical neurosciences*. 24:E37.
163. Mariani JJ, Pavlicova M, Mamczur AK, Bisaga A, Nunes EV, Levin FR (2014): Open-label pilot study of quetiapine treatment for cannabis dependence. *The American journal of drug and alcohol abuse*. 40:280-284.
164. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, et al. (2012): A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology*. 37:1689-1698.
165. Greenwald MK, Stitzer ML (2000): Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug and alcohol dependence*. 59:261-275.
166. Wachtel SR, de Wit H (2000): Naltrexone does not block the subjective effects of oral Delta(9)-tetrahydrocannabinol in humans. *Drug and alcohol dependence*. 59:251-260.
167. Haney M (2007): Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. *Neuropsychopharmacology*. 32:1391-1403.
168. Cooper ZD, Haney M (2010): Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology*. 211:141-148.
169. Haney M, Bisaga A, Foltin RW (2003): Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology*. 166:77-85.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

170. Gray KM, Watson NL, Carpenter MJ, Larowe SD (2010): N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. *Am J Addict*. 19:187-189.
171. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al. (2012): A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry*. 169:805-812.
172. Tirado CF, Goldman M, Lynch K, Kampman KM, Obrien CP (2008): Atomoxetine for treatment of marijuana dependence: a report on the efficacy and high incidence of gastrointestinal adverse events in a pilot study. *Drug and alcohol dependence*. 94:254-257.
173. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, White KG, Brady KT (2010): A placebo-controlled trial of atomoxetine in marijuana-dependent individuals with attention deficit hyperactivity disorder. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 19:481-489.
174. Shafa R (2009): COMT- Inhibitors may be a Promising Tool in Treatment of Marijuana Addiction Trials. . *American Journal on Addictions*. 18:322.
175. Vandrey R, Haney M (2009): Pharmacotherapy for cannabis dependence: how close are we? *CNS drugs*. 23:543-553.
176. Nordstrom BR, Levin FR (2007): Treatment of cannabis use disorders: a review of the literature. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 16:331-342.
177. Hart CL, Haney M, Vosburg SK, Comer SD, Foltin RW (2005): Reinforcing effects of oral Delta9-THC in male marijuana smokers in a laboratory choice procedure. *Psychopharmacology*. 181:237-243.
178. Devane WA, Axelrod J (1994): Enzymatic synthesis of anandamide, an endogenous ligand for the cannabinoid receptor, by brain membranes. *Proceedings of the National Academy of Sciences of the United States of America*. 91:6698-6701.
179. Martin AR, Consroe P, Kane VV, Shah V, Singh V, Lander N, et al. (1987): Structure-anticonvulsant activity relationships of cannabidiol analogs. *NIDA Research Monograph*. 79:48-58.
180. Desarnaud F, Cadas H, Piomelli D (1995): Anandamide amidohydrolase activity in rat brain microsomes. Identification and partial characterization. *The Journal of biological chemistry*. 270:6030-6035.
181. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB (1996): Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. *Nature*. 384:83-87.
182. Giang DK, Cravatt BF (1997): Molecular characterization of human and mouse fatty acid amide hydrolases. *Proceedings of the National Academy of Sciences of the United States of America*. 94:2238-2242.
183. Ueda N, Kurahashi Y, Yamamoto S, Tokunaga T (1995): Partial purification and characterization of the porcine brain enzyme hydrolyzing and synthesizing anandamide. *The Journal of biological chemistry*. 270:23823-23827.
184. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, et al. (2001): Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc Natl Acad Sci U S A*. 98:9371-9376.
185. Fegley D, Gaetani S, Duranti A, Tontini A, Mor M, Tarzia G, et al. (2005): Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester (URB597): effects on anandamide and oleoylethanolamide deactivation. *J Pharmacol Exp Ther*. 313:352-358.
186. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, et al. (2001): Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proceedings of the National Academy of Sciences of the United States of America*. 98:9371-9376.

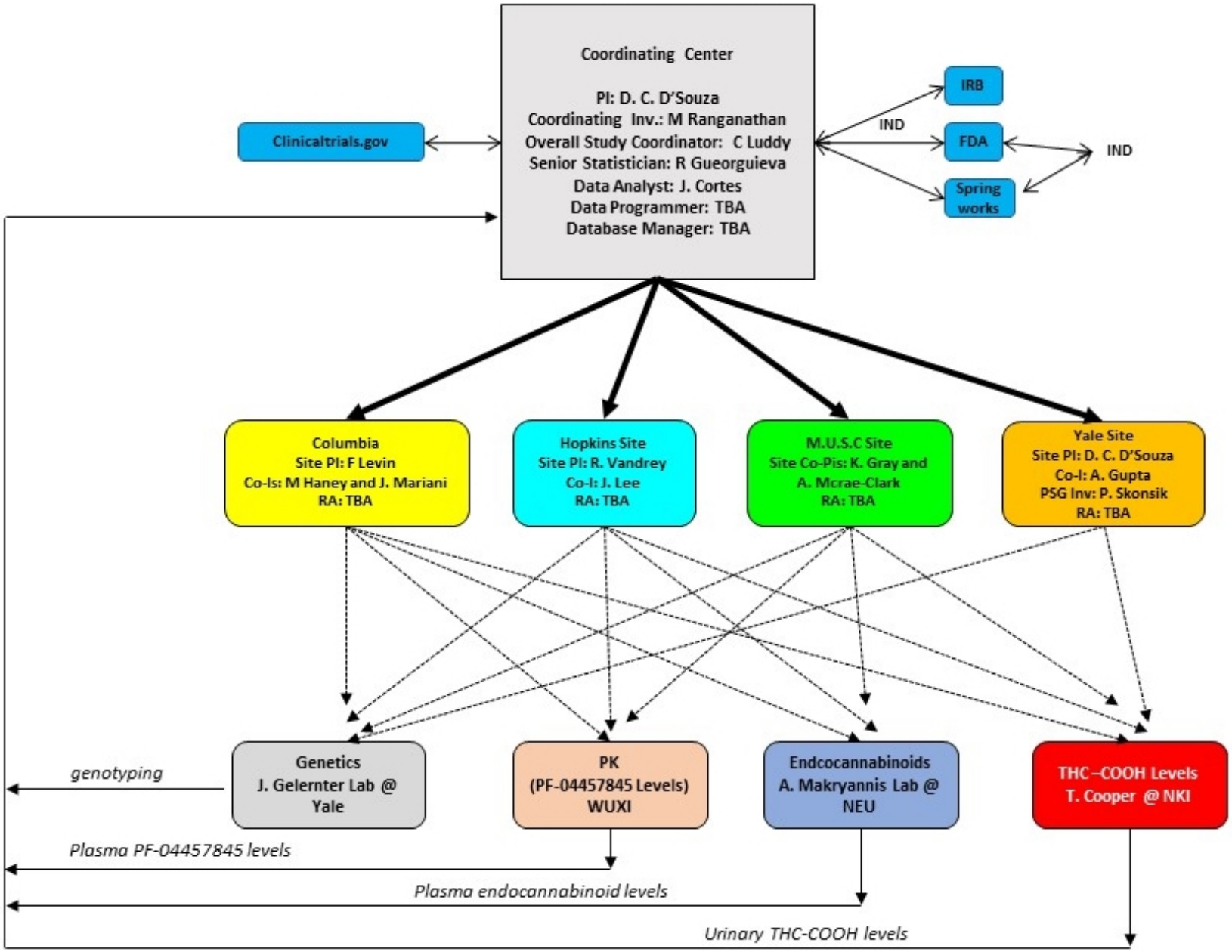
187. Falenski KW, Thorpe AJ, Schlosburg JE, Cravatt BF, Abdullah RA, Smith TH, et al. (2010): FAAH-/- mice display differential tolerance, dependence, and cannabinoid receptor adaptation after delta 9-tetrahydrocannabinol and anandamide administration. *Neuropsychopharmacology*. 35:1775-1787.
188. Lichtman AH, Hawkins EG, Griffin G, Cravatt BF (2002): Pharmacological activity of fatty acid amides is regulated, but not mediated, by fatty acid amide hydrolase in vivo. *J Pharmacol Exp Ther*. 302:73-79.
189. Lichtman AH, Shelton CC, Advani T, Cravatt BF (2004): Mice lacking fatty acid amide hydrolase exhibit a cannabinoid receptor-mediated phenotypic hypoalgesia. *Pain*. 109:319-327.
190. Di Marzo V (2009): The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation. *Pharmacol Res*. 60:77-84.
191. Piomelli D, Tarzia G, Duranti A, Tontini A, Mor M, Compton TR, et al. (2006): Pharmacological profile of the selective FAAH inhibitor KDS-4103 (URB597). *CNS Drug Rev*. 12:21-38.
192. Justinova Z, Mangieri RA, Bortolato M, Chefer SI, Mukhin AG, Clapper JR, et al. (2008): Fatty acid amide hydrolase inhibition heightens anandamide signaling without producing reinforcing effects in primates. *Biological psychiatry*. 64:930-937.
193. Solinas M, Tanda G, Justinova Z, Wertheim CE, Yasar S, Piomelli D, et al. (2007): The endogenous cannabinoid anandamide produces delta-9-tetrahydrocannabinol-like discriminative and neurochemical effects that are enhanced by inhibition of fatty acid amide hydrolase but not by inhibition of anandamide transport. *J Pharmacol Exp Ther*. 321:370-380.
194. Solinas M, Justinova Z, Goldberg SR, Tanda G (2006): Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats. *Journal of neurochemistry*. 98:408-419.
195. Schlosburg JE, Carlson BL, Ramesh D, Abdullah RA, Long JZ, Cravatt BF, et al. (2009): Inhibitors of endocannabinoid-metabolizing enzymes reduce precipitated withdrawal responses in THC-dependent mice. *Aaps J*. 11:342-352.
196. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. (2005): Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences of the United States of America*. 102:18620-18625.
197. Ahn K, Johnson DS, Mileni M, Beidler D, Long JZ, McKinney MK, et al. (2009): Discovery and characterization of a highly selective FAAH inhibitor that reduces inflammatory pain. *Chem Biol*. 16:411-420.
198. Ahn K, Smith SE, Liimatta MB, Beidler D, Sadagopan N, Dudley DT, et al. (2011): Mechanistic and pharmacological characterization of PF-04457845: a highly potent and selective FAAH inhibitor that reduces inflammatory and noninflammatory pain. *J Pharmacol Exp Ther*.
199. Johnson DS, Stiff C, Lazerwith SE, Kesten SR, Fay LK, Morris M, et al. (2011): Discovery of PF-04457845: A Highly Potent, Orally Bioavailable, and Selective Urea FAAH Inhibitor. *ACS medicinal chemistry letters*. 2:91-96.
200. Li GL, Winter H, Arends R, Jay GW, Le V, Young T, et al. (2012): Assessment of the pharmacology and tolerability of PF-04457845, an irreversible inhibitor of fatty acid amide hydrolase-1, in healthy subjects. *British journal of clinical pharmacology*. 73:706-716.
201. Huggins JP, Smart TS, Langman S, Taylor L, Young T (2012): An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain*. 153:1837-1846.

202. Collie A, Darekar A, Weissgerber G, Toh MK, Snyder PJ, Maruff P, et al. (2007): Cognitive testing in early-phase clinical trials: development of a rapid computerized test battery and application in a simulated Phase I study. *Contemporary clinical trials*. 28:391-400.
203. DeWorsop D, Creatura G, Bluez G, Thurnauer H, Forselius-Bielen K, Ranganathan M, et al. (2016): Feasibility and success of cell-phone assisted remote observation of medication adherence (CAROMA) in clinical trials. *Drug Alcohol Depend*. 163:24-30.
204. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. (2004): The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 29:1558-1572.
205. Shaw LM, Edling-Owens J, Mattes R (1991): Ultrasensitive measurement of delta-9-tetrahydrocannabinol with a high energy dynode detector and electron-capture negative chemical-ionization mass spectrometry. *Clinical chemistry*. 37:2062-2068.
206. Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE (2010): Individual and additive effects of the CNR1 and FAAH genes on brain response to marijuana cues. *Neuropsychopharmacology*. 35:967-975.
207. Haughey HM, Marshall E, Schacht JP, Louis A, Hutchison KE (2008): Marijuana withdrawal and craving: influence of the cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH) genes. *Addiction*. 103:1678-1686.
208. Schacht JP, Selling RE, Hutchison KE (2009): Intermediate cannabis dependence phenotypes and the FAAH C385A variant: an exploratory analysis. *Psychopharmacology*. 203:511-517.
209. Sherva R, Wang Q, Kranzler H, Zhao H, Koesterer R, Herman A, et al. (2016): Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks. *JAMA psychiatry*. 73:472-480.
210. First MB, Spitzer RL, Gibbon M, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders- Non-patient Edition* Washington,DC.: American Psychiatric Association.
211. Heatherton T, Kozlowski L, Frecker R, Fagerstrom K (1991): The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Brit J Addiction*. 86:1119-1127.
212. Sobell LC, Toneatto T, Sobell MB, Leo GI, Johnson L (1992): Alcohol abusers' perceptions of the accuracy of their self-reports of drinking: implications for treatment. *Addictive Behaviors*. 17:507-511.
213. Budney AJ, Novy PL, Hughes JR (1999): Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction*. 94:1311-1322.
214. Heishman SJ, Singleton EG, Liguori A (2001): Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. *Addiction*. 96:1023-1034.
215. Heishman SJ, Evans RJ, Singleton EG, Levin KH, Copersino ML, Gorelick DA (2009): Reliability and validity of a short form of the Marijuana Craving Questionnaire. *Drug and alcohol dependence*. 102:35-40.
216. Slavet JD, Stein LA, Colby SM, Barnett NP, Monti PM, Golembeske C, Jr., et al. (2006): The Marijuana Ladder: measuring motivation to change marijuana use in incarcerated adolescents. *Drug and alcohol dependence*. 83:42-48.
217. Clyde DJ (1986): SAFTEE: data system for side effect assessment scale. *Psychopharmacol Bull*. 22:287.
218. Levine J, Schooler NR (1986): SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 22:343-381.
219. Levine J, Schooler NR (1992): General versus specific inquiry with SAFTEE. *J Clin Psychopharmacol*. 12:448.

220. Kosmadopoulos A, Sargent C, Darwent D, Zhou X, Roach GD (2014): Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system. *Behav Res Methods*. 46:1032-1041.
221. Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. (2007): Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep*. 30:519-529.
222. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP (2003): The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*. 26:342-392.
223. Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM, et al. (2013): Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep*. 36:1747-1755.
224. Baandrup L, Jennum PJ (2015): A validation of wrist actigraphy against polysomnography in patients with schizophrenia or bipolar disorder. *Neuropsychiatric disease and treatment*. 11:2271-2277.
225. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999): Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 141:385-394.
226. Brunner E, Domhof S, Langer F (2002): *Nonparametric analysis of longitudinal data in factorial experiments*. New York: John Wiley and Sons.
227. Noguchi K, Gel YR, Brunner E, Konietschke F (2012): nparLD: An R software package for the nonparametric analysis of longitudinal data in factorial experiments. *Journal of Statistical Software*. 50:1-23.
228. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

APPENDIX A: STUDY ORGANIZATION CHART



APPENDIX B: ADVERTISEMENTS

Radio Advertisement:

Do you smoke marijuana/cannabis? Is it interfering with work or school? If you want to quit using marijuana you may be eligible for a paid research study. A research clinic at __(study site)__ is studying a medication that may help people quit marijuana/cannabis, __(IRB number)__. If you are male or female, between the ages of 18 and 60, smoke marijuana/cannabis, and want to quit, please call us at __(phone number)__. All calls and information gathered are confidential. Again that's __(phone number)__.

Online Advertisement:

Title: SMOKE MARIJUANA/CANNABIS? Want to quit?
Do you smoke marijuana regularly and want to quit?
A research group at __(study site)__ is running a paid clinical trial investigating a medication designed to help with the symptoms of marijuana withdrawal.
Participants must be:

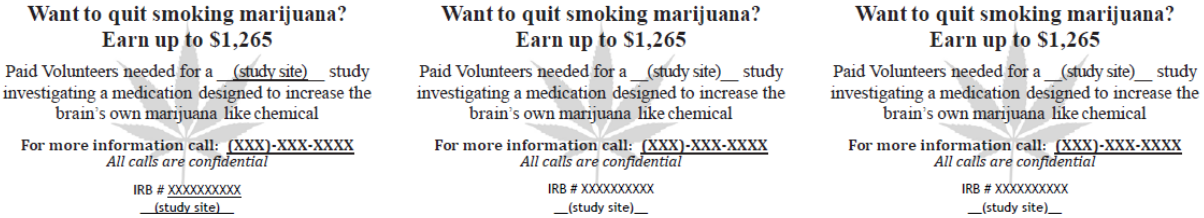
- Ages 18-50
- In good physical and mental health
- Willing to try quitting marijuana/cannabis for eight weeks

Participants must NOT be:

- Abusing any other drugs or alcohol

If you would like to try quitting marijuana/cannabis and want more information about this study, please call us at (XXX) XXX-XXXX
All information is kept confidential.
IRB # XXXXXXXXXX

Mini-Flier Advertisement:



Full Page Advertisements:

APPENDIX C: PHONE SCREEN QUESTIONNAIRE

Read Verbatim to Participant:

"We would like to ask you some general information to determine whether you might qualify for studies at our research group. This information will only be used to determine your eligibility to participate in research. This information will be stored in secure research files. If you do not want any information about you stored, we will terminate this interview now. If you agree to proceed ahead with this preliminary interview and seem to be eligible to participate in this study, we may invite you for a face to face meeting. Would you like to continue?"

YES / NO

Name (First Last): _____

Age at Phone Screen: _____ DOB: _____ Gender: _____

Phone #1: _____ Phone Type: _____

Phone #2: _____ Phone Type: _____

Email Address: _____

Preferred contact? Phone #1 / Phone #2 / Email Address

Highest level of education: _____

What race do you identify with: _____

Are you currently participating in research or within the past 30 days (Details: Where, Meds, Blood, etc): YES / NO

_____

_____

Can we keep your information on file to be able to contact you for future studies: YES / NO

Are you currently working? YES / NO

If yes, current job: _____ How long at current job: _____

If no, why: _____

Do you have a flexible Schedule: YES / NO

_____

Do you use marijuana/cannabis: YES / NO

How often do you typically use

marijuana/cannabis:_____

How much do you spend per month on marijuana/cannabis:

_____

How long have you smoked at this rate:_____

Would you say that marijuana/cannabis is your primary drug of choice (or do you like to use anything else with marijuana/cannabis)? Yes / No

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

About how many drinks do you have a week? What days do you typically drink? What types of alcohol do you consume? (determine alcohol for the month):

_____

_____

Date of your last drink: _____

How many drinks did you have: _____

Has alcohol ever been a problem for you: YES / NO Have you ever had a DWI: YES / NO

Have you used any other street drugs in the past 3 months? (MJ, Salvia, Spice, Cocaine, Heroin, Speed, Hallucinogens, prescription meds recreationally? etc.): Yes / No

_____

_____

_____

_____

Can you remember the last time you quit smoking even if it was just for a few days or weeks (why, when, how long, etc.)

_____

_____

What street drugs have you used over your lifetime? (MJ, Salvia, Spice, Cocaine, Heroin, Speed, Hallucinogens, prescription meds recreationally, etc.)?

Drug	Date of last use	Time period of Heaviest Use	Frequency (daily, weekly….)	Approx amount per use (gram, oz., joint, # pills)

How much caffeine do you have per day? _____

Do you currently smoke or use tobacco: Yes / No

How much tobacco do you currently use:_____

Were you ever a cigarette smoker? Yes / No When and how much did you use?:_____

Do you have any medical problems right now: Yes / No

Do you use any prescription or over the counter medication or vitamins or supplements (type and duration)?

_____

_____

Do you have diabetes: Yes / No _____

Any Surgeries: Yes / No
(what and when) _____

Any seizures or fainting spells: Yes / No

_____

_____

Are you allergic to any medications? Yes / No

_____

_____

Are you allergic to any food? Yes / No

_____

_____

Have you had any medical problems in the past: Yes / No
If yes, please specify:

Head (Such as: Head Injury? Loss of consciousness or Infection of the brain?)

_____

Heart (Such as: Heart Attack or Heart disease?)

_____

Lungs or Asthma (Such as: Lung disease?)

_____

Liver (Such as: Liver disease?)

_____

Kidney (Such as: Kidney disease?)

_____

Stomach (Such as: Intestinal problems?)

_____

Circulatory (Such as: High blood pressure?)

_____

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

Have you given any blood donations recently: Yes / No When: _____

Any other medical issues or important things that we should be aware of?

_____

_____

_____

_____

Have you ever seen a counselor or therapist: Yes / No

If yes, please explain (Duration, Diagnosis, Time-period, Meds, problem resolved?):

_____

_____

Have you ever been hospitalized for any psychiatric, mental, or emotional problems: Yes / No
If yes, please explain (when, how long, how close to event):

_____

Notes:_____

_____

_____

_____

_____

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

APPENDIX D: CONSENT QUESTIONNAIRE

This is a questionnaire to help us to test your understanding of the study protocol. For you to qualify for this study, you will need to pass this quiz. To pass, you will need to score at least a 75%, and you will have 2 chances to do so. Incorrect answers on your first attempt will tell us those parts of the study you did not understand well, so that we can go over the consent form again with you.

1. You are invited to participate in this study because of (choose one best response):
    a. use of heroin
    b. use of cannabis
    c. use of alcohol
    d. use of tobacco

2. Is this study voluntary? YES NO

3. Once you start the study, are you free to stop at any time? YES NO

4. Please circle the names of the 2 study medications that you may receive in this study:

TX-12235946	Abilify	Placebo
Thiothixene	PF-04457845	Methadone

5. What is the chance of you receiving the active study medication?
    a. 50:50 c. 30:70
    b. 60:40 d. 90:10

6. Will you be told what medication you have been assigned to take? YES NO

7. How long will you be asked to take the study medication?
    a. 2 weeks d. 8 weeks
    b. 4 weeks e. 10 weeks
    c. 6 weeks

8. Do you have to pay for the study medication? YES NO

9. Will urine be collected for drug testing? YES NO

10. Will blood be drawn in this study? YES NO

APPENDIX E: INCLUSION / EXCLUSION CRITERIA CHECKLIST

INCLUSION CRITERIA

1. Ages 18-60 years, inclusive (age verified picture identification).	Yes ☐ No ☐
2. Male or Female.	Yes ☐ No ☐
3. Individuals with DSM-V criteria for CUD of at least moderate severity (≥ 4 [of 11] symptoms).	Yes ☐ No ☐
4. Current cannabis consumption greater than or equal to 30 joints/month (approximately daily) over the past 3 months	Yes ☐ No ☐
5. Positive for urinary THC-COOH on two separate occasions during screening (> 50ng/ml).	Yes ☐ No ☐
6. Primary drug of choice cannabis.	Yes ☐ No ☐
7. Must express a willingness at screening to set a date within the first week of randomization to *attempt* to quit using cannabis.	Yes ☐ No ☐
8. Physically healthy i.e., no clinically unstable medical conditions at the discretion of the investigator.	Yes ☐ No ☐
9. Have given written informed consent, and have capacity to consent and comply with study procedures.	Yes ☐ No ☐
10. Must be able to read English as per the judgment of the site investigators. Participants are required to be able to read because there are several self-administered measures that they must read, understand and provide written answers.	Yes ☐ No ☐
11. Must provide the name of at least 1 contact (preferably 2), who would assist study staff in locating them during the study period.	Yes ☐ No ☐
12. For women of childbearing potential (WOCBP) and men, willingness to practice birth control and to inform study staff immediately if either they (for women) or their partner (for men) becomes pregnant.	Yes ☐ No ☐
13. Must be willing to complete a number of study assessments and procedures remotely.	Yes ☐ No ☐

EXCLUSION CRITERIA

1. Clinically significant unstable medical disorders (as determined by the site investigator) that will increase potential risk or interfere with study participation e.g., ongoing seizure disorder, uncompensated congestive heart failure, uncontrolled severe diabetes, uncontrolled severe hypertension, etc.	Yes ☐ No ☐
2. Laboratory tests with clinically significant abnormalities (as determined by the site investigator)	Yes ☐ No ☐
3. Positive urine toxicology screen for another drug with clinical evidence of use disorder for that drug (with the exception of THC-COOH at screening).	Yes ☐ No ☐
4. Pregnancy by history and or laboratory confirmation (serum HCG).	Yes ☐ No ☐
5. Lactation.	Yes ☐ No ☐
6. Other DSM-5 substance use disorder in the past three months (excluding cannabis, nicotine, caffeine, and mild alcohol use disorder [≤ 3 criteria]).	Yes ☐ No ☐
7. Physiological dependence on another prescribed (e.g. benzodiazepine), not prescribed licit (e.g. alcohol or benzodiazepine) or illicit substance	Yes ☐ No ☐

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

(e.g. opioid) requiring medical management, such as alcohol, opioids, or benzodiazepines, excluding caffeine, and nicotine.	
8. Abstinence from cannabis for more than 1 week at the time of randomization.	Yes ☐ No ☐
9. Meeting DSM-5 criteria for current serious mental illness (e.g., major depression, bipolar disorder, schizophrenia, any psychotic illness, including substance-induced psychosis, and current substance-induced mood disorder. Individuals who meet criteria for current major depression at a mild severity may be included at the discretion of the site principal investigator.	Yes ☐ No ☐
10. Lifetime history of DSM-5 bipolar disorder or any psychotic disorder.	Yes ☐ No ☐
11. Meeting DSM-5 criteria for any psychiatric disorder that may, according to the investigator's judgment, require initiation of a pharmacological or non-pharmacological intervention over the course of the study.	Yes ☐ No ☐
12. Taking psychotropic medication/s that could interfere with interpretation of the study results or interact with study medication. Includes but is not limited to opioid analgesics, sedative hypnotics, or other known CNS depressants, etc. Exceptions include preexisting treatment with sleep agents, antidepressants for preexisting stable insomnia or depression, respectively.	Yes ☐ No ☐
13. Current moderate risk for suicide as measured by the Columbia Suicide Severity Rating Scale (CSSRS) suicidal ideation (in the last month) score of greater than 2 and a history of recent (past 1 year) serious suicide attempt (lethality score of >2 on CSSRS).	Yes ☐ No ☐
14. Current or past history of significant violence (past 2 years).	Yes ☐ No ☐
15. Currently in a residential treatment setting in which substance use is monitored and restricted, since the restricted access to drugs could represent an important confounding variable.	Yes ☐ No ☐
16. Participants who, in the investigator's opinion, would be unable to comply with study procedures or assessments, or would be unacceptable study candidates (e.g., poses threat to staff).	Yes ☐ No ☐
17. Participation in a clinical trial and receipt of investigational drug(s) during past 30 days.	Yes ☐ No ☐
18. Known allergy to FAAH-inhibitors	Yes ☐ No ☐
19. Co-medication with CYP3A inhibitor, CYP3A inducers, or P-glycoprotein substrates, within 48 hours or 5 half-lives prior to baseline, at the discretion of the site investigator	Yes ☐ No ☐

Eligible: Y / N

PI Signature: _____ Date: ___ / ___ / ____

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022

APPENDIX F: COLLATERAL CONTACT QUESTIONNAIRE

Date: ___ / ___ / _____

Collateral Contact Name: _____

Phone Number: (___) ____ - _____

Relationship to Participant: _____

Dear _____,

__(participant)__ is being considered for a research study at our center. To qualify for the study, participants are expected to be free of any medical or psychiatric history. __(participant)__ has identified you as a reliable source of information. __(participant)__ has signed a release of information to permit us to contact you.

To the best of your knowledge, does __(participant)__ have any history of mental illness? Y / N

If yes, please explain:_____

To the best of your knowledge, does (participant) have any history of medical problems? Y / N

If yes, please explain:_____

To the best of your knowledge, does __(participant)__ have any history of substance abuse problems with marijuana/cannabis? Y / N

To the best of your knowledge, does _(participant)_ have any history of substance abuse problems with any substance other than marijuana/cannabis (i.e. alcohol, cocaine, heroin, etc.)? Y / N

To the best of your knowledge, is there any reason __(participant)__ should not participate in a research study? Y / N

If yes, why not? _____

Thank you for your time.

Sincerely,

__(site principal investigator)__

APPENDIX G: COMMITMENT TO ATTEMPT QUITTING QUESTIONNAIRE

1. Identify your personal reasons for quitting. For some, those reasons are to feel better, to live longer, to set a good example for their children, to cut their risk of heart attack or to save money. Of all the reasons to quit, yours matter most.

My main reasons for quitting are:

_____

_____

2. Think of people, places and things that you associate with using. Identify ways to change your routine to make using more difficult, impossible or unnecessary. For example, ride your bike, go to the movies, walk the dog, try a new recipe, visit the dentist for a cleaning, get a manicure, start a garden, write a love letter . . .

My new routines and behaviors:

_____

_____

3. What sets off cravings? List as many as you can think of, such as drinking alcohol or coffee, being around other smokers or working under pressure. Plan ways to avoid these triggers and quell urges.

My strategies for overcoming cravings include:

_____

_____

4. Where can you find support and encouragement? Think of family members, friends and co-workers who are willing to help you if you need them to.

My support network includes:

_____

_____

5. You should set a quit date that falls within the first week of the treatment phase. For you the first week of treatment will begins on __/__/__ and ends on __/__/__. If you use mostly when relaxing or socializing, pick a weekday. If you smoke mostly at work, pick a day on a weekend or during a vacation. Once you set the date, try and share this with those who support you, and stick to it.

I agree that I will attempt to quit using cannabis or cannabis based products during the first week of the treatment phase of the study, and if successful I could receive $50. My quit date is: __/__/__

Committed to and signed by: _____on __/__/__

In the presence of: _____ on __/__/__

APPENDIX H: CELL PHONE ASSISTED REMOTE OBSERVATION OF ADHERENCE (CAROMA) INSTRUCTIONS

Cellphone Assisted Remote Observation of Medication Adherence (CAROMA) refers to the system of visually confirming daily medication compliance for the purposes of a clinical trial using cellphones. Participants in this trial are provided with a cellphone with video capabilities (iPhone) and video calling software (Skype) necessary to transmit high quality video. Video calling is conducted using the Skype application over a cellular network, without relying on whether the participant has internet access. Participants are instructed to not use the phone for personal reasons.

At the baseline visit, the research team trains participants on how to use the phone prior to the initiation of study medication. Several practice runs are conducted with the participant during the in person visit, where participants are observed taking M&Ms using Skype. Upon showing sufficient understanding of the phone itself and the CAROMA protocol, participants are given a phone to bring home during the duration of the treatment phase of the trial. For the duration of the treatment phase, participants are contacted daily, Monday through Friday, at a pre-determined time for observation of medication dosing. Each CAROMA call proceeds as follows:

1) Greet the participant and ask them how they are doing.
2) Ask the participant if they have their study medication and water (or preferred beverage).
3) Instruct the participant to put the medication in their hand and display this to research staff.
4) Instruct the participant to open their mouth and put the study medication on their tongue so that research staff could verify that the medication has been placed in the participant's mouth.
5) Ask the participant to swallow the medication and take a few sips of their drink.
6) The participant should then open their mouth and move their tongue from side to side so that the research staff could verify the medication has been swallowed.
7) Thank the participant for their time and remind them of the following day's CAROMA visit or of their next study visit, as appropriate.

Please Note:

- Successful CAROMA check-in's last under 5 minutes per participant. Unsuccessful CAROMA calls should be followed by a second attempt at contact via Skype, and then a phone call to the participant's personal cell phone (or preferred method of contact).
- CAROMA calls are not for AE assessment. However, if a participant is to report an AE it should be captured and reported to the site principal investigator.

The following information should be documented for each CAROMA call:

Day # _____ of Dosing Date: ___ / ___ / _____ Rater: _____

☐ Visual Assessment of Dosing Compliance

Participant compliant with dosing regimen?

☐ Yes ☐ No: _____ (# pills / doses missed)

# of Pills Expected to be Taken: _____

# of Pills Actually Taken: _____

Time Medication Taken: ____ : ____ am / pm

APPENDIX I: BMI CALCULATION TABLE

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Height (inches)	Body Weight (pounds)																	
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295

BMI	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body Weight (pounds)																	
58	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

APPENDIX J: RESPONSIBILITIES OF THE INVESTIGATOR

The responsibilities imposed on investigators by the FDA are summarized in the “Statement of Investigator” (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all members of the study team assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each participant who participates in the study, and document the date of consent in the participant’s medical chart. Valid informed consent is the most current version approved by the IRB. Each informed consent form should contain a participant authorization section that describes the uses and disclosures of a participant’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant’s legally acceptable representative.
9. Maintain current records of the receipt, administration, and disposition of SpringWorks/Jazz Pharmaceuticals-supplied drugs, and return all unused PF-04457845/placebo to Jazz Pharmaceuticals at the end of the study.
10. Report adverse reactions to the Coordinating Center (Yale University) every 6 months. In the event of an SAE, notify the Coordinating Center within 24 hours.
11. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

APPROVED BY THE YALE UNIVERSITY IRB 5/1/2022