

***Blunting Cannabis Use Disorder***  
**by Targeting the**  
**Endocannabinoid System!**



***Deepak Cyril D'Souza***

# Disclosures and Acknowledgements

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  - NIH: NIDA, NCATS, NIAAA, NIMH,
  - Industry: Boehringer Ingelheim, Takeda, CH-TAC, Biogen
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- Dept. of Veterans Affairs
- Consultant: Abide, Jazz, BioHaven, Shulgin Institute, Atai, France Foundation
- **I am not paid by cannabis producers/retailers/interest groups OR opponents of legalization.**

# Targets of Tx

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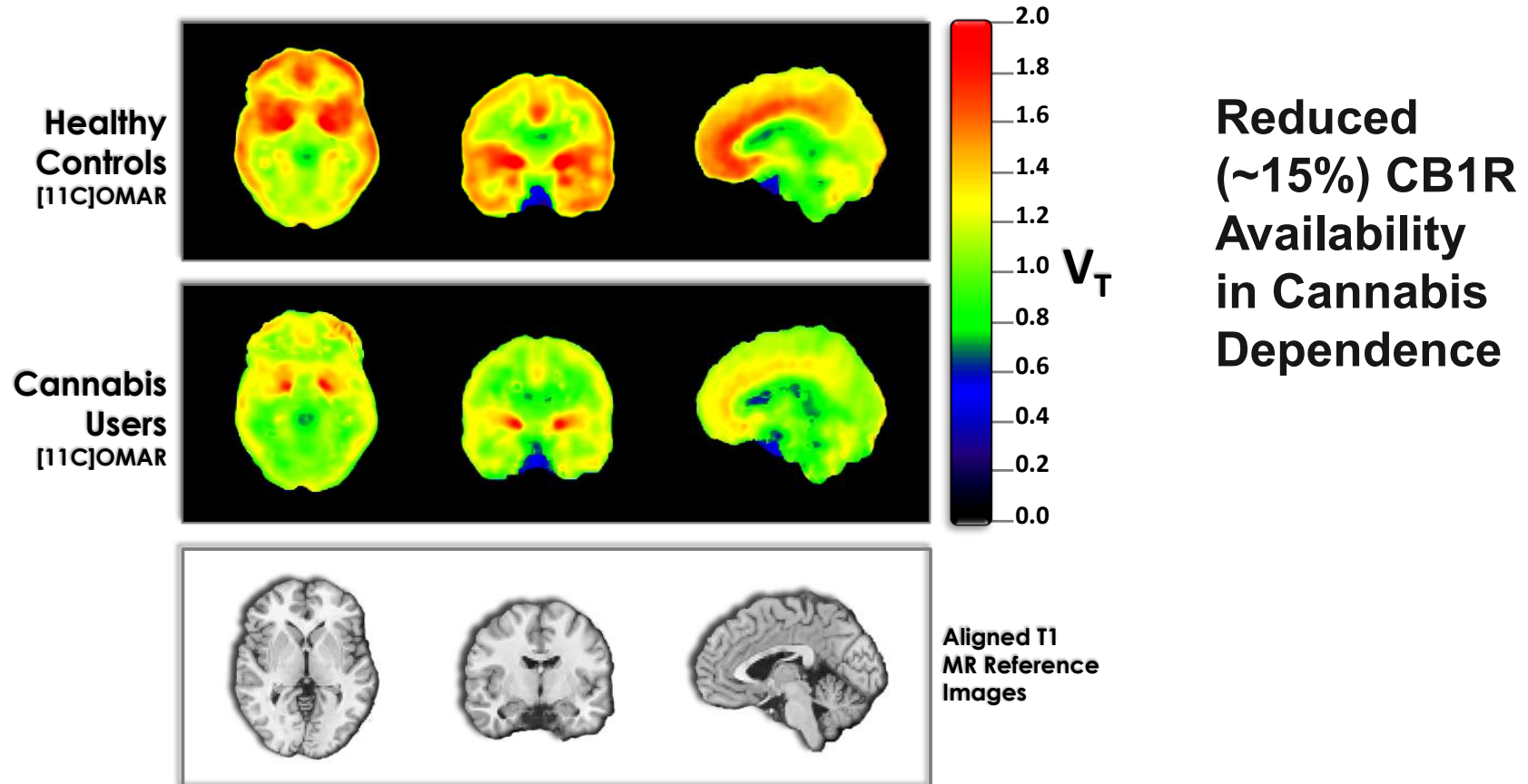
- Withdrawal:
  - Anxiety
  - Insomnia
- Reduced use
- Craving
- Relapse in those who become abstinent

# Approaches Tested

- CB1R agonists: THC, Nabilone, Nabiximols
- Cannabidiol
- CB1R antagonists
- Opioid Antagonists
- Antidepressants: SSRIs, bupropion, nefazodone, lithium, atomoxetine, venlafaxine
- Buspirone
- Clonidine, N-acetylcysteine
- Varenicline
- Gabapentin, topiramate, baclofen
- Depakote, entacapone, lofexidine
- Quetiapine
- Zolpidem + Nabilone
- Guafacine
- rTMS

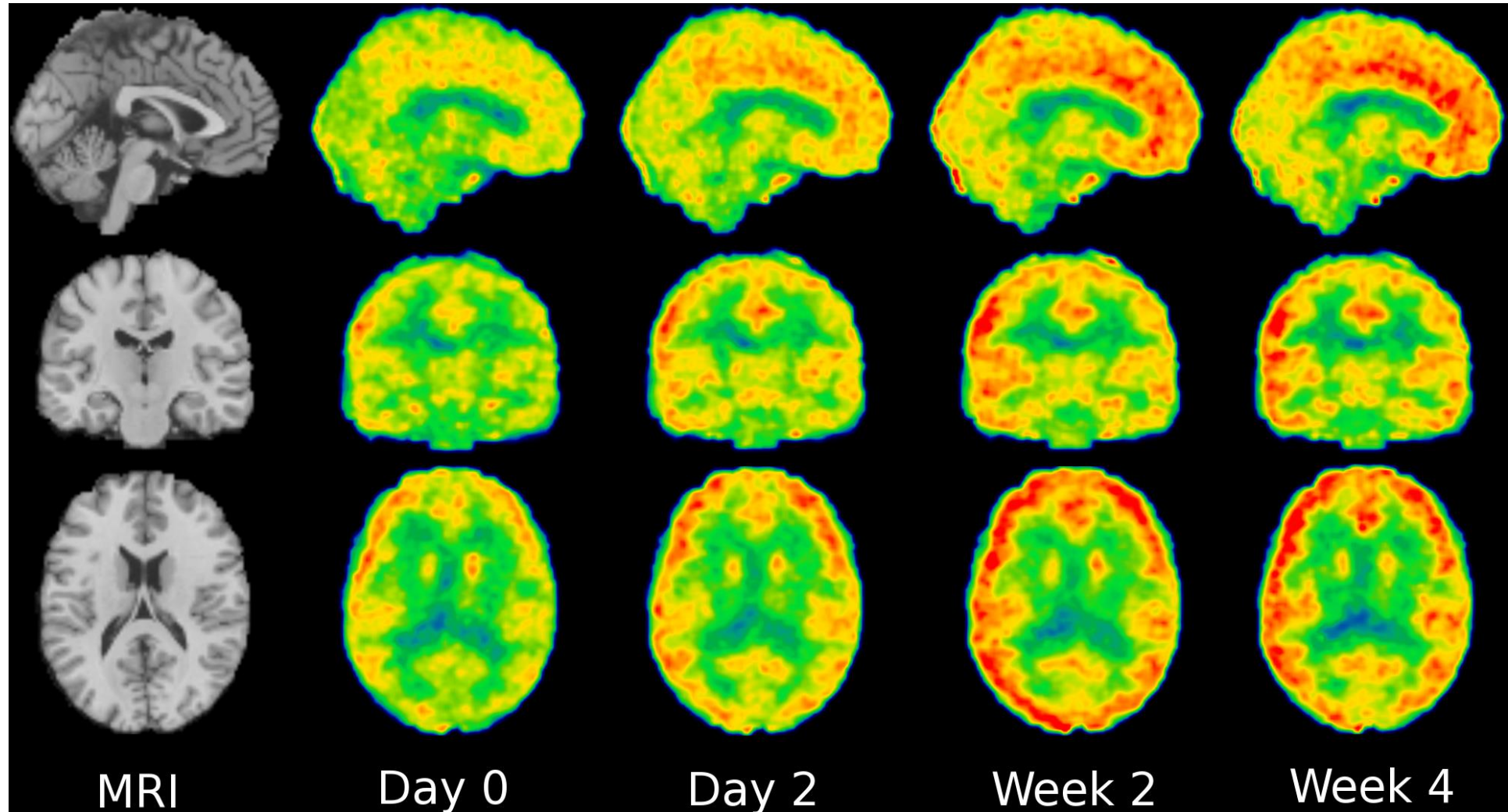
No FDA approved tMS

# Effects of Chronic Cannabis Exposure on CB1R availability

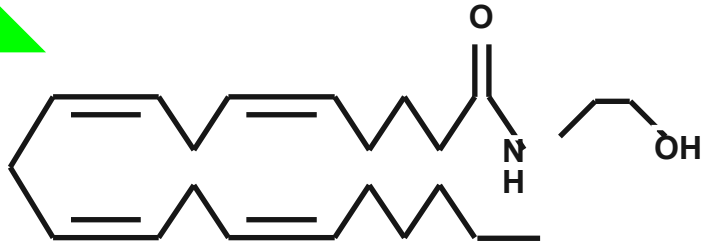
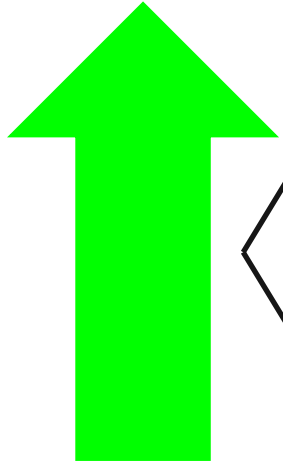


# Normalization of CB1 Receptor Availability Over Time with Abstinence from Cannabis

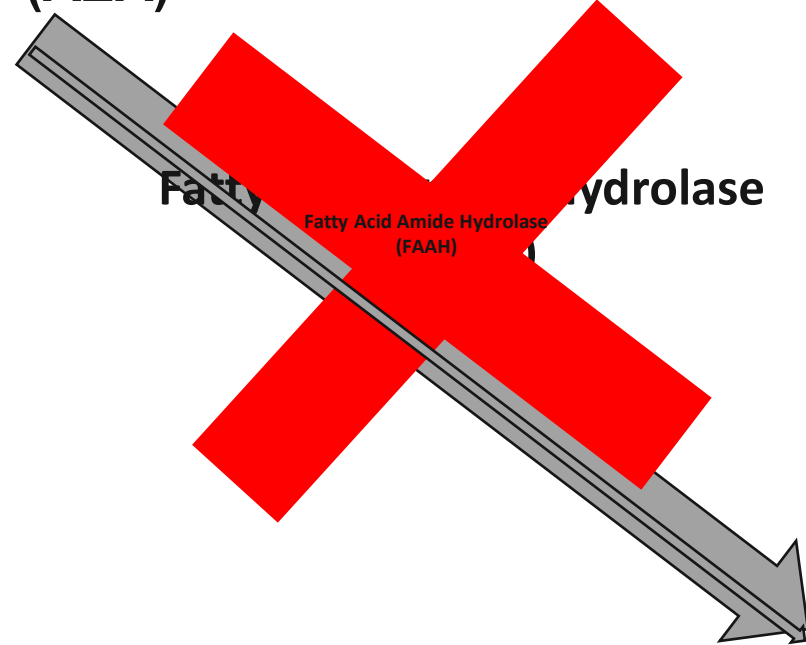
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# **Targeting the Endocannabinoid System**



**Anandamide (AEA)**



**Fatty Acid Amide Hydrolase**

Fatty Acid Amide Hydrolase  
(FAAH)

**Arachidonic Acid**  
Arachidonic Acid

**Ethanolamine**  
Ethanolamine



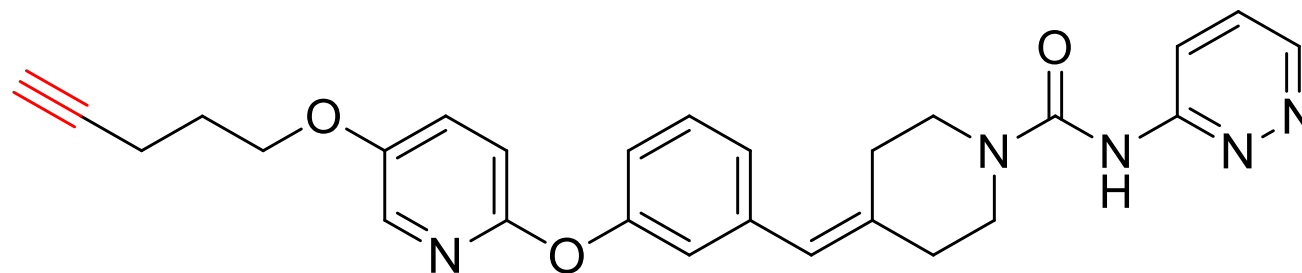
# FAAH-Is

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- Not associated with withdrawal/tolerance/dependence?
- Not psychoactive?
- Not rewarding?
- Do not have negative interactions with THC
- Acute administration of both FAAH and MAGL inhibitors significantly attenuated antagonist-precipitated and THC-withdrawal signs
- Subchronic exposure to AEA is associated with an attenuated withdrawal syndrome
- Individuals carrying a genetic variation of FAAH that causes reduced enzyme expression and activity are less susceptible to develop CUD.

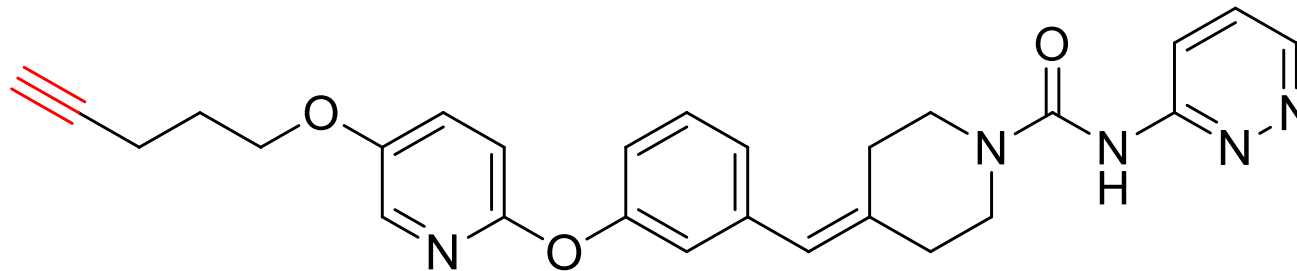
# PF-04457845 / JZP150

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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

John P. Huggins\*, Trevor S. Smart, Stephen Langman, Louise Taylor, Tim Young



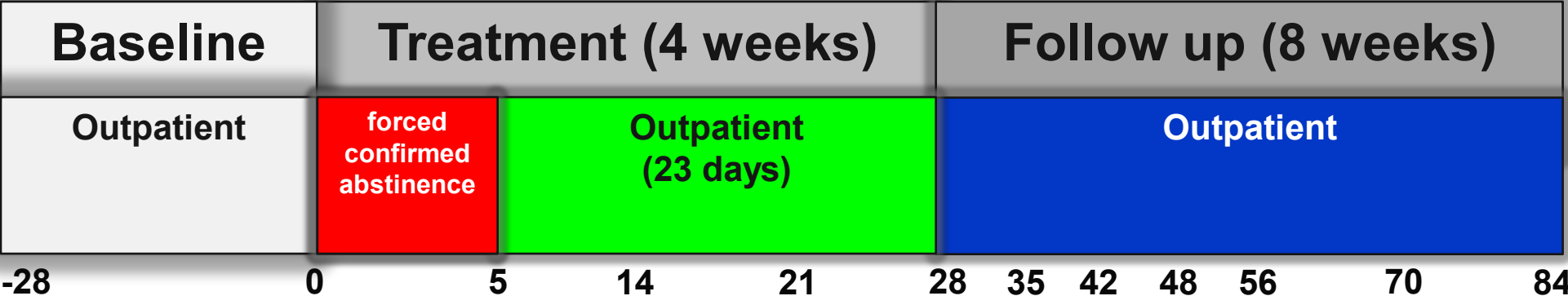
- PF-04457845 was well tolerated in osteoarthritis patients,
- No evidence of cannabinoid-type adverse events,
- **Did not reduce OA pain**

# Hypothesis

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- PF-04457845 will attenuate cannabis withdrawal.
- PF-04457845 will attenuate cannabis use.

End of  
forced  
abstinence



# Sample

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- Males 18-55 years
- Individuals with a DSM-IV-TR diagnosis of cannabis dependence
- Currently using  $\geq 30$  joints/month or equivalent over the past 6 months: TLFB
- Regular cannabis use  $\geq 2$  years
- Lifetime exposure  $\geq 1000$  times
- Positive urine screen for cannabinoids (THC-COOH) at screening and admission
- *History of one or more periods of cannabis abstinence lasting  $\geq 3$  days associated with cannabis withdrawal symptoms*
- Primary drug of abuse cannabis
- No other serious mental illness

# Cellphone Assisted Remote Observation of Medication Adherence (CAROMA)

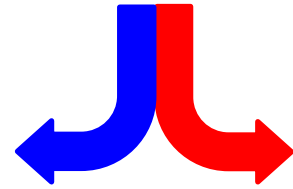
- 5 times per week
- participants contacted via video,
- hold the pill up to the camera,
- show the medication on the tongue
- hold the camera up to his mouth for a “mouth check” after swallowing
- Subjects paid for every CAROMA visit.
- Failure to make the CAROMA visit resulted in nonpayment and an assumption of nonadherence



# Results

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Placebo  
(n=24)

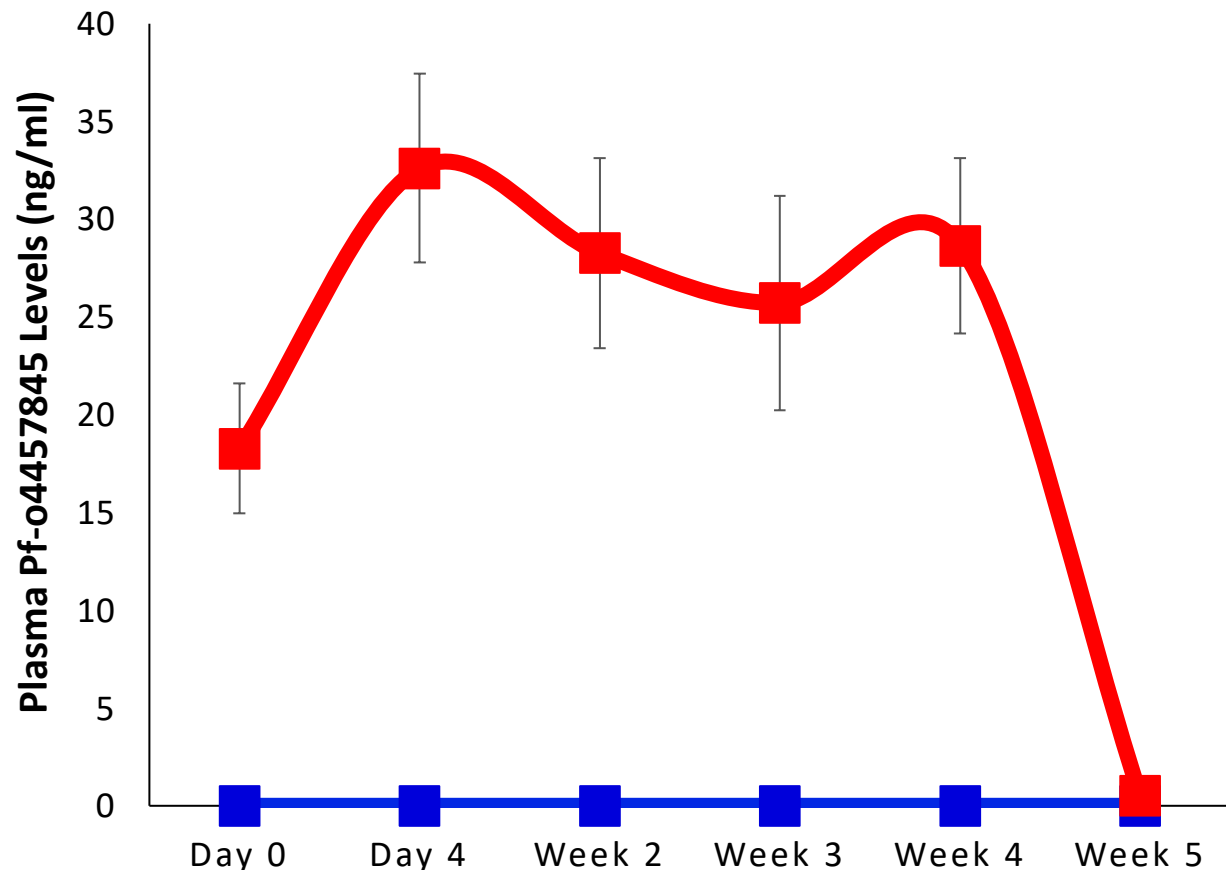


PF-04457845  
(n=46)



<b>Table 1 Demographics*</b>			<b>Placebo (n=24)</b>	<b>PF-04457845 (n=46)</b>
Age in years			27.5 (8.7)	28.5 (8.5)
Education in years			12.7 (2.0)	12.8 (1.5)
Alcohol consumption (drinks/day)			0.7 (0.7)	0.64 (1.0)
Tobacco consumption (cigarettes/day)			1.5 (2.7)	2.4 (3.0)
Desire to quit using cannabis	Low	None	3 (12.5%)	1 (2.2%)
		Considering (but not important)	5 (20.8%)	16 (34.8%)
	High	Definitely	12 (50.0%)	23 (50.0%)
		Have to	4 (16.7%)	6 (13.0%)
Cannabis at baseline (joints/day)			<b>3.8 (3.1)</b>	<b>3.6 (5.2)</b>
Urinary THC-COOH Level at baseline (ng/dl)			536.3 (628.4)	550.7 (984.5)
Days since last use			1.1 (1.0)	0.9 (1.4)
Age of first use			14.9 (5.3)	15.0 (2.8)
*Data are means (SD) or numbers. N for all between 61 and 70.				
There were no statistically significant differences between the two groups across these demographic variables.				

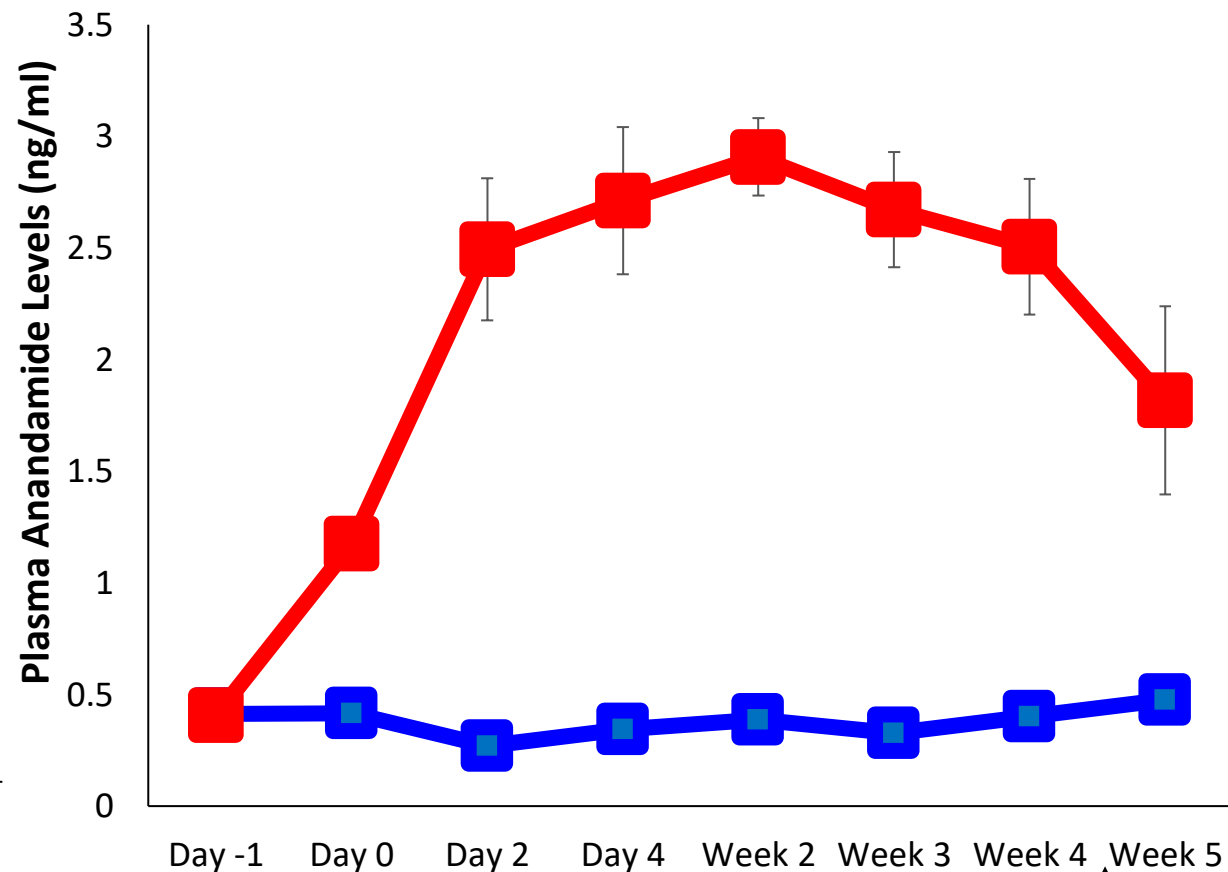
# Plasma PF-04457845 Levels



↑  
start of  
abstinence

↑  
End of  
treatment

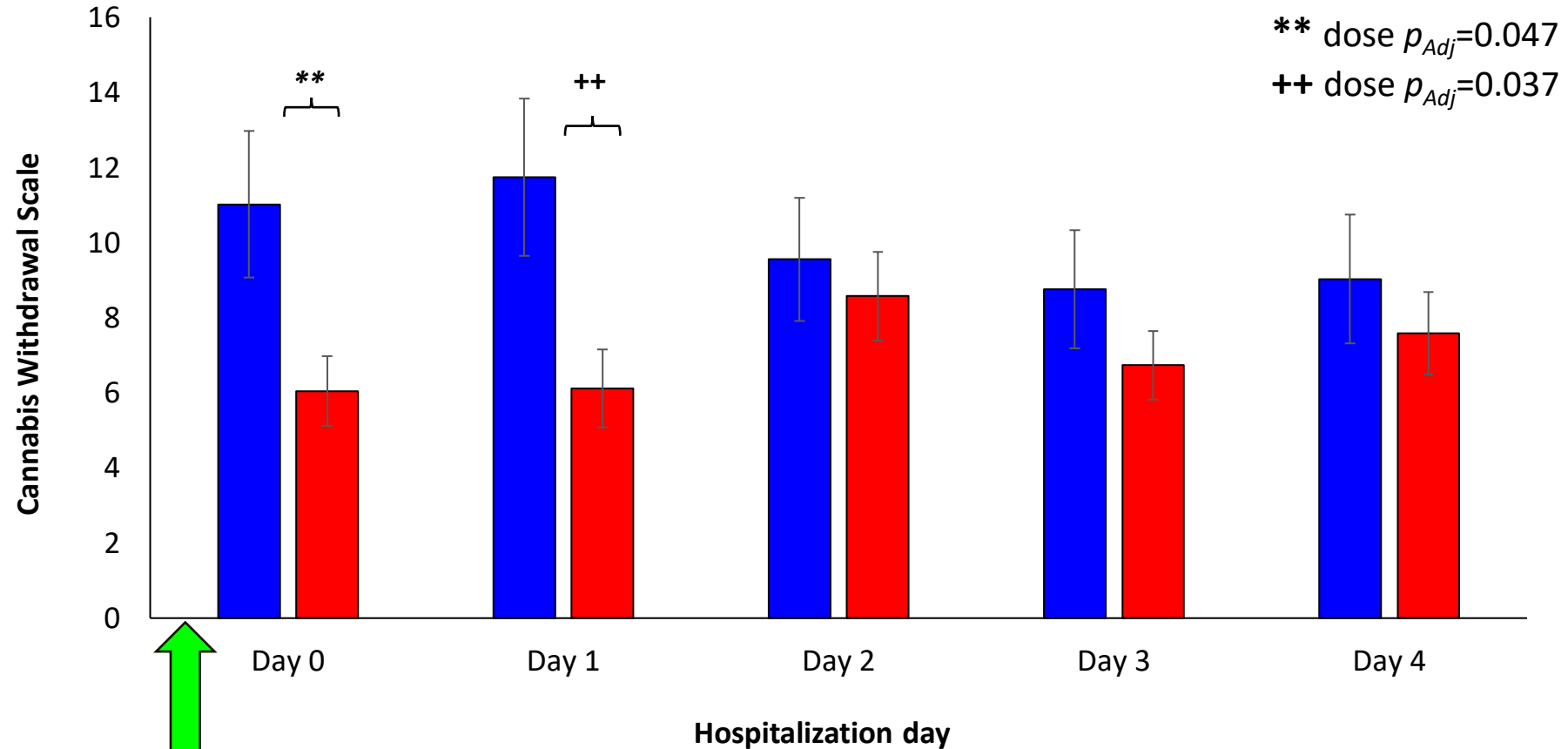
# Plasma Anandamide (AEA) Levels



↑  
End of  
treatment

■ PF-04457845 ■ Placebo

# Cannabis Withdrawal (Inpatient)



start of  
abstinence

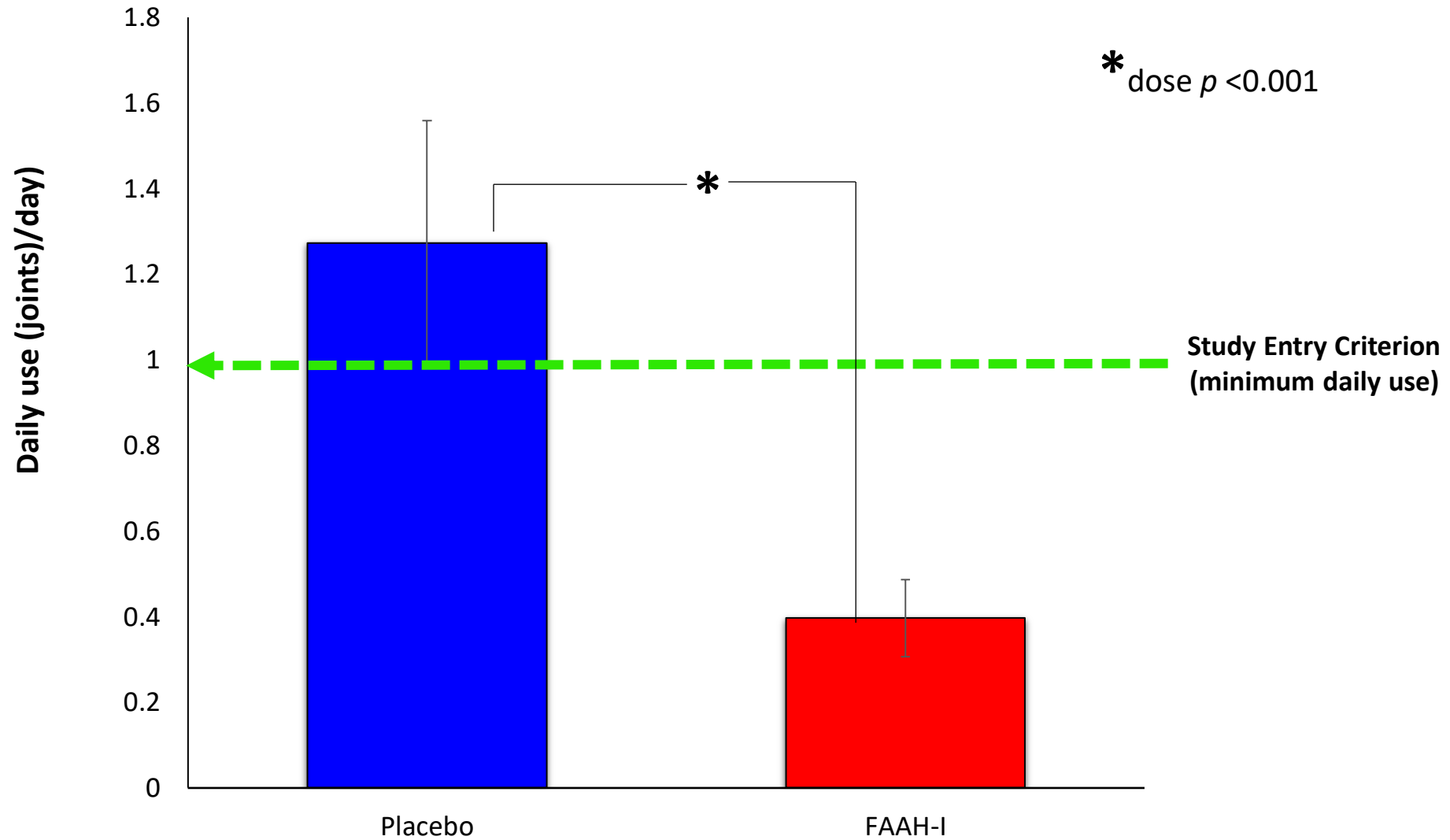
PF-04457845

Placebo

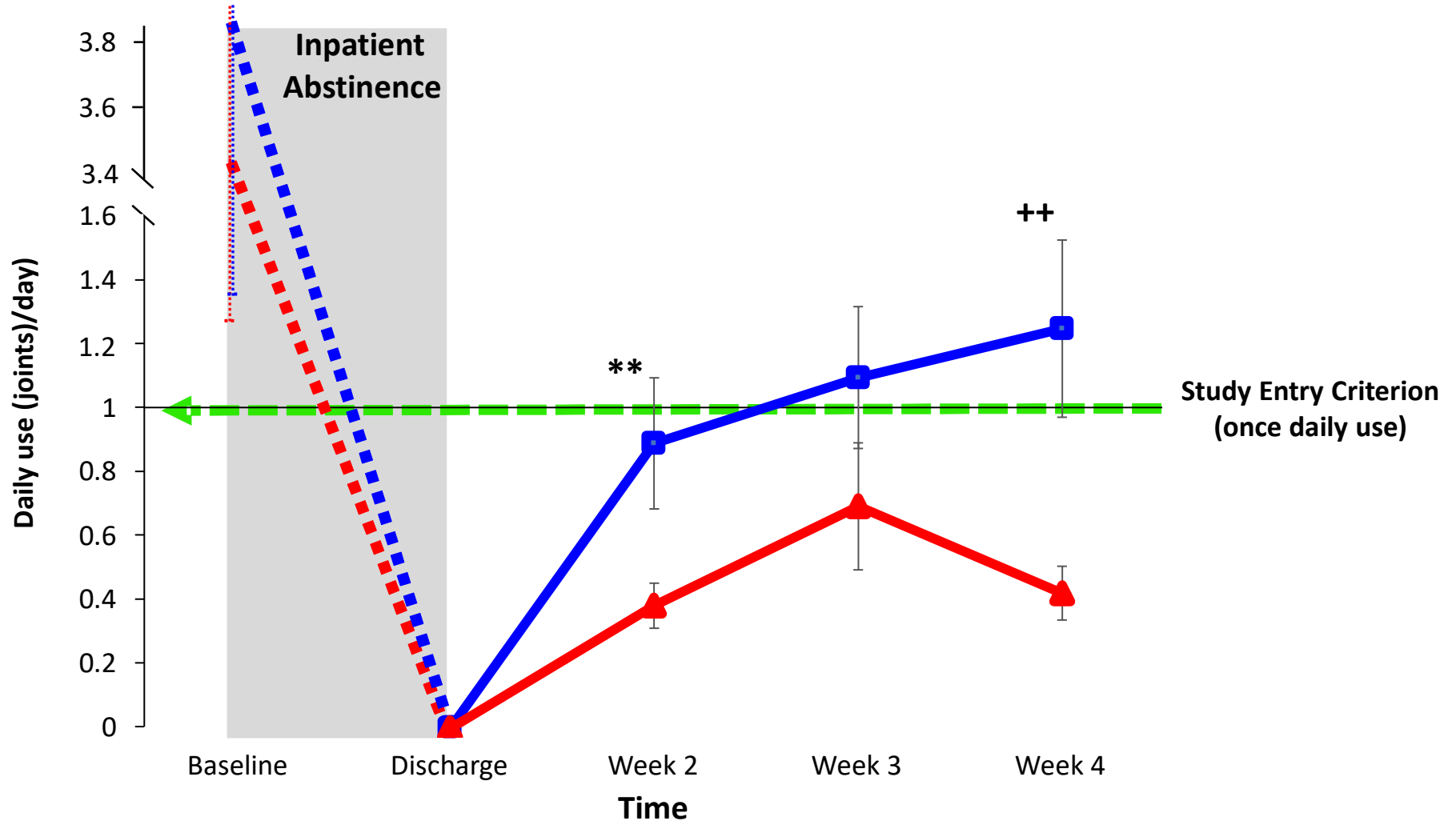
**Effect of Drug on Feeling States (Visual Analog Scale) During Acute Withdrawal (Inpatient)**

<b>Measure</b>	<b>Effect</b>	<b>Placebo</b>	<b>PF-04457845</b>	<b>Effect (Difference)</b>	<b>p-value</b>
<b>Anxious</b>	Day 0	25.02 (15.9 to 39.37)	13.61 (9.01 to 20.56)	11.41 (-1.25 to 24.07)	<b>0.052</b>
	Day 1	13.61 (8.18 to 22.63)	14.2 (9.78 to 20.62)	-0.59 (-9.31 to 8.12)	ns
	Day 2	13.79 (6.89 to 27.6)	13.29 (9.1 to 19.4)	0.5 (-10.31 to 11.31)	ns
	Day 3	12.21 (6.2 to 24.07)	12.1 (8.34 to 17.58)	0.11 (-9.33 to 9.55)	ns
	Day 4	22.06 (12.09 to 40.26)	14.32 (9.37 to 21.88)	7.75 (-6.85 to 22.34)	ns
<b>Irritable</b>	Day 0	26.63 (17.58 to 40.34)	13.11 (9.13 to 18.84)	13.52 (1.48 to 25.55)	<b>0.012</b>
	Day 1	29.64 (19.29 to 45.54)	14.14 (9.67 to 20.67)	15.5 (1.69 to 29.32)	<b>0.011</b>
	Day 2	23.65 (16.29 to 34.32)	18.49 (12.38 to 27.61)	5.16 (-6.35 to 16.67)	ns
	Day 3	20.51 (13.32 to 31.59)	17.43 (12.65 to 24)	3.09 (-7.38 to 13.55)	ns
	Day 4	18.7 (12.06 to 29.01)	15.04 (10.13 to 22.34)	3.66 (-6.48 to 13.8)	ns

# Daily Cannabis Use At End of Treatment

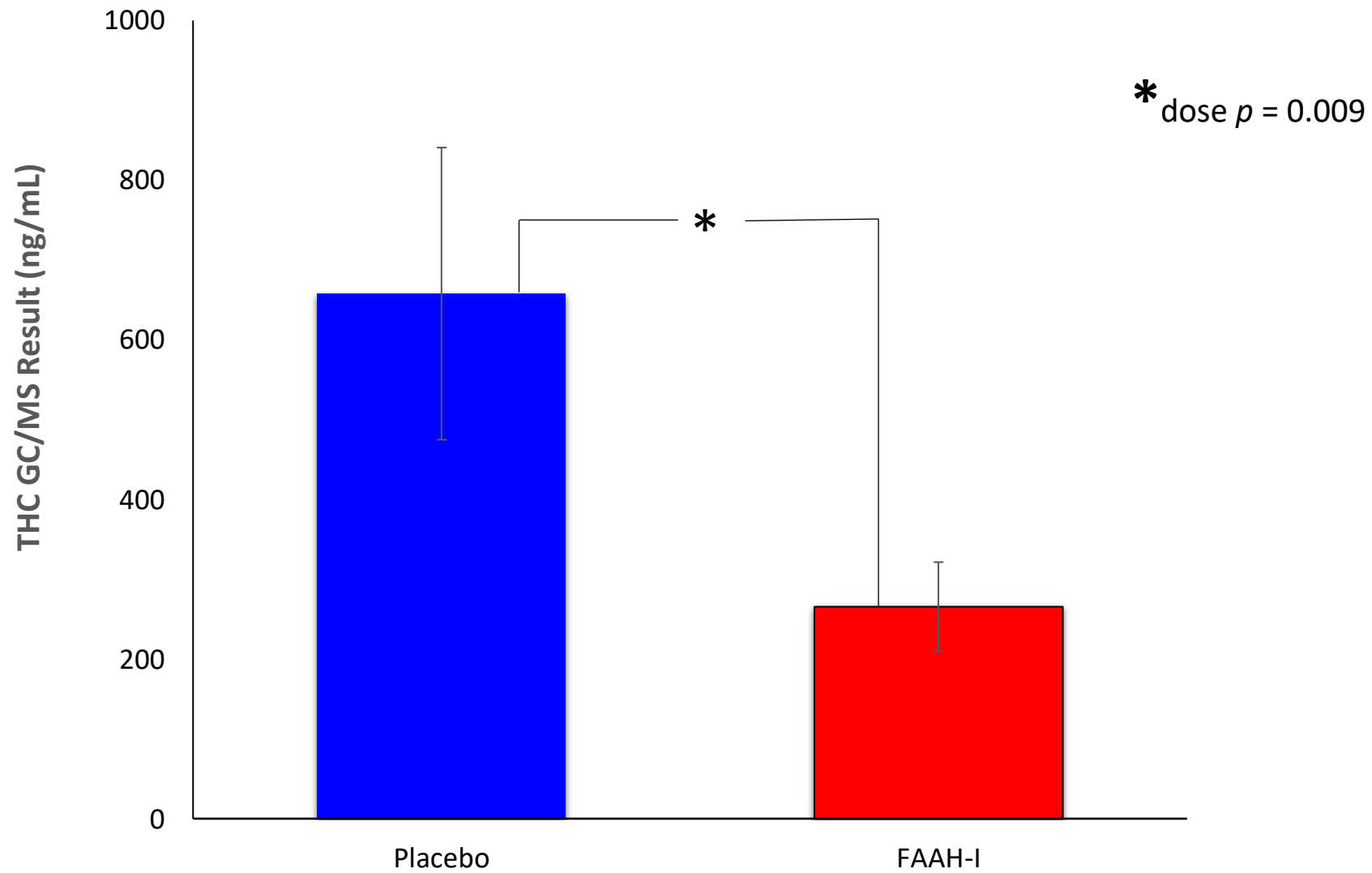


# Daily Cannabis Use Over Time

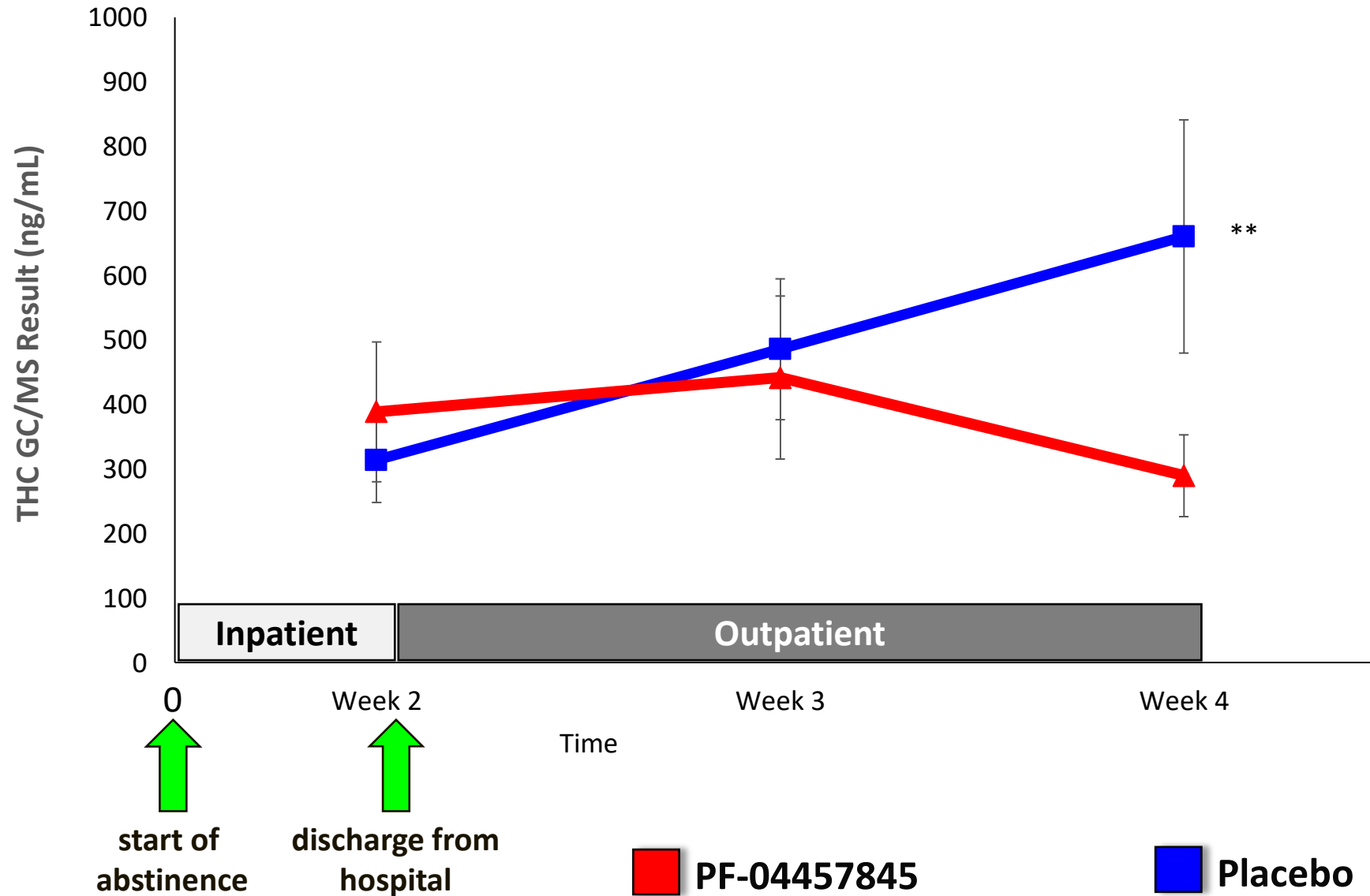


■ PF-04457845      ■ Placebo

# Urinary THC-COOH Levels (End of Treatment)



# Urinary THC-COOH Levels Over Time





## Correlations between self reported use and urine THC-COOH

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Week #	rho	p	n
2	0.364	=0.007	53
3	0.568	<0.001	50
4	0.54	<0.001	55

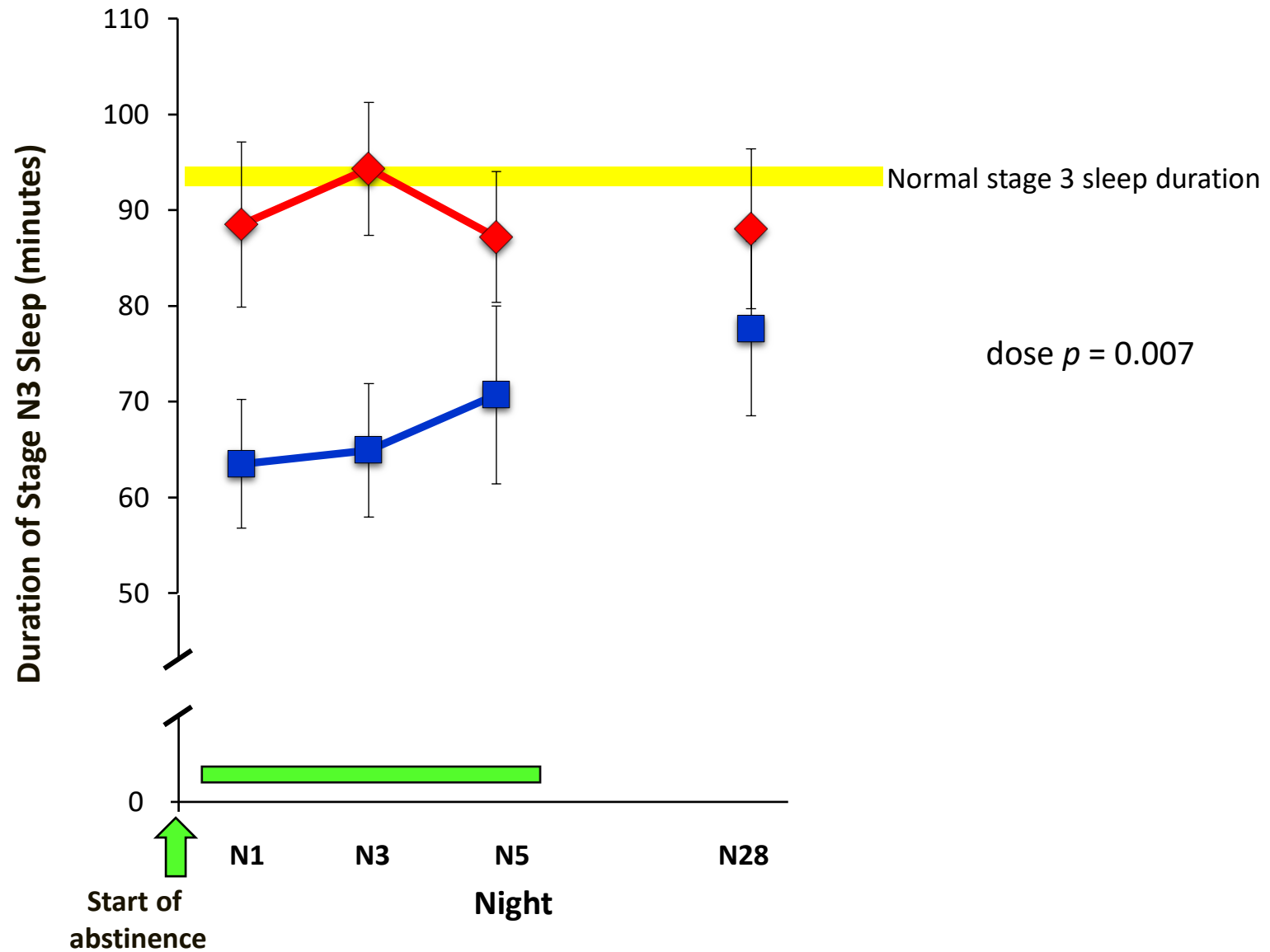
# Sleep

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In the PF-04457845 group, better self-reported:

- Overall sleep and
- Deep sleep

# Time in Stage N3 (Deep) Sleep



<b>Incidence of Adverse Events during Treatment Phase (4 weeks)</b>		
	<b>PF-04457845 (n=46)</b>	<b>Placebo (n=24)</b>
Number	20	11
Percentage	43	46

**No SAEs**

# Safety

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- Clinical laboratory tests for safety completed at screening, during inpatient stay, at all weekly appointments during treatment, and during follow up phase
- Subjects monitored by inpatient and outpatient

	<b>Placebo (n=24)</b>	<b>PF-04457845 (n=46)</b>
Mild AEs	26	46
Moderate AEs	7	17
Serious AEs	0	0
Total	33	63

- DSMB review Q6 months: no recommendations

# Summary

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- 95% visually confirmed adherence;
- PF-04457845 increases plasma eCBs;
- PF-04457845 reduced peak CB withdrawal symptoms and feeling states associated with withdrawal (depression, anxiety, irritability);
- PF-04457845 reduced daily CB consumption and urinary THC-COOH;
- Disruptions in stage N3 (deep sleep) during cannabis withdrawal attenuated by PF-04457845.
- **PF-04457845 safe and well-tolerated**
- modulation of the eCB system by increasing levels of the endogenous agonist might be preferable to CB1R activation with direct agonists.

# Limitations

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- Inpatient
- Forced abstinence
- No requirement for treatment seeking
- Only men
- No adjunctive therapy
- Limited treatment duration

***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 Design:

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Tx Study	Screening		Treatment Phase								Follow Up Phase				
Week	-1	-2	1	2	3	4	5	6	7	8	9	10	11	12	
Day	-14	-7	1	8	15	22	29	36	43	50	57	64	71	78	85
virtual	x	x		x		x		x		x		x	x	x	
in-person		x	x		x		x		x		x				x



**Randomization**

# Study Population

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- Diagnosed with Moderate to Severe DSM-5 Cannabis Use Disorder
- Treatment seeking
- 70% male 30% female
- Randomize 237 participants → 178 completers study-wide
- Per site = 60 participants randomized → 45 completers

# Primary Endpoints and Outcome Measure

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- **Primary Objective:** To determine whether PF-04457845 is superior to placebo in reducing self-reported frequency of cannabis use
- **Primary Endpoint:** Change from baseline in the average **number of times per day** of self-reported consumption of cannabis or a cannabis containing product
- **Co-Primary:** Change from baseline in **urinary THC-COOH levels**
- **Outcome:** 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 and **urinary TH-COOH levels**

# Quantifying Marijuana Use:

Defining an occasion of use:

Every time a	Joint, blunt, roach, etc.	is lit and used
	Bong	is prepared for use, and used
	Bowl	is packed and used
	Vapepen	is puffed
	Edible	is consumed

Measuring quantity:



# An occasion of cannabis use

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Every time a	Joint, blunt, roach, etc.	is lit and used
	Bong	is prepared for use, and used
	Bowl	is packed and used
	Vapepen	is puffed
	Edible	is consumed

Objective/s	Instrument/s	Endpoint/s	Outcome/s
Is PF-04457845 <b>safe and tolerable</b> ?	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	% of participants who meet the markedly abnormal criteria for safety laboratory tests at least once post-dose.	
	BP, HR	% of participants who meet the markedly abnormal criteria for vital sign measurements at least once post-dose.	
Is PF-04457845 superior to placebo in <b>reducing cannabis use</b> ?	TLFB	$\Delta$ in amount (grams) used	Change from baseline (2 weeks prior to randomization) until the last dose
Is PF-04457845 superior to placebo in reducing the <b>problems associated with cannabis use</b> ?	Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	$\Delta$ in total score	
Is PF-04457845 superior to placebo in <b>reducing sleep disturbances</b> ?	Actigraphy	$\Delta$ in duration of sleep latency, total sleep, wake after sleep onset, sleep efficiency, and ambient light	
Is PF-04457845 superior to placebo in <b>improving quality of life</b> ?	Quality of Life Scale Short Form	$\Delta$ in total and subscale scores	

# e-checkup

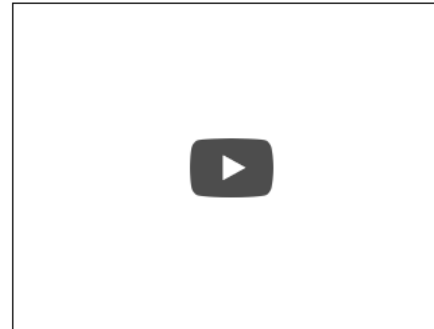
2/1/2019

Marijuana eCHECKUP TO GO at Yale University School of Medicine



- [Welcome](#)

## Welcome to the Marijuana *eCHECKUP TO GO* at Yale University School of Medicine



[play](#) [\[f\]](#) [pause](#) [\[p\]](#) [mute](#) [\[m\]](#) [vol+](#) [\[+\]](#) [vol-](#) [\[-\]](#) [Text](#)

Hello, and welcome to the Marijuana eCHECKUP TO GO program.

The eCHECKUP TO GO is designed to provide you with personalized information and feedback regarding your marijuana use, and how it might affect your health, your relationships, and your career and life goals.

<https://interwork.sdsu.edu/echeckup/usa/mj/adult/index.php?id=yale-nida>

1/3

# e-checkup/e-Toke

## eCHECKUP TO GO Input Summary

User ID:	Episode:	Date Completed: 4:00 pm, December 31, 1969
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### Demographic Information

Sex:	Age:	Weight: <b>pounds</b>
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### About Your Marijuana Use

At what age did you first use marijuana?

How long has it been since you last used marijuana in any form? 0 months, 0 weeks, 0 days, 0 hours

How many weeks in a typical month do you smoke at least once? weeks

For the past month, please describe your marijuana use during a TYPICAL WEEK in which you did use marijuana:

A. Please place a check mark next to the time(s) of day you smoked marijuana or were under the influence of marijuana.

	Mon.	Tue.	Wed.	Thur.	Fri.	Sat.	Sun.
Morning (6am-12pm)							
Afternoon (12pm-6pm)							
Evening (6pm-12am)							
Late Night (12am-6am)							

B. Please enter the number of HOURS your were under the influence of marijuana each day.

How much money would you estimate you spend on marijuana in a TYPICAL WEEK? \$

How many days in the last month did you drive within 5 hours of using marijuana? days

How many days in the last month did you ride with a driver who had used marijuana within 5 hours prior to driving? days

On the occasions when you use marijuana, how often do you also drink alcohol?

What do you like about Marijuana? What are the "good things" or benefits you experience from using marijuana?

None selected

## Marijuana eCHECKUP TO GO Input Summary

During a TYPICAL week, how many HOURS do you estimate you spend:

	In Total	Under the influence
Studying		
In Class		
Exercising/Playing Sports		
Partying/Socializing		

ON AVERAGE, how many hours do you sleep a night? Hours

How much is your average monthly cell phone bill? \$

How much is your monthly car payment? \$

How much is your monthly rent or house payment? \$

After expenses, rent, and bills, how much "spending money" do you have in a TYPICAL MONTH? \$

### My Peers

What percent of Americans in your age group ( ) use marijuana at least once in a typical month? %

What percent of Americans in your age group ( ) who use marijuana at least once in a typical month, use less frequently than you do? %

### Alcohol & Tobacco

In a TYPICAL WEEK how many standard drinks containing alcohol do you consume?

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

How much money would you estimate you spend on alcohol in a TYPICAL WEEK? \$

During the PAST MONTH, how many CIGARETTES did you smoke on a TYPICAL DAY?

If you're a CIGARETTE smoker, for how many years have you smoked regularly?

How much money would you estimate you TYPICALLY spend on each PACK of cigarettes? \$

### The "Not-So-Good" Things About Marijuana

How would you like to spend your time?

### Changes?

How important is it to you to make any change in your personal use of marijuana? (Scale of 1-10)

How confident are you that you are able to make any change in your personal use of marijuana? (Scale of 1-10)



# e-Checkup/e-Toke

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## **Output Summary**

- Your personal use profile
- The cost to you
- Potential risks
- How your use compares to others
- Impact of marijuana use on lifestyle and choices
- Goals and Aspirations
- Making a change?

# e-checkup e-Token



Yale University School of Medicine

UID: 196933657447

## Your pattern of use

### In a TYPICAL MONTH:

You use marijuana on **30** days.  
You drink **39** standard alcoholic drinks.  
You smoke **301** cigarettes.  
During the 5 years you have been smoking, you have smoked about 18060 cigarettes.

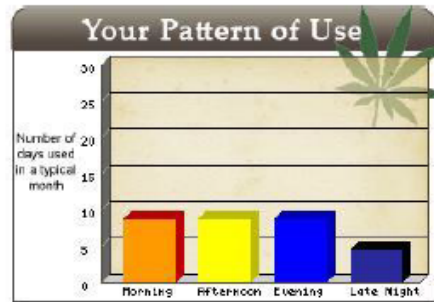
### When and how often do you use?

Counselors working with people who use marijuana **more than one time** during the day find they have more social and physical problems than those who only use in the evenings. It is also common to discover that people who use at **multiple times** are also more likely to be smoking to avoid problems they feel unable to confront.

### Mixing Marijuana and Alcohol

You indicated that you drink about **39** alcoholic drinks in a typical month.

Using marijuana in addition to alcohol can put you at increased risk. The effects of some drugs become exponentially greater when taken together. In addition, the physical tolerance that one drug produces can sometimes affect another drug, which can lead to dependence on multiple substances.



## How do you spend your time?

The graph below shows you what percent of your waking hours you spend engaged in the activities listed. In a TYPICAL MONTH, you spend:

- **34%** of your time **working**
- **8%** of your time **exercising**
- **13%** of your time **socializing/partying**



## Time spent under the influence

### In a TYPICAL MONTH:

You spend **73.1** hours under the influence of marijuana. That's **14%** of your waking hours.



You are under the influence of marijuana **25%** of the time you **study**



You are under the influence of marijuana **20%** of the time you are **exercising or playing sports**



You are under the influence of marijuana **100%** of the time you are **socializing/partying**



## The Cost to You

### Per YEAR

You spend about **\$9852.00** per year on marijuana, alcohol and/or cigarettes, which means you spend about **410.5%** of your spending money on marijuana, alcohol and/or cigarettes.



You spend about \$5200.00 (216.7%) on **marijuana**



You spend about \$1040.00 (43.3%) on **alcohol**



You spend about \$3612.00 (150.5%) on **cigarettes**



## Spend your money on what you choose:

By way of comparison, the amount of money you spend on marijuana, alcohol, and/or cigarettes would be enough to:

Buy about **7637** music downloads



Buy **98.5** movie tickets (avg. \$15 per ticket)



Go out to dinner **98.5** times (avg. \$60 for 2 people)



Pay your cable bill for **98.5** months (avg. \$80 per month)



Pay your cell phone bills for **98.5** months



Pay **49.3** of your car payments



Pay for housing for **12.3** months



# Quit Date

- Participant must be willing to make an attempt to quit during the first week after randomization, at least two days after taking study medication.
  - A successful quit attempt during the first week= \$50 compensation
- Participant completes a Willingness to Attempt to Quit questionnaire at the screen 1 visit; questionnaire is reviewed and signed during screen 2 visit.

**COMMITMENT TO ATTEMPT QUITTING MARIJUANA**

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 \_\_\_/\_\_\_/\_\_\_

# Randomization

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- 1:1
- Stratified by site and degree of use
  - Moderate CUD = 4-7 of 11 symptoms
  - Severe CUD = 8-11 of 11 symptoms

# CAROMA + (Cellphone Assisted Remote Observation of Medication Adherence)

- HIPAA Compliant process
- Participants are given cell phones for the duration of the treatment phase of the study to collect the following ...



- 1) 5 days per week
- 2) Visual confirmation of medication adherence
- 2) Ask if Any Adverse Events
- 3) Collect Previous Day Marijuana Use (Yesterday's Use)

Yesterday's Date ____/____/____ (MM/DD/YY)	Did you use MJ? <input type="checkbox"/> YES <input type="checkbox"/> NO	If marijuana was used yesterday, complete the following:				
		time	# of Uses	Method Used	Quantity	Cost
		0:00-5:59				
		6:00-11:59				
		12:00-17:59				
		18:00-23:59				

- 4) Collect Information on Participant's Sleep for Previous Night

# Urinary THC-COOH

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- Onsite Quick Dip performed at every weekly visit
- Quantification of THC-COOH by Columbia Core Biomarker Lab

# Wrist Actigraphy – Proxy Measure of Sleep

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Wrist actigraph [wgt3x-bt Monitor (Actigraphcorp®)]

Measures 1) arm accelerations and hence is a proxy for activity and 2) ambient light (to assist in determining sleep onset/wake times).

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).

Data uploaded and device charged once weekly.

Outcome measures: *sleep latency, total sleep time, wake after sleep onset, sleep efficiency, and ambient light.*



wgt3x-bt Monitor (Actigraphcorp®)

# Safety

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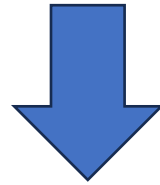
- Self-report
- Clinician queried
- Lab tests
  
- AE reporting



Consented  
n=608



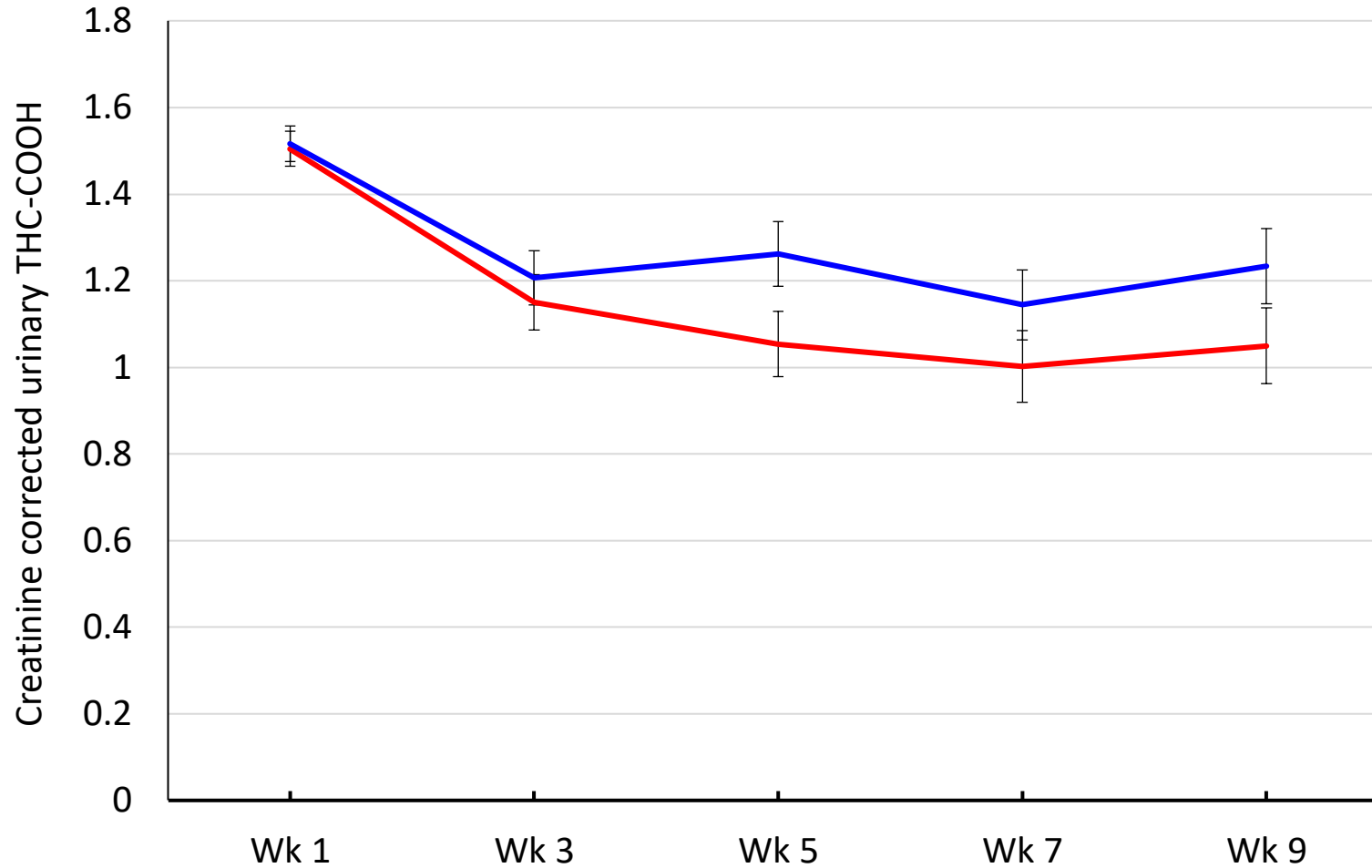
Randomized  
n=230



Completed Treatment Phase  
N = 180

<b>Cannabis Use Characteristics</b>		
	<b>FAAH-I</b>	<b>Placebo</b>
	<b>N = 116</b>	<b>N= 114</b>
Average Number of Occasions of MJ Use per Day in Past Month	3.96 (2.96)	4.11 (3.59)
Average Total Number of MJ Using Days in Past Month	28.66 (2.76)	28.41 (2.99)
Average Age of First Use of MJ	15.26 (3.23)	16.00 (3.65)

# Change in Baseline-adjusted Cr-Corrected Urinary THC-COOH Levels (log-transformed)

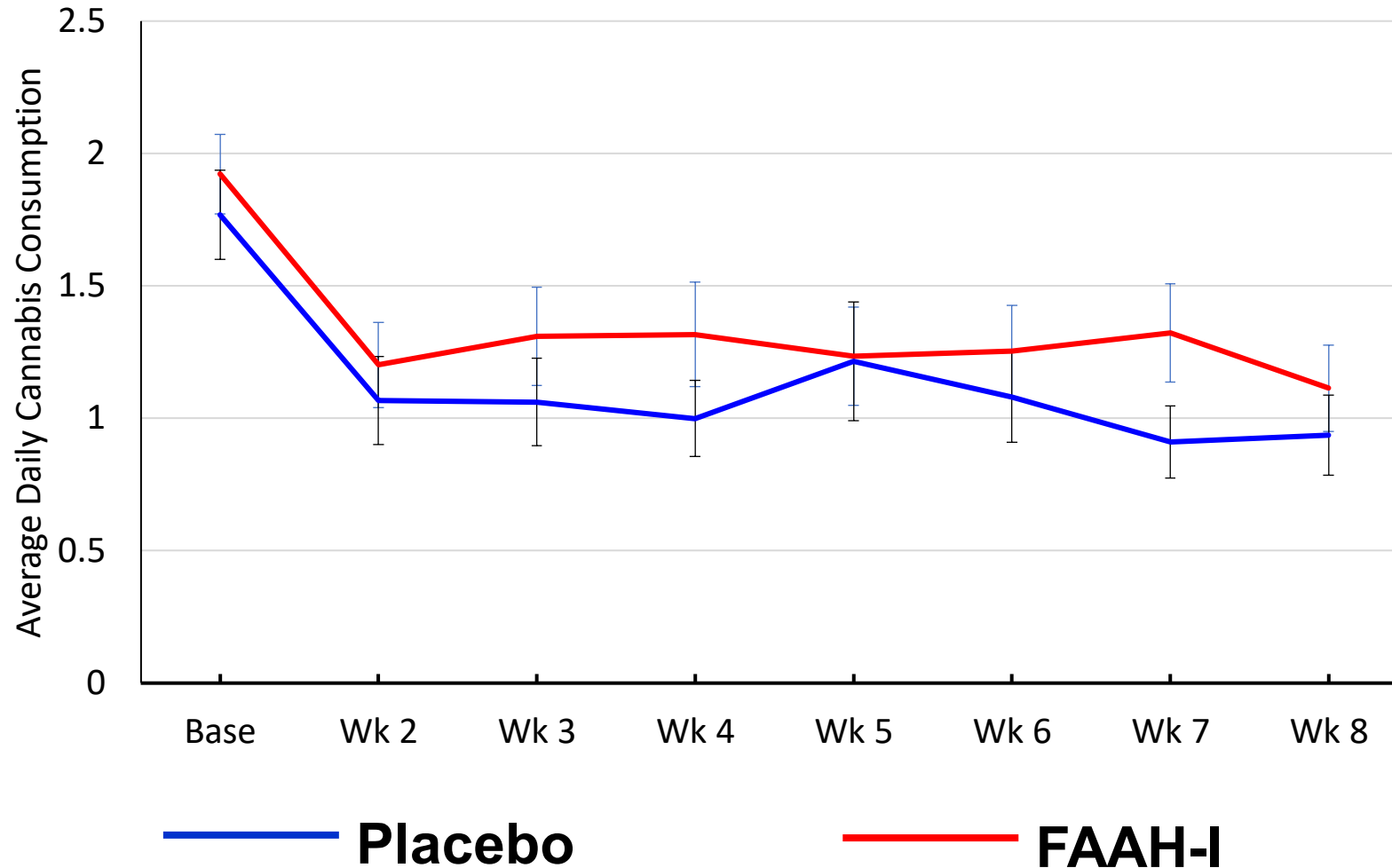


— Placebo

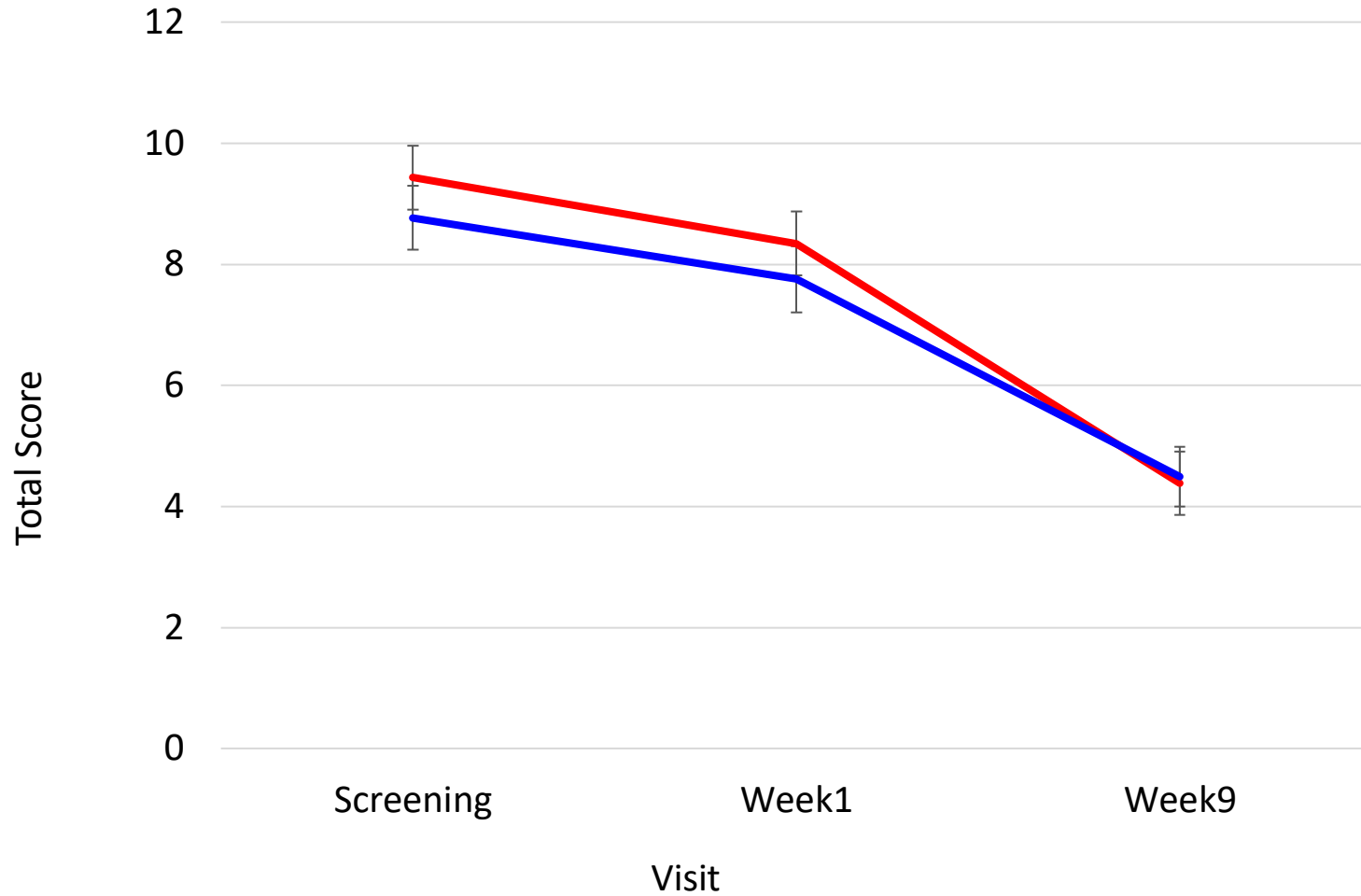
— FAAH-1

Effect	Num DF	Den DF	F Value	Pr > F
Group	1	204	2.16	0.1432
Time	4	204	18.59	<.0001
Group*Time	4	204	1.55	0.1881

# Change in Average Daily Occasions of Cannabis Use by Week (CAROMA) (raw data)



# Marijuana Problems Scale



	Sig.
drug	0.669
visit	0.000
drug * visit	0.783

— Placebo

— FAAH-I

# Summary

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- Co-Primary:
  - No difference in daily occasions of use.
  - No difference in creatinine corrected THC-COOH.
- Secondary:
  - Reduction in anxiety
  - Safe and well-tolerated.
  - No significant differences in problems, withdrawal, craving
  - No difference on actigraphy

# Contrasting Design, Sample and Results

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## Single Site trial

- Nontreatment seekers
- Forced confirmed inpatient withdrawal and abstinence
- Clear assay to measure withdrawal
- Clear assay to measure relapse
- FAAH-I reduced withdrawal
- FAAH-I reduced self-reported and objective measure of cannabis use

## Multicenter Trial

- Treatment seekers
- Voluntary abstinence
- Ecological validity
- FAAH-I did not reduce withdrawal
- FAAH-I reduced objective measure of use but not self-reported use