COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD

CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

Protocol #:17-2318

Project Title: A randomized, double blind, placebo-controlled parallel study of tolerability and efficacy of Cannabidiol (CBD) on motor symptoms in Parkinson's disease

Principal Investigator: Maureen Anne Leehey, MD

Version Date: June 9, 2020

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Version Date: December 17, 2019

I. Hypotheses and Specific Aims:

Parkinson disease (PD) is a relatively common, progressive, disabling disorder that responds partially to symptomatic treatments. Since cannabis has become legal in Colorado, many persons with PD have been trying it to see if it relieves any of their symptoms. Cannabis is composed of many cannabinoids, with delta-9-tetrahydrocannabinol (THC) the major constituent. THC has been shown to induce a "high," psychosis, cognitive dysfunction and anxiety – all of which would be problematic in PD. Cannabidiol (CBD) is also a component of cannabis, and, according to published reports, has potential beneficial medical uses in PD. However, the literature regarding the use of cannabis in PD is minimal and inconclusive.

There are many forms of cannabis being marketed, which range in potencies of THC and CBD. Since CBD is likely to be safer and more beneficial than THC, our study drug is primarily CBD, i.e., CBD:THC is 30:1. The dose used will deliver an amount of THC too low to cause a "high."

The major purpose is to assess the effect of CBD on motor symptoms in PD, and secondarily to study its safety, tolerability, and effect on other motor and non-motor symptoms that occur frequently in PD. This is a parallel, double-blind, randomized controlled trial (RCT) with 60 participants.

Our **Hypotheses** are:

1. CBD has a significant treatment effect on PD motor symptoms.
2. CBD is safe and tolerated in PD.
3. CBD has some beneficial effect on other conditions that occur in PD, including tremor, night-time sleep, rigidity, emotional control, anxiety, pain, cognition, psychosis, and other motor and non-motor related PD signs.
4. Plasma cytokine levels (Tumor Necrosis Factor TNF-alpha, interleukin (IL)-2,4,6) elevate in PD and are neurotoxic during the progress of PD. CBD has some beneficial effect on reducing cytokine levels in PD.

Our **Specific Aims** are:
Primary Specific Aim: To evaluate the efficacy of CBD on motor symptoms in PD, specifically on the motor section of the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS).

Secondary Specific Aim: To assess the safety and tolerability of CBD in PD and to examine the effect of CBD on severity and duration of intractable tremor, night-time sleep, rigidity, emotional dyscontrol, anxiety, and pain in PD.

Exploratory Analyses:

To study the efficacy of CBD on cognition, psychosis, sleep, daytime sleepiness, mood, fatigue, impulsivity, bladder function, other motor and non-motor PD signs, restless legs syndrome, and REM sleep behavior disorder and quality of life.

To explore the effect of CBD on plasma levels of cytokines in PD.

II. Background and Significance:

Parkinson disease

Persons with PD have progressive disabling tremor, slowness, stiffness, balance impairment, cognitive deficits, psychiatric symptoms, autonomic dysfunction, fatigue, and insomnia. Tremor may interfere with necessary daily and work functions. The disorder affects approximately seven million people globally [Yao, S.C, et al. 2013; de Lau LM, et al. 2006]. The total economic cost in the US is around 23 billion dollars [Findley LJ. 2007]. In addition to economic costs, PD reduces quality of life of those affected and their caregivers.

Cognitive impairment is a common feature and ranges from delayed recall in early stages to global dementia in up to 80% at end stage. PD with dementia has been associated with reduced quality of life [Schrag A, et al. 2000], shortened survival [Nussbaum M, et al. 1998], and increased caregiver distress [Aarsland D, et al. 1999]. Community-based studies have estimated the point prevalence for dementia in PD to be 28% and 44% [Mayeux R, et al. 1992; Aarsland D, et al. 1996; Hobson P, et al. 2004; Marttila RJ, et al. 1976].

Depression, anxiety, and psychosis are also common and are particularly disabling in PD, even at the earliest stages. These symptoms have important consequences for quality of life and daily functioning, and are associated with increased career burden and risk for nursing home admission. Anxiety affects up to 40% of patients with PD [Menza MA, et al. 1993; Richard IH. 2005; Leentjens AF, et al. 2008; Stein MB, et al. 1990; Nuti A, et al. 2004; Lauterbach EC, et al. 2004; Aarsland D, et al. 2009], and may predate motor symptoms by several years. The most common anxiety disorders in PD are panic attacks (often during off-periods), generalized anxiety disorder, and simple and social phobias. Psychotic symptoms vary in frequency according to the definition used. If mild forms are included, these affect up to 50% of patients [Aarsland D, et al. 2009, Soulas T, et al. 2008]. Visual hallucinations are the most common type. However, hallucinations occur in all sensory domains and delusions of various types are also relatively common. The impact of psychosis is substantial in that it is associated with dementia, depression, earlier mortality, greater caregiver strain, and nursing home placement. Thus, it is crucial to treat these symptoms in order to optimize the management of PD patients.

In PD the levels of various cytokines (tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-2, IL-4, IL-6, epidermal growth factor (EGF), transforming growth factor (TGF)-alpha, TGF-beta1) were found significantly increased in the striatum of the postmortem brain and in ventricular or spinal cerebrospinal fluid [Nagatsu T, et al. 2000]. Cytokines may be initially neuroprotective, but may later become neurotoxic during the progress of PD [Sawada M, et al. 2006].

Generally, however, current therapies are inadequate. Medications have improved the prognosis of PD, but also have problematic adverse effects [Poewe W. 2006].

Cannabis use in PD

Since treatment of PD is often unsatisfactory and since cannabis has recently become legal and readily available in Colorado, persons with PD have been trying it. Patients have heard from the internet, support groups, and other sources that marijuana is helpful. Most are doing so on their own, without the supervision or even knowledge of their neurologist. In a survey conducted in the spring of 2014 in University of Colorado Hospital Movement Disorders clinic about 5% of 207 PD patients, average age 69, reported using cannabis [Finseth TA. et al. 2015]. In another study Katerina Venderova and colleagues reported that 25% of PD patients had taken cannabis in the General University Hospital in Prague [Venderova K, et al. 2004]. In our clinics, about 30% of the PD patients have asked doctors during their clinic visits over the past six months about cannabis. In an anonymous web-based survey, 72% PD patients reported current or past use of medical cannabis, and 48% reported reducing prescription medication since beginning cannabis use [Kindred, et al. 2017].

PD mostly affects the elderly, and affected persons often have cognitive, psychiatric, and motor problems, such as being prone to falling. Cannabis is well documented to cause psychosis, anxiety, slowness, and incoordination. Studies have also shown that chronic users have structural and functional CNS alterations [Sneider JT., et al. 2013; Matochik JA., et al. 2005; Jager G., et al. 2010; James A, et al. 2011; Battistella G., et al. 2014; Gruber SA., et al. 2005; Stone JM., et al. 2012]. Thus cannabis is expected to be risky in persons with PD. Further, there are many components of cannabis, and the cannabis preparations being sold in Colorado vary widely in composition. There are no definitive data regarding the benefits and risks in of these various preparations in PD. Studies on safety and efficacy are greatly needed to protect this fragile Colorado population.

THC vs. CBD

Many clinicians who suspect cannabis may have a positive effect upon a particular patient group do not know the cannabinoid profile that is being used. Without knowing the composition, it is impossible to draw any conclusions simply because of the huge variety of strains utilized. CBD is present to a lesser extent in street marijuana, and has been shown to limit THC's so called "psychoactive" effect [Bhattacharryya S et al, 2010; Hayakawa K, et al. 2008; Atakan Z. 2012], meaning the "high."

CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic, and antipsychotic agent, and therefore has potential beneficial medical uses [Zhornitsky S, et al. 2012; Crippa JA, et al. 2011; Iuvone T, et al. 2009; Vuolo F, et al. 2015]. Further, animal studies suggest that CBD is neuroprotective, perhaps due to reported anti-oxidative [Lastres-Becker I, et al. 2005; García-Arencibia M et al. 2007; Hayakawa K, et al. 2007] and anti-inflammatory actions [Mecha M, et al. 2013]. The ratio of THC to CBD plays a role in the preparation's therapeutic outcome: strains of cannabis with higher concentrations of CBD did not produce short-term memory impairment vs. strains with similar concentrations of THC, but lower concentrations of CBD [Englund A et al. 2013]. THC is associated with psychosis, cognitive impairment, anxiety, and psychomotor slowing [Hall W., et al. 1998, Hindocha C., et al. 2017]. **Thus, CBD has likely beneficial effects in PD, but THC may have harmful effects.**

CBD undergoes a significant first-pass effect leading to the formation of a number of metabolites, most notably, 7-hydroxy-CBD and CBD-7-oic acid [Agurell, S. et al. 1986; Harvey, D.J. 1990]. The half-life of CBD in humans was found to be between 2–5 days following oral administration. Bioavailability of oral CBD in humans was found to be around 6%, [Agurell, S. et al. 1986; Consroe, P. et al. 1991; Ohlsson, A. et al. 1986; Guy, GW. et al. 2004]. Oral administration of CBD (~700 mg) over six weeks to 14 Huntington's disease patients resulted in a low, narrow plasma range of 5.9–11.2 ng/mL [Consroe, P. et al. 1991].

Literature review of studies of cannabis in neurological disorders, especially PD

The American Academy of Neurology (AAN) Guideline Development Subcommittee performed a systematic review of medical marijuana to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders [Koppel BS, et al. 2014]. In patients with MS, oral cannabis extract is effective, and nabiximols (Sativex, GW Pharmaceuticals, 1:1 ratio of CBD to THC, with a fixed dose of 2.7 mg THC and 2.5 mg CBD) and THC are probably effective for spasticity, central pain, or painful spasms; nabiximols is probably effective for reducing bladder voids/day. Oral cannabis extract is probably ineffective for treating levodopa-induced dyskinesia in patients with PD. Oral forms of cannabis are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy.

A few studies have been reported that tested varied cannabis compositions in PD. A Class I double-blind crossover study examined the effectiveness of an extract of cannabis sativa standardized to 2.5 mg of Δ^9 -THC and 1.25 mg of cannabidiol per capsule in the treatment of levodopa-induced dyskinesias in 19 patients [Carroll CB, et al. 2004] and concluded that cannabis is probably ineffective. Note that the CBD dose used was very low. In an open-label observational study, 22 patients with PD were evaluated at baseline and 30 minutes after smoking cannabis to assess the clinical effect of cannabis on motor and non-motor symptoms of PD. There was significant improvement of sleep and pain scores. No significant adverse effects of the drug were observed [Lotan I, et al. 2014]. An anonymous questionnaire sent to all PD patients attending the Prague Movement Disorder Centre revealed that 85 (25%) out of 339 respondents had taken cannabis and 39 patients (45.9%) described mild or substantial alleviation of their PD symptoms in general, 26 (30.6%) improvement of rest tremor, 38 (44.7%) alleviation of bradykinesia, 32 (37.7%) alleviation of muscle rigidity, and 12 (14.1%) improvement of L-dopa-induced dyskinesias. Only 4 patients (4.7%) reported that cannabis actually worsened their symptoms [Venderová K, et al. 2004]. In another study, five patients with PD and severe tremor were given marijuana smoked as a cigarette in addition to other medications, including diazepam, levodopa/carbidopa and apomorphine. None of the patients experienced relief or demonstrated improvement of tremor following marijuana [Frankel J.P., et al. 1990].

Also, a few studies have been reported that tested CBD in PD. In a double-blind trial [Chagas MH, et al. 2014], 21 PD patients without dementia or comorbid psychiatric conditions were assigned to three groups of seven participants each who were treated with placebo, CBD 75 mg/day or CBD 300 mg/day for six weeks. The study found significant improvements in measures of functioning and well-being of PD patients treated with CBD 300 mg/day compared to a group that received placebo, with no psychiatric comorbidities. In another study, six PD patients with psychosis symptoms for at least three months were recruited in an open-label pilot study to evaluate the efficacy, tolerability,

and safety of CBD on PD patients who had psychosis. All patients received CBD in flexible doses (starting with an oral dose of 150 mg/day) for four weeks, in addition to their usual therapy. The psychotic symptoms showed a significant decrease under CBD treatment. CBD did not worsen the motor function and decreased the total scores of the UPDRS. No adverse effect was observed during the treatment [Zuardi A.W., et al. 2009].

Literature review of safety and tolerability of CBD

There are more than 30 reported human trials testing CBD, but doses, cannabinoid compositions, and results vary widely. Generally, the studies find CBD is well tolerated. Several studies suggest that CBD does not affect food intake, affect physiological parameters (heart rate, blood pressure and body temperature), affect gastrointestinal transit, or alter psychomotor or psychological functions [Zuardi AW, et al. 2009; Riedel G, et al. 2009; Scopinho AA, et al. 2011; Gomes FV, et al. 2013; Bergamaschi MM, et al. 2011; Bhattacharyya S, et al. 2010]. Also, chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans [Zuardi AW, et al. 1995]. Conversely, some studies reported that this cannabinoid has adverse effects, including inhibition of hepatic drug metabolism, alterations of in vitro cell viability, and decreased fertilization capacity [Bergamaschi MM, et al. 2011; Bornheim LM, et al. 1994; Narimatsu S, et al. 1990],

Extensive reports of CBD administration across a wide range of concentrations did not detect important adverse or toxic effects [Bergamaschi MM, et al. 2011]. With a median Lethal Dose (LD50) of 212 mg/kg in rhesus monkeys, CBD has a low toxicity [Rosenkrantz H, et al. 1981]. Some studies investigated mutagenic or teratogenic effects and describe no such events [Matsuyama SS, Fu TK. 1981; Dalterio S, et al. 1984]. We reviewed the tolerability of CBD doses used in human studies to date – one study suggested over 300 mg per day may exacerbate bradykinesia [Consroe P, et al. 1986], but other studies used 7.5 to 1500 mg per day without significant adverse effects [Bergamaschi MM, et al. 2011; Zuardi AW, et al. 1995]. Most studies used doses in the range of 200 - 600 mg/day.

Summary

Human trials report that CBD decreases anxiety and causes sedation in healthy individuals, decreases psychotic symptoms in schizophrenia [Zuardi AW, et al, 2006; Leweke FM et al. 2012] and PD [Zuardi AW, et al. 2009], and improves motor and non-motor symptoms and alleviates levodopa-induced dyskinesia in PD [Venderova K., et al. 2004; Lotan I, et al. 2014; Chaqas MH, et al. 2014; Zuardi AW, et al. 2009]. Given the current literature regarding CBD's possible neuroprotective effect, good tolerability, anxiolytic and antipsychotic effects and general lack of information in PD, including its effect on tremor, we feel that it is important to study its use in PD further. We hypothesized that it would reduce tremor, anxiety, and psychosis, and would be well tolerated in PD.

III. Preliminary Studies/Progress Report:

Rationale of study design

With the long term goal of determining the safety and effects of CBD in PD, we designed our study to be conducted in two stages: an open label dose escalation study, to be followed by the current parallel, randomized, double-blind, placebo-controlled study (RCT). Here we provide a progress report that describes result of the open label study, and how the findings shape the design of the randomized, controlled parallel study.

First a study drug was needed:

- We wanted a pure CBD product (as pure as possible) so that the results of the study could be assumed to be strictly from the CBD - not from THC, not from other cannabis components, and not from the "entourage' effect. Also, we did not want to expose patients to the presumed risks of THC, described in the Background and Significance, THC vs. CBD section.
- Since we would need to get an IND from the FDA the study drug would need to be of consistent good quality, made with good manufacturing processes (GMP).
- We wanted an oral preparation, since smoking was not healthy and vaporization would be challenging for PD patients. Also it would be harder to give precise doses via smoking and vaporization compared to oral. Further the oral route has longer a half-life so we could achieve a steady state with twice daily administration for a number of days that is feasible for this study.

The usual source of cannabis for study in the US is the National Institute of Drug Abuse (NIDA), but only material with THC and with a CBD:THC ratio that was too low was available. Also, only plant material was available, which would need to be taken via smoking or vaporization.

GW Pharmaceuticals was conducting Phase III trials with Epidiolex®, a 99% pure CBD preparation, in pediatric epilepsy. Epidiolex® was a good choice for our study because it had <0.1% THC, and the FDA already had the data it would require for an IND for use in our PD study. Further, it was an oil based solution that could be readily taken by our PD cohort, and there existed reasonable data on dosing. GW was finding Epidiolex® to be tolerated and beneficial in pediatric epilepsy at doses titrated up to 20-25 mg/kg/day. GW agreed to supply Epidiolex® at no cost.

We based our titration schedule and dosage on the dose that GW was finding to be effective in reducing seizures in pediatric epilepsy. Here we present the design and findings of the first stage study.

<u>Overview of open label dose-escalation study goals and methodology</u>

We conducted a Phase IIa, open label dose-escalation tolerability study (NCT02818777) in 13 PD patients at the University of Colorado between October 2016 and June 2017, using Epidiolex®. The primary outcome was safety and tolerability, measured by adverse events, changes in examinations, labs, EKGs and percentage of participants that discontinued study drug due to intolerability. The major secondary outcome measure was change in the total of two items on rest tremor in the MDS-UPDRS, and others were measures of most motor and non-motor symptoms that occur in PD. Participants had a screening visit, a baseline visit within the next three weeks, a final dose assessment visit when they have been on the maximal tolerated or the targeted study dose for 10-15 days, and a safety visit 2 weeks later. From the baseline visit, qualified participants took Epidiolex® in a 100 mg per mL sesame oil-based solution orally twice daily. Since somnolence was a reported adverse effect in the pediatric epilepsy population, and Epidiolex® had not been used in persons over age 50, we elected to be cautious and instructed participants not to drive while on study drug.

CBD was started at 5 mg/kg/day and the dose could be increased or decreased by up to 2.5 to 5 mg/kg/day until the study participants reached a maximum targeted dose (20-25 mg/kg/day) or experienced intolerable adverse events (AEs), in which case the dose would be dropped to the last

tolerated dose. Tolerability was assessed via collection of AEs during administration of the standardized phone script by study staff on the third or fifth day of each dose, and the participants were instructed whether or not to change the dose at the end of phone call. Participants filled out home diaries to increase and monitor compliance.

Participants were called at the end of each dose level. During phone calls participants were monitored for AEs, especially excessive daytime sleepiness, symptoms of hepatotoxicity, as well as changes in medical history and concomitant medications. Participants were also called three days after stopping CBD to check for signs of withdrawal. The primary outcome was safety and tolerability of CBD and the secondary and exploratory outcomes examined the effect of CBD on severity and duration of tremor and other conditions that occur in PD.

Results

Figure 1 shows the trial profile. Data from all participants that took the study drug were analyzed for safety and tolerability, while only data from those that completed a final dose assessment were analyzed for efficacy. Table 1 shows the baseline clinical and demographic characteristics of safety and efficacy analysis groups.

Figure 1. Open label study profile

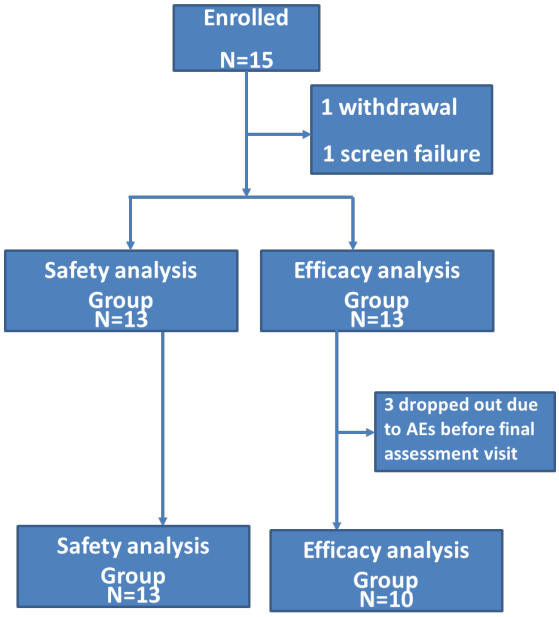


Table 1. Baseline demographics of the safety and efficacy analysis groups

	Safety analysis group (n=13)	**Efficacy analysis group (n=10)**
Age (years) (mean, SD)	68.1 (6.05)	68.7 (6.65)
Male (n, %)	10 (77%)	8 (80%)

Total MDS UPDRS score (mean, SD)	39.23 (13.32)	43.20 (12.21)
Motor MDS UPDRS score (mean, SD)	22.92 (9.30)	24.70 (8.93)
Disease duration, years (mean, SD)	6.08 (3.99)	6.30 (4.52)
Hoehn & Yahr Scale (mean, SD)	1.73 (0.56)	1.75 (0.59)
MoCA (mean, SD)	28.1 (1.63)	27.9 (1.60)
Levodopa Daily Dose Equivocation (LDDE) (mean, SD)	398.3 (331.00)	443.8 (348.97)

The demographics show that, in general, the participants had an age of onset consistent with the general population of persons with PD and they had early to early-middle stage PD. Generally they had mild bilateral motor symptoms, walked without assistance, had disease for six years, and required a relatively low dose of medication for their motor symptoms. An entry criteria required them to have a relatively significant tremor, but it would be a resting tremor and thus as a general group these participants likely had very little disability. These participants had scored in the normal range on the entry cognitive screening test.

The original protocol was that participants start at 5 mg/kg/day and titrate up to 25 mg/kg/day. Participants were to remain on each dose for three days, until the maximal tolerated dose was reached, and they were to be on that dose for 10-15 days, during which time they came in for an assessment visit.

Due to AEs experienced by our first five enrolled participants and the recommendations of the two PharmDs in our study, the protocol was changed to a slower titration and the maximal targeted dose was reduced from 25 to 20 mg/kg/day, since December 2016. There had been increased AEs and no evidence of additional benefit in the five participants beyond 20 mg/kg/day. Therefore, participants started at 5 mg/kg/day and increased every three to five days by 2.5 to 5 mg/kg/day until reaching a maximal targeted dose (20 mg/kg/day) or experiencing intolerable adverse effects.

The mean maximum CBD dose was 19.23 mg/kg/day (SD 5.44) in the safety analysis group and 20.25 mg/kg/day (SD 3.43) in the efficacy analysis group. The average length of time (SD) on study drug was 26.8 (8.0) days in safety group and 28.5 (3.4) days in efficacy group.

AEs were reported in 13 (100%) of participants, and are shown in Table 2.

Table 2. Adverse effects reported among the safety analysis group (n=13)

Adverse Effects*	**Frequency n (%)**
Diarrhea	11 (84.6)
Somnolence	9 (69.2)
Fatigue	8 (61.5)
Weight gain	4 (30.8)

Abdominal pain	3 (23.8)
Dizziness	3 (23.1)
Weight loss, nausea, anorexia, increased appetite, headache	2 (15.4)
Vomiting, flatulence, gastroesophageal reflux disease, allergic reaction, spasm, fever, weakness	1 (7.7)

*Adverse effects terminology and severity is per the Common Terminology Criteria for Adverse Events (CTCAE)

AEs were transient, and mild on average. Diarrhea, which increased with increasing doses: 1/13 (8%) at 5 mg/kg/day, 5/10 (50%) at 20 mg/kg/day, and 3/3 (100%) at 25 mg/kg/day, may be related to the increasing amount of sesame oil consumed at higher doses. There were no serious adverse events.

Elevated liver enzymes occurred in five (38.5%) participants, one symptomatic and four asymptomatic, were all on 20-25 mg/kg/day, were transient, and resolved after discontinuation of the study drug. None were associated with elevated bilirubin or INR, thus suggesting no change in liver function. CBD002, the one symptomatic participant, also had a liver ultrasound, which was normal. The DSMB and a Hepatology consultant reviewed the findings as they occurred and recommended continuing the study with close monitoring.

There were no clinically significant changes in vital signs, electrocardiogram, or physical and neurological exams or labs (complete blood count, renal function and liver function) other than the one symptomatic participant with elevated liver enzymes.

Three participants (23%) stopped study drug due to intolerability, one due to rash at 5 mg/kg/day, one to abdominal pain and gas at 17.5 mg/kg/day and one to fatigue, diarrhea, and elevated liver enzymes at 25 mg/kg/day.

The efficacy analysis found no change in the designated major secondary outcome, total of two items on rest tremor in the MDS-UPDRS, at the final maximal targeted dose compared with baseline. However, there were improvements in some motor signs, Table 3, and some non-motor signs, Table 4.

Table 3. Change in motor scores among efficacy analysis group (n=10)

	Baseline Mean (SD)	**Final Mean (SD)**	**Change Mean (SD)**	**P Value***
Total MDS UPDRS**	43.20 (12.21)	35.50 (14.31)	-7.70 (9.39)	0.0115
Motor MDS UPDRS**	24.70 (8.93)	18.60 (9.66)	-6.10 (6.64)	0.0041

*paired T-test, permutation distribution

**Higher scores reflect more severe symptoms; reduction in scores from baseline means improvement

Table 4. Change in non-motor scores among efficacy analysis group (n=10)

	Baseline	**Final**	**Change**	**P Value***

	Mean (SD)	Mean (SD)	Mean (SD)	
SCOPA Sleep Night-time**	5.70 (2.95)	2.90 (2.60)	-2.80 (3.91)	0.0401
Emotional behavioral dyscontrol short form**	44.39 (7.91)	39.70 (6.75)	-4.69 (6.14)	0.0474

*paired T-test, permutation distribution
**Higher scores reflect more severe symptoms; reduction in scores from baseline means improvement

The other motor and non-motor assessments were not changed – however, participants had very little daytime sleepiness, fatigue, pain, cognitive dysfunction, psychosis, impulsivity, depressed mood, anxiety, levodopa induced dyskinesia, REM sleep behavior disorder, or restless legs syndrome, which often occur in PD. Thus our testing of these symptoms was not meaningful. Interestingly, although participants frequently reported daytime somnolence and fatigue, there was no change on the formal assessments tools.

Upon completion of the study each participant and their study partner was interviewed regarding driving. Responses were obtained from 12/13 participants and their study partners. Eleven in each group thought that the participant would have been safe to drive while on the study drug. The one other participant and their study partner thought that the participant should not drive during the first couple of days when he started a new higher dose, due to somnolence. No participants reported feeling "high." No study partners thought the participant got "high" from the study drug.

Discussion

The primary outcome was safety and tolerability. Generally, the study drug, Epidiolex®, was well tolerated. While adverse effects, mainly somnolence, fatigue, and diarrhea, were frequent, they were generally mild, and there was a relatively low percent of participants, i.e., 23%, that stopped study drug due to intolerability, and no clinically significant abnormalities in testing except for elevated liver enzymes.

Regarding the elevated liver enzymes, GW had seen elevations in their pediatric group, but the pattern was hepatocellular, not cholestatic as in our population. Perhaps age contributed to the difference, since GW had not used Epidiolex® in persons over age 50. In our study liver enzymes were only checked on the highest dose and most of the affected participants were asymptomatic, so it is not clear at what dose the liver enzymes became elevated. **Lisa Forman, MD, Hepatologist, reviewed detailed information on these participants and of all the liver function results in all participants, commented that the changes may represent early liver injury and felt that with close monitoring it was reasonable to move on with the next study. She will be a consultant on the randomized controlled parallel study.** The DSMB also reviewed all the data and noted that all changes resolved with cessation of treatment and discussed the possibility the elevations may be related to medication vehicle, i.e., sesame oil. Most participants were talking 10-20 ml per day on the final maximal dose when the testing occurred. **The DSMB agreed with continuation of the study with the monitoring plan in this protocol.**

Solid conclusions regarding efficacy are not possible from an open label trial, but this study suggested benefit in motor symptoms, night-time sleep, and emotional dyscontrol.

In summary, findings from the open label study suggest that CBD may be efficacious in PD, and that a lower dose may offer the best benefit to risk ratio, compared to the higher dose that GW reports is useful in pediatric epilepsy. Therefore, a lower dose will be used in the randomized controlled parallel study.

GW declined to provide Epidiolex® for the randomized controlled parallel study, as they are focused on getting FDA approval for it in pediatric epilepsy. We therefore searched for other study drug options. We want to give a dose that provides a reasonable dose of CBD, per the PI's judgement, and that provides a low enough THC dose so that participants will not get "high."

The PI (Dr. Leehey) considers the following to judge what would be a reasonable dose of CBD:

- That is <1/2 of what we were giving on the open label study, i.e., <12.5 mg/kg/day
- That is at least the minimal amount that persons are likely getting from dispensaries, e.g., estimate that a minimal dose some persons see some benefit from would be 1.67 mg/kg/day mg pure CBD (if they could get pure CBD); this is based on my experience with what patients tell me they feel when they take specific products
- that is in the range of 100-200 mg/day, since this is the range that Professor Raphael Mechoulam has found to be effective based on his experience in a variety of medical illnesses [personal communication]

Several factors need to be considered when determining the minimal dose of THC that will cause a person to feel "high," including route of delivery, peak and half-life of THC, active metabolite (11-OH-THC), co-existing CBD content, participant's prior cannabis exposure, etc. The maximal oral dose of THC one would want to give that would not cause a person to feel high is approximately <5 mg, and varies depending on these many factors. Also the timing of repeated dosing should be ≤ 6 hours, given the pharmacodynamics and pharmacokinetics of THC [Raphael Mechoulam, personal communication, 2017; Colorado Department of Revenue, 2015; L.E. Hollister, et al. 1981; Grotenhermen F et al. 2003; Oviedo A et al. 1993].

Another consideration regarding selecting the study drug for the randomized controlled parallel study is that we have to use a study drug that is either from the only approved federal source, i.e., NIDA, or that the FDA has already evaluated and approved for use in clinical trials. Given that we have to complete this study before funding ends, June 2019, our timeframe does not allow the time the FDA would probably needed to ensure any drug that has not yet been evaluated meets its requirements. Further, the DEA has restrictions on what cannabis products can be studied under a given, e.g., Dr. Leehey's, Schedule 1 license.

We considered other factors while choosing a study drug to use in the randomized controlled parallel study. While Epidiolex® was the best option for our open label dose-escalation study, we recognized that a disadvantage of using a pure CBD preparation and such a high dose is that it is different from what persons with PD obtain from local dispensaries. While local dispensaries sell cannabis that is

high in CBD, their products are not pure CBD and markedly lower doses are used, so our findings would not be very applicable to the products our PD patients are taking. The study drug and dosage to be used in the randomized controlled parallel study will be more similar to what persons with PD are obtaining from local dispensaries. Another consideration is that THC, CBD, and the other components of the cannabis plant interact, e.g., the "entourage" effect, and this interaction may have a meaningful effect, which would not be occurring in Epidiolex® since it is such a pure CBD product.

Therefore, we will use a cannabis extract with 59.3% CBD and 1.96% THC (30:1 CBD:THC) from NIDA. We will give 1.25 mg/kg twice daily of CBD and 0.041 mg/kg twice daily of THC. This equals 2.11 mg/kg twice daily (4.22 mg/kg/day) of the NIDA extract. For our average sized PD participant (84 kg) in our prior trial this will be approximately 100 mg CBD and 3.3 mg THC twice daily (morning and evening - > 6 hours apart). Therefore, the THC dose is below the threshold, ~5mg, that is expected to cause a person to feel "high." The interval of >6 hours is to minimize the possibility of the THC effect to overlap/build up. The extract solution will be in a sesame oil formulation, 100 mg/ml of CBD, so the participant would ingest 1 ml (100 mg CBD) twice daily. This much smaller amount of CBD and of oil is expected to be better tolerated, including less likely to cause liver enzyme elevations, than the study drug in the open label study.

In comparison to the open label study, the amount of CBD in this study is less than 15% (19.23/2.5). This dose and the fact that there is a small amount of THC is in the product makes this study drug more similar to what persons are receiving from local dispensaries, although it may generally have a higher in CBD content. Therefore, the results of the study using this product will be more generalizable to the Colorado PD population.

Whether participants should be allowed to drive has been carefully considered:

- Medical problems (motor and/or cognitive issues) can affect the ability of older adults to drive safely. Persons with PD are permitted to drive until they develop significant motor and/or cognitive issues, and this is monitored by their treating physician.
- Colorado law prohibits driving while intoxicated with cannabis - because of the "high" produced by THC component. CBD does not produce the high that occurs from THC [Niesink RJ, 2013].
- The amount of THC in this randomized controlled parallel study is very unlikely to cause any "high" effect.
- In the open label study participants and their study partners felt participants would have been safe to drive, and that study involved doses of CBD >7 times higher than participants in this randomized controlled parallel study will be taking. The only concern was from one participant regarding having somnolence with increases in the dosing. In the randomized controlled parallel study the dose will be started and increased only once, and, again, the dosage will be markedly lower.
- Generally, medications that may cause somnolence or CNS adverse effects have warnings provided on the packaging. For example, patients who take opioid products are instructed that opioids may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Persons are warned not to drive or operate dangerous machinery unless they know they are tolerating the effects of the medication and know how they will react to it. Patients who take clonazepam, a medication related to

diazepam (Valium), are also told not to drive, operate heavy machinery, or do other dangerous activities until they know how the clonazepam affects them. This labeling was directed by the FDA.

Our study DSMB met October 29, 2017, considered the points above, and suggested that the study should include a clear statement that the effects of CBD on driving are not well known, that some users experience significant sedation but the effects vary among individuals, and that participants should not drive until they know how the drug will affect them. The DSMB also asked that the PI consider a systematic assessment of sedation after administration of the first dose of study drug. Therefore, our protocol includes:

- To help the participant understand how the study drug affects them we will monitor them in clinic. A validated Alertness Scale will be administered before the dose and again when the blood level is expected to reach peak – in three hours.
- We will have the following language in the consent form and will emphasize it verbally: "Whether or not the study drug affects driving ability is not known. You should not drive or operate heavy machinery while taking study drug."

IV. Research Methods

A. Outcome Measure(s):

Primary Specific Aim: To evaluate the efficacy of CBD on motor symptoms in PD.
Primary Outcome Measures: Change of MDS-UPDRS Part III (motor examination) from baseline to the end of 2.5 mg/kg/day of CBD. MDS-UPDRS Part III assesses the motor signs of PD.
Secondary Specific Aim: To examine safety and tolerability of CBD and the effect of CBD on severity and duration of tremor, night-time sleep, rigidity, emotional dyscontrol, anxiety, and pain in PD.
Secondary Outcome Measures:

1. To evaluate the safety and tolerability of CBD in PD:

1.1 By examining the frequency of study-related adverse events at each dose level between the two groups (treatment vs. placebo). Adverse events are measured at study visits, starting with an open ended question (Do you notice any effects, good or bad, of the study drug?) and followed by a series of yes/no questions regarding adverse effects (including previously reported adverse effects of CBD and general common adverse effects of medications and the hepatotoxicity), and all the effects we hypothesize in the study. For each adverse and beneficial reported effect, further questions will be asked, such as when did the effect start and how is it progressing, etc. In addition, since a major dose limiting effect is somnolence, the daytime sleepiness part of the SCOPA-sleep is included.

Tolerability is judged and supervised by PI and sub-I (who are MDs), based on their clinical expertise.

Abuse-related AEs will also be collected at screening, each dose assessment visit, liver function monitoring visit, and safety follow up visit. The abuse-related AEs is provided by MedDRA Preferred Terms (PTs), including:

Euphoria-related terms: Euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect.

Terms indicative of impaired attention, cognition, and mood: Somnolence, mood disorders, and disturbances.

Dissociative/psychotic terms: Psychosis, aggression, confusion, and disorientation.
Related terms not captured elsewhere: Drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders.
The Abuse-related AEs will be collected and recorded on a CRF that includes timing of the event, duration, severity, indication if more than one event was observed simultaneously, if other drugs were taken by subjects at the time of the event, correlation between the onset of the event, and the use of study drug.
Well trained investigators will capture and report cases of abuse, misuse, or addiction and monitor for drug accountability discrepancies before starting trials.

1.2 Liver monitoring plan: Liver function tests (including Alk Phos, ALT, AST, GGT, Total Bili) will be tested at each dose during treatment phase. Study participants will be asked to check for symptoms of hepatotoxicity when on study drug. A Hepatology consultant, Lisa Forman, MD., has agreed advise on liver function aspects of the study.

1.3 By monitoring and comparing vital signs, orthostatic blood pressures, physical exam, EKG, and labs (hematology, complete metabolic profile, and urinalysis) between the two groups. These are collected during study visits.

1.4 By conducting standardized assessment tools on cognition, anxiety, psychosis, sleep, daytime sleepiness, alertness, mood, fatigue, pain, impulsivity, suicidality, and motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder, and quality of life during study visits. The change from baseline to each dose is compared. The assessment tools are:

<u>Cognition:</u>

- MoCA - is designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visual-constructional skills, conceptual thinking, calculations, and orientation. [Freitas S, et al. 2013].
- Cognitive assessment battery:
  Intellectual Functioning Estimate
  1) Wechsler Test of Adult Reading (WTAR) - Word reading tests are an established method of establishing a premorbid estimate of verbal intellectual functioning, which will serve as an estimate of premorbid cognitive reserve.
  Attention/Processing Speed/Executive Functioning
  2) Grooved Pegboard Test: Manipulative dexterity, including finger speed, is assessed.
  3) Symbol Digit Modalities Test (SDMT) - The SDMT is a measure of processing speed and working memory that has proven to be sensitive to cognitive impairment in MS that has both oral and written trials (only the oral trial will be administered given the anticipated difficulty patients will have with tremor). Participants are presented with a key at the top of a page pairing unique symbols with single digits. Participants are required to provide the correct digit with symbols that are presented on the rest of the page. The number of correct responses provided in 90 seconds on the oral and written trials, respectively, is recorded.
  4) Paced Auditory Serial Addition Test (PASAT) - The PASAT is a more complex measure of processing speed and working memory in which a series of digits is presented to participants at varying intervals (i.e., 2 seconds, 3 seconds). Participants must add each

digit to the immediately preceding digit for the duration of each trial. The number of correct responses for each trial is recorded.

5) Controlled Oral Word Association Test (COWAT) - The COWAT is a measure of speeded verbal fluency and word retrieval in which participants are asked to say as many words as they can that begin with each of three letters for 60 seconds. The total number of words generated across all three trials is recorded.

Memory Functioning

6) Hopkins Verbal Learning Test-Revised (HVLT-R) - The HVLT-R is a measure of verbal learning and memory in which participants are asked to learn a 12-item word list over three trials (total immediate learning). A delayed free recall trial is administered after 20 minutes, followed by a yes/no recognition trial.

Visuospatial construction

7) Judgment of Line Orientation (JOLO) - The JOLO is test of visuospatial functioning which measures a person's ability to match the angle and orientation of lines in space. Patients are asked to match two angled lines to a set of 11 lines that are arranged in a semicircle and separated 18 degrees from each other.

Language Functioning

8) Semantic Verbal Fluency – Semantic Verbal fluency is a measure of speeded verbal fluency and word retrieval in which participants are asked to say as many animal names/fruits and vegetables for 60 seconds. The total number of words generated across all three trials is recorded.

<u>Anxiety:</u>

- Anxiety short form - is component of the Neurol-QOL (Quality of Life in Neurological Disorders) Measurement System, which is a collaborative effort of the National Institute of Neurological Disorders and Stroke and a number of partnering institutions. This measurement system was designed to be responsive to the needs of researchers in a variety of neurological disorders and to facilitate comparisons of data across clinical trials in different diseases. The short form is comprised of eight items that were selected from the respective item bank. Items have five response options (e.g., 1=Never, 2=Rarely, 3=Sometimes, 4=Often, 5=Always). Respondents generally can answer five questions per minute.

<u>Psychosis:</u>

- Neuropsychiatric Inventory (NPI) - is a valid and reliable scale. It was developed to provide a means of assessing neuropsychiatric symptoms and psychopathology of patients with Alzheimer’s disease and other neurodegenerative disorders. It has proven to be sensitive to change and has been employed to capture treatment related behavioral. The NPI is administered to a caregiver/significant other who has detailed knowledge of the participant’s behavior.

<u>Sleep and daytime sleepiness:</u>

- Scales for Outcomes in Parkinson’s disease (SCOPA)sleep - is a valid, reliable, short scale for assessing nighttime sleep (NS) and daytime sleepiness (DS) in patients with PD [Marinus J, et al. 2003]. The SCOPA-Sleep consists of two parts. The NS subscale addresses sleep problems and includes five items with four response options. Participants

have to indicate how much they were bothered by particular sleep problems, ranging from 0 (not at all) to 3 (a lot). The five items address sleep initiation, sleep fragmentation, sleep efficiency, sleep duration, and early wakening. The maximum score of this scale is 15, with higher scores reflecting more severe sleep problems. One additional question evaluates overall sleep quality on a 7-point scale. The DS subscale evaluates daytime sleepiness and includes six items with four response options, ranging from 0 (never) to 3 (often). Participants indicate how often they fell asleep unexpectedly, fell asleep in particular situations, how often they had difficulty staying awake, and whether falling asleep in the daytime was considered a problem. The maximum score is 18, with higher scores reflecting more severe sleepiness. The average score for PD is 5.2 ± 4 for DS and 4.9 ± 4 for NS.

- Stanford Sleepiness Scale (SSS): The Stanford Sleepiness Scale is a quick and easy way to assess how alert the participant is feeling. SSS is validated and probably the most widely used instrument for the assessment of participant's sleepiness [Maclean AW, et al. 1992, Hoddes et al, 1972].

<u>Mood:</u>

- Depression short form - is a component of the Neurol-QOL (Quality of Life in Neurological Disorders) Measurement System, which is a collaborative effort of the National Institute of Neurological Disorders and Stroke and a number of partnering institutions. This measurement system was designed to be responsive to the needs of researchers in a variety of neurological disorders and to facilitate comparisons of data across clinical trials in different diseases. The short form is comprised of eight items that were selected from the respective item bank. Items have five response options (e.g., 1=Never, 2=Rarely, 3=Sometimes, 4=Often, 5=Always). Respondents generally can answer five questions per minute.
- Emotional and behavioral dyscontrol short form - is a component of the Neurol-QOL Measurement System, which is a collaborative effort of the National Institute of Neurological Disorders and Stroke and a number of partnering institutions. This measurement system was designed to be responsive to the needs of researchers in a variety of neurological disorders and to facilitate comparisons of data across clinical trials in different diseases. The short form is comprised of eight items that were selected from the respective item bank. Items have five response options (e.g., 1=Never, 2=Rarely, 3=Sometimes, 4=Often, 5=Always). Respondents generally can answer five questions per minute.

<u>Fatigue:</u>

- Fatigue Severity Scale (FSS) - is a self-report nine-item questionnaire with questions related to how fatigue interferes with certain activities and rates its severity. The items are scored on a seven point scale with 1= strongly disagree and 7= strongly agree. The minimum score is 9 and maximum score possible is 63. The higher the score, the greater the fatigue severity.

<u>Pain:</u>

- Pain Intensity 3a short form and Pain Interference 4a short form - are components of the Patient Reported Outcome Measurement Information System (PROMIS), which was

developed by the NIH to provide a standardized metric for measuring physical, mental, and social health across chronic diseases. PROMIS instruments were developed using item response theory and have been tested in more than 20,000 individuals drawn from the general US population. The Pain Intensity instrument assesses how much a person hurts. The Pain Interference instrument measures the self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Each question has five response options ranging in value from one to five.

Impulsivity:

- Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) is a rating scale designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD. QUIP-RS has four primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the four ICDs (compulsive gambling, buying, eating, and sexual behavior) and three related disorders (medication use, punding, and hobbyism). It uses a five-point Likert scale (score 0-4 for each question) to gauge the frequency of behaviors, and instructs patients to answer questions based on behaviors that occurred in the preceding four weeks (or any four-week period in a designated time frame). Scores for each ICD and related disorder range from 0 to 16, with a higher score indicating greater severity (ie, frequency) of symptoms. The total QUIP-RS score for all ICDs and related disorders combined ranges from 0 to 112 [Weintraub D, et al. 2012].

Suicidality:

- The Columbia-Suicide Severity Rating Scale (C-SSRS) is a suicidal ideation rating scale. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." The scale identifies behaviors which may be indicative of an individual's intent to commit suicide. The C-SSRS has been found to be reliable and valid in the identification of suicide risk in several research studies.

Motor and non-motor PD signs:

- Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)- The MDS UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerning a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers and IB that is completed by the patient with or without the aid of the caregiver, but independently of the investigator. It can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This

part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

- Unified Dyskinesia Rating Scale (UDysRS) is developed to evaluate involuntary movements often associated with treated Parkinson's disease. There are two primary sections: Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)] and Objective [Part 3 (Impairment) and Part 4 (Disability)]. On-Dyskinesia refers to the choreic and dystonic movements described to the patient as "jerking or twisting movements that occur when your medicine is working." Off-Dystonia should be described to the patient as "spasms or cramps that can be painful and occur when your Parkinson's disease medications are not taken or are not working."
- Timed Up&Go (TUG) test: The TUG test is a validated, widely used test for evaluating balance and walking ability associated with advancing age, neurological (especially PD), or other disorders [Bohannon RW, et al. 2006].
- Non-motor symptoms Scale for Parkinson's disease (NMSS): NMSS is a validated 30-item scale for the assessment of NMS in PD. NMSSS contains nine dimensions: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany.

Restless Legs Syndrome:

- International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome (IRLS): IRLS is a ten-question instrument for measuring severity of restless legs syndrome (RLS). The scale reflects participants assessment of the primary features (reflected in questions 1 through 3 and 6 of the scale), intensity and frequency of the disorder (questions 7 and 8 of the scale) and associated sleep problems (reflected in questions 4 and 5 of the scale). The scale also includes questions which probe the impact of symptoms on the patients' mood and daily functioning (question 9 and 10 of the scale). Each question has a set of five response options graded from no RLS or impact (score=0) to very severe RLS or impact (score=4). This produced a total scale whose overall score could range from 0 to 40. IRLS sum score and subscales (symptoms in questions 1, 2, 4, and 6 through 8; symptoms impact in questions 5, 9, and 10) at every time point will be recorded. Item 3 is used for the total score for overall RLS severity.

REM Sleep Behavior Disorders:

- REM sleep behavior disorder screening questionnaire (RBDSQ) – is a 10-item, patient self-rating instrument assessing the participant's sleep behavior with short questions that have to be answered by either "yes" or "no". Items 1 to 4 address the frequency and content of dreams and their relationship to nocturnal movements and behavior. Item 5 asks about self-injuries and injuries of the bed partner. Item 6 consists of four sub items assessing nocturnal motor behavior more specifically, e.g., questions about nocturnal vocalization, sudden limb movements, complex movements, or bedding items that fell down. Items 7 and 8 deal with nocturnal awakenings. Item 9 focuses on disturbed sleep in general and item 10 on the presence of any neurological disorder. The maximum total score of the RBDSQ is 13 points.

Bladder function:

- Overactive Bladder Symptom Score (OABSS) is a validated self-administered questionnaire consisting of seven questions on a five-point Likert scale. Five questions are related to urinary urgency and two are related to daytime and nighttime urinary frequency.

Quality of Life

- Parkinson's Disease Questionnaire (PDQ-39): is a reliable, valid, responsive, acceptable, and feasible as the tool for the assessment of quality of life in Parkinson's disease patients. There are 39 questions in the long form Parkinson's Disease Questionnaire, with eight discrete scales: mobility (10 items), activities of daily living (six items), emotional well-being (six items), stigma (four items), social support (three items), cognitions (four items), communication (three items), and bodily discomfort (three items). Patients are asked to think about their health and general well-being and to consider how often in the last month they have experienced certain events. Patients are asked to indicate the frequency of each event by selecting one of five options (Likert Scale): never/occasionally/sometimes/often/always or cannot do at all.
- EuroQoL-5 Dimension-5 level (EQ-5D-5L): consists of two pages-the EEQ-5D-5L descriptive system and the EQ Visual Analogue Scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problem, slight problems, moderate problems, severe problems, and extreme problems. This is a widely used well validated simple assessment that is comparable across disease populations.

1.5 By assessing and comparing the proportion of participants that discontinue the study due to study drug intolerance in the two groups (treatment vs. placebo).

2. Overall PD status - Change of total MDS UPDRS scores from baseline to the end of 2.5 mg/kg/day visit.

3. Tremor - Change of Severity and duration of tremor from baseline to the end of 2.5 mg/kg/day visit: Tremor is measured by the change from baseline to the end of 2.5 mg/kg/day between the two groups:

3.1 Total of scores on items 3.17 and 3.18 in part III of the MDS-UPDRS in the ON state (when anti-PD medication is working). Item 3.17 is rest tremor amplitude. Extremity ratings range from 0: Normal, No tremor to 4: Severe, >10 cm in maximal amplitude. Lip/Jaw ratings are similar but smaller amplitudes. Item 3.18 is constancy of rest tremor: 0 (no tremor) to 4 (present >75% of the exam).

3.2 Item 2.10 in part II of the MDS-UPDRS in the ON state. Item 2.10 is patient's tremor experience: 0 (Not at all. I have no shaking or tremor) to 4 (Shaking or tremor causes problems with most or all activities).

3.3 Total of scores on items 3.15 and 3.16 in part III of the MDS-UPDRS in the ON state. Item 3.15 is postural tremor of the hands: 0: Normal (No tremor) to 4: Severe (Tremor is at least 10 cm in amplitude). Item 3.16 is kinetic tremor of the hands: 0: Normal (No tremor) to 4: Severe (Tremor is at least 10 cm in amplitude).

3.4 Constancy and amplitude of tremor measured by Tremor GUI MATLAB package: Tremor will be measured at clinic and at home (twice a day, two hours after breakfast dose and two hours after dinner dose, for 2 consecutive days after screening visit, three consecutive days before baseline visit and each dose assessment visit). Each time tremor will be measured for

90 seconds. The constancy (percentage of tremor per minutes) and amplitude will be recorded using the package. See Appendix 2. Dr. John Thompson is collaborating on the tremor device.

4. Motor sub-scores - Rigidity, bradykinesia, axial, and bulbar sub-scores will also be calculated – these are pulled from the motor MDS-UPDRS – the change from baseline to the end of 2.5 mg/kg/day visit.
5. Emotional control - Emotional and behavioral dyscontrol short form score change from baseline to the end of 2.5 mg/kg/day visit.
6. Anxiety – Anxiety short form score change from baseline to the end of 2.5 mg/kg/day visit.
7. Pain - Pain intensity short form score change from baseline to the end of 2.5 mg/kg/day visit.
8. Sleep sub-study- The primary outcome is the change from baseline to the end of 2.5 mg/kg/day visit on wake after sleep onset (WASO, length of periods of wakefulness occurring after sleep onset), secondary outcomes are changes from baseline to the end of 2.5 mg/kg/day visit on: percentage of total sleep time spent in each sleep stage (N1, N2, N3, and REM), frequency of leg movements during REM, sleep efficiency (proportion of total time in bed spent asleep), total sleep time and the scales of SCOPA-night-time sleep, ISI, DBAS-16, and Pittsburgh Sleep Quality Index.
   - **8.1** Night-time sleep - SCOPA-night-time sleep score change from baseline to the end of 2.5 mg/kg/day visit.
   - **8.2** Insomnia Severity Index (ISI): ISI is a verified seven-item self-report questionnaire assessing the nature, severity, and impact of insomnia. A five-point Likert scale is used to rate each item (e.g., 0=no problem; 4=very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).
   - **8.3** Modified Dysfunctional Beliefs and Attitudes about Sleep Questionnaire (DBAS-16): A validated self-reported questionnaire designed to identify and assess various sleep/insomnia-related cognitions (e.g., beliefs, attitudes, expectations, appraisals, attributions).
   - **8.4** Pittsburgh Sleep Quality Index: is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.
   - **8.5** Home Sleep Monitoring: Polysomnography (PSG) will be performed using a Type II portable, unattended monitor in patients’ home. Study subjects will come to clinic to have electrodes and equipment attached by the study coordinator for electroencephalogram (EEG), electro-oculogram (EOG: bilateral), electrocardiogram (EKG), chin electromyogram (EMG), abdominal and thoracic effort belts, oxyhemoglobin saturation (SpO2; finger pulse oximetry; Nonin, Minneapolis, Minnesota), airflow (oral-nasal thermistor), and pressure transducer. Explicit instructions will be reviewed with each subject prior to leaving clinic: directions, timing for completing each questionnaire and initiating sleep recording. A registered polysomnographic technologist (PRSGT) will download and inspect the quality of the recorded signal of the PSG prior to scoring the data. Drs. Russell Bowler and Greg Kinney are collaborating on conduct of the polysomnograms.
9. Skin evaluation for seborrheic dermatitis in collaboration with Drs. Robert Dellavalle and Andrea Steel: Dermatology Quality of Life Index (DLQI) and dermatology photography. DLQI is a dermatology-specific quality of life instrument. It is a simple 10-question validated questionnaire that has been used in over 40 different skin conditions. Dermatology photography (Appendix 3):

take a picture of the central face, as this is the most common area of seborrhea, and send it, with appropriate privacy safeguards, to dermatologists, Dr. Robert Dellavalle, MD., and Dr. Andrea Steel.

10. Changes of outcome measures 1-7 and 8.1-8.4 from baseline to the end of 1.25 mg/kg/day will be compared between the two groups.

Exploratory Analyses:

To study the efficacy of CBD on the aspects of PD listed in Section IV, 1.4 and plasma levels of cytokine in PD.

Exploratory Outcome Measures: The efficacy of CBD on these aspects of PD are measured by the same standardized tools used for safety and tolerability (listed in Section IV, 1.4). The effect of CBD is also measured by Clinical Global Impression (CGI) and Patient Global Impression-improvement (PGI-I) and Change (PGI-C). CGI is a three-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The CGI is rated on a seven-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the more severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately. PGI-I is a global index that may be used to rate the response of a condition to a therapy (transition scale). It is a simple, direct, easy to use scale that is intuitively understandable to patients. PGI-C is rated on a seven-point scale, evaluating all aspects of patient' health and determining if there has been an improvement or not. The change from baseline to the end of 2.5 mg/kg/day is compared between the two groups.

Change of plasma levels of cytokine from baseline to the end of 2.5 mg/kg/day will be compared between the two groups.

Table 5. Measurement tools performed in current study.

Assessments	Primary (efficacy)	Secondary (safety +tolerability)	Exploratory (efficacy)
MDS UPDRS Part III motor score	X		
MoCA		X	X
Detailed cognitive battery		X	X
Anxiety short form		X	X
NPI		X	X
SCOPA-Sleep		X	X
Sleep sub-study		X	X
Stanford Sleepiness Scale (SSS) "Alertness Test"		X	
Depression short form		X	X
Emotional and Behavioral dyscontrol short form		X	X
Fatigue Severity Scale		X	X
Pain Intensity 3a and Interference 4a short forms		X	X

QUIP-RS		X	X
MDS UPDRS total and sub-scores		X	X
Unified Dyskinesia Rating Scale (UDysRS)		X	X
NMSS		X	X
OABSS		X	X
TUG		X	X
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)		X	X
The Columbia-Suicide Severity Rating Scale (C-SSRS)		X	
International Restless Legs Syndrome Study Group Rating Scale (IRLS)		X	X
PDQ-39		X	X
EQ-5D		X	X
CGI			X
PGI			X
Tremor measure			X
Skin tests		X	X
Plasma levels of cytokine			X

B. Description of Population to be Enrolled:

Parkinson disease - Persons with PD have progressive disabling tremor, slowness, stiffness, balance impairment, cognitive deficits, psychiatric symptoms, autonomic dysfunction, fatigue, and insomnia. Tremor may interfere with necessary daily and work functions. The disorder affects approximately seven million people globally [Yao, S.C, et al. 2013; de Lau LM, et al. 2006]. PD usually begins around age 60, but it can start earlier. Treatment, typically medications such as levodopa and dopamine agonists, improve early stage symptoms. As the disease progresses and dopaminergic neurons continue to be lost, these drugs become less effective, and levodopa produces disabling motor fluctuations in most patients. PD invariably progresses with time. Untreated individuals are expected to lose independent ambulation after an average of eight years and be bedridden after ten years [Poewe W. 2006]. In people taking levodopa the progression of symptoms to a stage of high dependency from caregivers is on average 15 years.

C. Study Design and Research Methods

C.1 Study design

The major purpose of this study is to assess the efficacy of CBD on motor symptoms of PD, and secondarily to study the safety and tolerability of CBD and other efficacy, particularly regarding tremor in PD. The study has been powered to detect a clinically significant reduction in MDS UPDRS Part III motor scores. This is a 1:1 parallel, double-blind, randomized controlled trial (RCT) with 60 participants. We will be recruiting up to 75 participants; the goal is to have 60 participants (30 in CBD group and 30 in placebo group) complete the study.

See Appendix 1 Schedule of Events for more detail on study design.
The study drug is obtained from NIDA. How the dose is started and escalated and what target dose is chosen is based on human literature and our open label study, as discussed in Section III under Discussion.

The study is a randomized, placebo controlled, double-blind parallel design with two treatment arms, each of approximately 2-3 weeks duration. In the 2-3 week treatment phase participants will start study drug and titrate up to the maximum tolerated or targeted dose (2.5 mg/kg/day of CBD). Each participant will have a screening visit, baseline visit within four weeks, 2 dose assessment visits (1.25 mg/kg/day and 2.5 mg/kg/day), and a safety visit (5 visits total). Participants will be evaluated at each dose level for monitoring adverse events, as well as changes in medical history and concomitant medications. Further, in case CBD alters the reliability of self - report, repeated measures will be taken on the third to fifth day at each dose during the clinic visits or at home. The assessments include the assessment of tolerability and symptoms of hepatotoxicity, SCOPA-sleep, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, and EQ-5D-5L. Participants are called 3 and 7 days after stopping the study drug to check for signs of withdrawal. At dose assessment visits, urinary CBD and metabolites will be tested. To maximize compliance the coordinator calls the participant to remind them the next day's clinical visit. To increase compliance with taking study drug, participants will be asked to fill out a diary at home. The diary will be a record of the date and time participants take study drug, dose of the study drug, and adverse and beneficial events. Study drug is dispensed at the baseline visit. Participants will measure their tremor using Tremor GUI MATLAB twice a day (two hours after breakfast dose and two hours after dinner dose) for two consecutive days after screening visit, three consecutive days prior to baseline and each dose assessment visit, as well as during the clinic visits. To evaluate the possible somnolence effect of CBD, participants will be evaluated their alertness before and three hours after they take the study drug at baseline visit.

<u>Inclusion and Exclusion criteria:</u>
Inclusion criteria:

- Male or female participants 40 - 85 years of age.
- Willing and able to give informed consent (including through use of a legally authorized representative (LAR), if necessary).
- Idiopathic PD, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria
- ON motor MDS UPDRS >20.
- Anti-parkinsonian medication is fixed for at least one month prior to the day the participant starts study drug treatment.
- If MoCA<22 participant must have a designated caregiver that agrees to ensure study protocols followed. This includes accompanying patient to study visits and being available for study phone calls.
- Must have a driver or available transportation (including provided Uber vouchers) to drive them to and from study visits and for other transportation needs during the treatment period.
- Has a significant other (someone who knows the participant well) that is appropriate for doing the NPI assessment, and agrees to do so
- Agrees to not take more than 1 gram per day of acetaminophen, due to a possible interaction with study drug that could increase risk of hepatotoxicity.

**Note: the LAR (if required for informed consent), caregiver (required for those with MOCA<22), and significant other (required for all participants) may be the same person in some cases. In other cases, these may be different people.

Exclusion criteria:

- Known or suspected allergy to cannabinoids or excipients used in the study drug formulation.
- Cannabis is detectable at the screening visit by blood testing or at the baseline visit by urine testing. If cannabis is detected at either the screening or baseline visit, then the participant is a screen fail and may return >14 days later for a repeat screening visit. If cannabis is again detected at either the screening or baseline visit, then the participant is excluded and not allowed to rescreen.
- History of drug or alcohol dependence; defined by prior inpatient stay(s) for this or that patient states s/he has a history of this.
- Use of dopamine blockers within 180 days and cocaine, and MAO-A inhibitors within 90 days of baseline.
- Currently taking tolcapone, valproic acid, felbamate, niacin (nicotinic acid) at ≥2000 mg/day or nicotinamide (nicotinic acid amide or nicotinamide) at ≥3000 mg/day, isoniazid and ketoconazole due to risk of liver injury and clobazam and ketoconazole because of risk of toxic interactions with the study drug. These medications need to be stopped 90 days before the baseline visit.
- Unstable medical condition.
- Any of the following laboratory test results at screening:
  - Hemoglobin < 10 g/dL
  - WBC <3.0 x 10^9/L
  - Neutrophils <1.5 x 10^9/L
  - Lymphocytes < 0.5 x 10^9/L
  - Platelets <100 x 10^9/L
  - Hemoglobin A1C > 9%
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 times the upper limit of normal. Persons with stable liver disease of known etiology can be included, unless total bilirubin or prothrombin time/INR is abnormal.
- Is pregnant or lactating, or has a positive pregnancy test result pre-dose.
- If a sexually active female, is not surgically sterile or at least two years post-menopausal, or does not agree to utilize an effective method of contraception from screening through at least four weeks after the completion of study treatment, using one of the following: barrier methods (diaphragm or partner using condoms plus use of spermicidal jelly or foam, preferably double-barrier methods); oral or implanted hormonal contraceptive; intrauterine device (IUD); or vasectomized male partner.
- Planned elective surgery during study participation.

Cytokines testing: Enrolled subjects who meet the following criteria will have blood collected for cytokines test, along with other blood tubes being collected, at screening and at 2.5 mg/kg/day dose assessment visit. If these criteria are not met at screening but are met at baseline visit, the draw for cytokines testing may be done at the baseline visit instead.

- Not currently taking or has not taken in the past 10 days chemotherapeutic or anti-inflammatory medications. A sample of such medications is listed in Appendix A, but it is not possible to list all medications in these broad classes. Thus, the PI will evaluate each subject's medications and decide if any meet this exclusion criteria.
- Does not have currently active cancer or is not currently being treated for cancer or inflammatory or atopic disease, listed in Appendix 8. It is not possible to list all such disorders, so the PI will evaluate each subject's medical status and decide if they have any meet that this exclusion criteria.
- No current kidney failure or renal dialysis, chronic respiratory disease requiring daily oxygen, active or treated seizures, and hyperthyroidism.
- No current or in the past seven days any infection, for example common cold or urinary tract infection, again to be at discretion of the PI.

Participants will be consented that the effects of CBD on driving are not known, that some users experience significant sedation but the effects vary among individuals and that participants should not drive while taking the study drug. A limited amount of Uber vouchers will be provided to subjects to assist with transportation needs during the treatment period. Alertness test will be done before and three hours after the first dosing is administered at baseline visit to judge the alertness degree for driving.

Dose escalation strategy:
Study product (CBD or placebo) will be started at 1.25 mg/kg/day of CBD (once a day) for four days and then increase to 2.5 mg/kg/day of CBD (twice a day) for 10 (+4) days. Tolerability will be assessed at each dose during each clinic visit. Subjects may take a reduced dose for the duration of the study according to the investigator's medical judgement.
Regarding possible drug interactions, study pharmacists will be provided the calculated dose based on body weight, the list of the subject's medications, and additional relevant clinical information. The final study drug dose will be that recommended by the study pharmacists.

Assessment of tolerability of each dose level
Tolerability will be assessed at each dose via collection of adverse events and administration of the standardized questionnaires by appropriate study staff during each clinic visit. Severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), which is published by the National Cancer Institute (NCI) of the National Institutes of Health (NIH):
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs. Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.
The protocol for dose adjustments, maintenance, and discontinuation based on adverse effects is as follows:

- For participants with a grade 1 adverse event the dose will be increased by up to 1.25 mg/kg/day, or if they are on the maximal targeted dose (2.5 mg/kg/day) it will be continued.
- For participants with a grade 2 adverse event the dose will be reduced by 1.25 mg/kg/day or less.
- For participants with a grade 3 or 4 adverse event that the Investigator determines is unrelated, the dose will be continued. When the adverse event is stabilized or resolved, e.g., participant is stable after a hip fracture repair, the dose will be increased unless they are already on the maximum targeted dose.
- For participants with a grade 3 or 4 adverse event that the Investigator determines is related the study drug will be stopped and not restarted.

The Investigator will determine relatedness as described in Section IV. C.6, and will consider the adverse event related if she determines there is at least a reasonable possibility.
The major dose limiting effect, is somnolence. To monitor for this closely, the daytime sleepiness part to the SCOPA-sleep will be administered during each clinic visit, thus before each increase in dose. A score of >7 (note that the average score for PD is 5.2 ± 4), if greater than before and considered problematic by the appropriate clinical staff, would result in the participant being instructed to drop to the prior dose for five more days before increasing the dose.
Liver function test is done at the study visit on the third to fifth day of each dose. Additional assessments of safety and tolerability is done at the study visit when the participant is on the maximum tolerated or targeted dose. The same protocol for dosing is applied for both adverse events found during study visits.
The CTCAE criteria are used to determine dose level adjustments and for participant and study stopping rules (Section IV C.5). Adverse events will be collected and reported as discussed in Section IV C.6.

Urine collection, storage and transfer for cannabis and metabolites test: The purpose of the urine cannabis and metabolites test is to develop a methodology to quantitate CBD metabolites. Participants will be given two urine cups, 100 mL each, at the baseline visit, 1.25 mg/kg/day dose assessment visit, and 2.5 mg/kg/day dose assessment visit. Urine cannabis and metabolites test will be done at dose assessment visits (1.25 and 2.5 mg/kg/day) and safety follow up visit. On the phone call before the day of dose assessment visits and safety follow up visit, participants will be reminded to collect urine in the morning of the study visit. They are asked to fill each up at least three-quarters full if possible, and to bring them to the visit (no refrigeration needed). Upon arrival of the visit the study coordinator will collect and store the urine cups in a -80°C freezer until shipment. For shipment, samples for each individual will be placed onto a sealable plastic bag together with an absorption pad. All the individual bags will be placed into a large sealable plastic bag with contains absorption material. Samples will be placed onto a Styrofoam box and will be shipped on dry ice. Urine samples will be labeled with the name of the study and the date and time of collection. Urine samples will be shipped for analysis to Dr. Jost Klawitter at iC42 Clinical Research and Development. Dr. Klawitter is in charge of analyzing the specimens as well as contributing to interpreting results and writing publications. He receives only coded specimens with no PHI.

The blood and urine samples will be stored in Dr. Klawitter's lab for possible unspecified future research under the consent of study subjects.

Procedures at each visit

Visit 1-Screening visit: Decisional capacity to provide informed consent will be evaluated as much as possible during prescreening as well as at screening visit during informed consent discussion. Capacity will be assessed by asking questions such as: Why is the study being done? What is the study asking you to do? What are the risks of the study? Is the study voluntary? Etc. If in PI's opinion the subject does not have cognitive capacity to provide informed consent, legally authorized representative (LAR) will be required to provide informed consent prior to any study procedures being completed.

Prior to onsite screening visit, the research coordinator sends the consent form to the study participant through email or mail and schedules a time to explain the study and discuss the consent form with the participant via phone Zoom, or other HIPAA-compliant platform. The study participant doesn't need to print the consent or sign the consent. We will finish the consent at on site screening visit with the PI or Sub-I. If the participant is unable to discuss the consent form in advance, consent discussion and review can be done in clinic.

On site screening visit: Consent, demographics, concomitant medications, family medical history, medical history and physical examination (complete physical exam and detailed neurological exam), vital signs, orthostatic blood pressures, tremor evaluation, MDS-UPDRS III, H&Y rating, MOCA, Drug, alcohol and tobacco abuse screening test, safety assessments (as listed in section IV A, including, QUIP-RS, C-SSRS, NPI, Emotional and behavioral dyscontrol short form, Drug abuse-related AEs), EKG and safety labs (including hematology, hemoglobin A1C, Complete metabolic profile and Liver Function Tests), blood cannabis analysis testing, plasma cytokine level tests, serum pregnancy test (for women childbearing potential), and inclusion/exclusion criteria are done. Study participants are instructed not to take cannabis from outside source throughout the study. Tremor constancy and amplitude measure device (Tremor GUI MATLAB package) is dispatched and participants are instructed to use the Tremor GUI MATLAB package to measure their tremors in the clinic and will perform it independently before they leave the clinic. They will measure the tremors at home twice a day (two hours after breakfast dose and two hours after dinner dose) for two days after screening visit and three days prior to the baseline visit.

To reduce in-person clinic visit time, part of the above procedures can be done remotely after onsite screening visit, including: demographics, concomitant medications, family medical history, medical history, safety assessments (C-SSRS, NPI, emotional and behavioral dyscontrol short form, drug abuse related AEs).

Visit 2- Baseline visit: Eligibility confirmation (including tremor evaluation), medical history, concomitant medications collection, formal drug interaction assessment, vital signs, orthostatic blood pressures, brief physical exam, MoCA, MDS-UPDRS, H&Y rating, UDysRS, NMSS, OABSS, tremor constancy and amplitude two hours after taking study drug, TUG test, cognitive assessment battery (including tests of verbal intellectual function, attention, processing speed, executive function, verbal learning and memory, visuospatial memory, speeded verbal fluency, and word retrieval), Anxiety short form, Depression short form, SCOPA-Sleep, ISI, DBAS-16, Pittsburgh Sleep Quality Index, Alertness test, RBDSQ, C-SSRS, IRLS, Fatigue severity scale, Pain intensity and interference short form, PDQ-39, EQ-5D, CGI, PGI, urine drug (THC) test (urine dipstick test), urine pregnancy test (women childbearing potential) and study drug dispensing is done and, if appropriate, randomization. Skin evaluation (Dermatology Intake Form, DLQI, and dermatology

photography) will be done. Alertness test (Stanford Sleepiness Scale) will be done before and three hours after the first dosing was administered at clinic. Tremor evaluations reviewed. Home diary is also dispensed. Participants will pick up PSG equipment and home sleep test instruction and do the home sleep test for up to 14 to three nights before the baseline visit. Participants will complete Morning Daytime Dysfunction questionnaire and sleep diary on the morning after the sleep test. PSG equipment and data collected before or at this visit. Participants take the first dose and are instructed on how to take the medication and how to fill out the diary at home. Participants will be monitored for 2 hours and vital signs and orthostatic blood pressures will be checked at one hour after taking the study drug. Participants are also told to bring in empty, partially used, and unused bottles of study drug at next clinical visit. Participants will be told not to take the study drug on the day of the next visit, as they will take it upon arrival under instruction by study staff. Participants will be given two urine cups, 100 mL each, and will be instructed to collect their urine the morning of the 1.25 mg/kg/day assessment visit. They are asked to fill each cup at least three-quarters full, if possible, and to bring them to the visit (no refrigeration needed). Participants are instructed to measure their tremors at home for three days prior to each dose assessment visit.
Part of the above procedures can be done remotely through Zoom or other HIPAA-compliant platform, between screening and onsite baseline visit: Eligibility confirmation, medical history, concomitant medications collection, NMSS, OABSS, Anxiety short form, Depression short form, SCOPA-Sleep, ISI, DBAS-16, Pittsburgh Sleep Quality Index, Dermatology Intake Form, DLQI, Alertness test, RBDSQ, C-SSRS, IRLS, Fatigue severity scale, Pain intensity and interference short form, PDQ-39, EQ-5D.

Visit 3 (3-4 days, 1.25 mg/kg/day) and Visit 4 (14 (+4) days, 2.5 mg/kg/day), dose assessment visits: On the morning of the visits, participants will collect their urine and bring it to the visits. Study coordinator will collect and store the urine cups in a -80°C freezer until shipment for urinary CBD and metabolites test. Concomitant medications, change in medical history, vital signs, orthostatic blood pressures, complete physical exam, detailed neurological exam, MDS-UPDRS, UDysRS, H&Y rating, tremor constancy and amplitude, NMSS, TUG, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, Fatigue Severity Scale, Pain Intensity and Interference short form, MoCA, RBDSQ, QUIP-RS, C-SSRS, NPI, SCOPA-sleep, ISI, DBAS-16, Pittsburgh Sleep Quality Index, IRLS, OABSS, EQ-5D, PDQ-39, CGI, PGI, blood draw for safety labs (hematology, Complete Metabolic Profile and Liver Function Tests) and blood cannabis analysis, urinalysis, ECG, and urine pregnancy test are done. Study drug compliance check, adverse event check and blinding assessment are done. Participants will take their study drug upon their arrival to the clinic and record the taking time. Blood is drawn for cannabis testing and safety labs three hours after the dose. Participants will be monitored and vital signs and orthostatic blood pressures will be checked at one and three hours (2.5 mg/kg/day dose assessment visit) after taking the study drug. Home diary is collected and reviewed. Urine cups dispensed.
In addition to the procedures above, for Visit 3 (3-4 days, 1.25 mg/kg/day), participants are told to bring in empty, partially used, and unused bottles of study drug at next clinical visit. Participants will be told not to take the study drug on the day of the next visit, as they will take it upon arrival under instruction by study staff. Participants are instructed to measure their tremors at home for three days prior to 2.5 mg/kg/day dose assessment visit. Participants will be given the questionnaires of SCOPA-sleep, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, EQ-5D-5L, C-SSRS. Study staff will call the participants on the 3rd to 5th day on 2.5 mg/kg/day to remind them to complete the questionnaires and bring it in at next clinic visit.

For 2.5 mg/kg/day dose assessment visit, participants will pick up PSG equipment and home sleep tests instructions, and perform PSG during the night after at least seven days on the 2.5 mg/kg/day or tolerated max dose, and until (and including) the third night before the visit. Participants will complete Morning Daytime Dysfunction questionnaire and sleep diary on the morning after the sleep test. PSG equipment and data are collected before or at this visit. Participants will also perform full cognitive assessment battery tests and skin evaluation (DLQI and dermatology photography) during this visit. Study drug participants returned are disposed per the SOP at 2.5 mg/kg/day dose assessment visit. Plasma cytokine levels test at 2.5 mg/kg/day visit.

Visit 5-Safety follow up: Vital signs, orthostatic blood pressures, history and complete physical examination, concomitant medications collection, MDS-UPDRS, H&Y rating, UDysRS, NMSS, RBDSQ, QUIP-RS, C-SSRS, NPI, SCOPA-sleep, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, Fatigue Severity Scale, Pain Intensity and Interference short form, IRLS, OABSS, PDQ-39, EQ-5D-5L, adverse event check, urine pregnancy test, and cannabis lab testing are done. Hematology, complete metabolic profile, urinalysis, and EKG will be done if there was a clinically significant change at the high dose evaluation visit compared to baseline visit. The PI will evaluate the participant for signs of withdrawal. On the morning of the visit, participants will collect their urine and bring it to the visit. Study coordinator will collect and store the urine cups in a -80°C freezer until shipment for urinary CBD and metabolites test.

Part of the above procedures can be done remotely 1-3 days prior to or after safety follow up visit: medical history, concomitant medications collection, NMSS, RBDSQ, C-SSRS, NPI, SCOPA-sleep, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, Fatigue Severity Scale, Pain Intensity and Interference short form, IRLS, OABSS, PDQ-39, EQ-5D-5L, adverse event check.

C.2 Study Drug: CBD:

The study drug is supplied by NIDA; see Appendix 4 for Certificate of Analysis (COA). The study drug (CBD) is provided in the form of a thick liquid and will be diluted into a 100 mg/ml formulation with sesame oil. This procedure will be done by the PharmDs (Jacci Bainbridge, PharmD, Matthew Makelky, PharmD, and Professor Tom Anchordoquy as a consultant) or PI, according to the protocol we develop with guidance from NIDA and the University of Mississippi researchers that produced the material. The placebo will be made by the study Pharm Ds from USP grade sesame oil and food coloring. Because the placebo may be slightly different in appearance or taste, two study modifications are being done to preserve the blind. First, the study drug will be put into brown opaque bottles and the only study personnel to see the actual study drug will be the unblinded PharmD and the blinded CTRC PA that instructs the subject on how to take study drug. Further, the study drug is administered in a closed, vented room in the CTRC that removes the odor of cannabis within four minutes. After the study drug is administered and the study drug bottle closed, the PA will stay with the subject in the closed room while it is being vented for at least 10 minutes. The study design of parallel groups is being used instead of the original crossover design that was planned.

ElSohy Laboratories, Incorporated (ELI) will perform the stability testing. The laboratory is registered with the FDA and the DEA (Manufacturing and Analytical), all the planned analytical

procedures are validated, and the lab has extensive experience with the drug substance (CBD extract) and with a very similar drug product to ours. Controls for both CBD and THC content are used. The stability testing will be done in real time.
The shelf life will be determined by the testing described below. The final drug product will be stored at room temperature, 25°C.
The microbial testing for the final drug product will be carried out according to UPS 61 (total aerobic microbial count and total combined yeast/mold count) and USP 62 (for salmonella and E. coli), and the specification and acceptance criteria will be the same as recommended in USP <111> (microbiological examination of non-sterile products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use for non-sterile, non-aqueous products with oral administration). This will be the same for the product and placebo.
Microbial Specifications:

- Route of Administration: Nonaqueous preparations for oral use.
- Total Aerobic Microbial Count:<103 cfu/mL
- Total Combined Yeasts/Molds Count: <102 cfu/mL
- Specified Microorganism(s): Absence of Escherichia coli (1 g or 1 mL)

The CBD extract will be shipped and stored frozen. The final drug product will be prepared within 24 hours of being given to the subject. Once prepared it will be kept at room temperature. The subject will take home the final drug product in 60 ml amber bottles and take it orally for up to 20 days. The stability study will be carried out only at room temperature at the following time points: 0, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, and 3 months. Duplicate analyses will be performed at each time point. Microbial testing will be carried out at the 0 time point for both drug product and placebo and again at the end of one month to show that no change in bioburden occurred during the one month storage at room temperature.
Three manufacturing batches will be prepared (validation lots). These will be subjected to analysis to show consistency of the manufacturing process.
The analytical specification will be that the analytical value should be within 10% of the nominal concentration (i.e. 100 mg CBD/ml should analyze for 90-110 mg/ml). The analytical method is validated for Linearity, LOD, LOQ, accuracy and precision for both CBD and THC.
The specification for the drug product will be:
Appearance: Greenish-yellowish brown, oily solution
Potency: CBD Concentration = 100mg/mL = 10% solution; ±10% variation in measured potency (90 to 110 mg/mL) is allowed due to manufacturing and analytical variation.
Other Cannabinoids:

- THC not greater than 5 mg/mL (0.5% solution)
- CBD:THC ratio not less than 20:1

We will provide the FDA with a final report with statistical analysis.
We will prepare oral solution of 100 mg/ml CBD (10% CBD) and 3.31 mg/ml THC (0.33% THC) in 60 ml capacity amber glass bottles.
Each bottle will have 30 or 40 mL depending on how much the subject weighs.

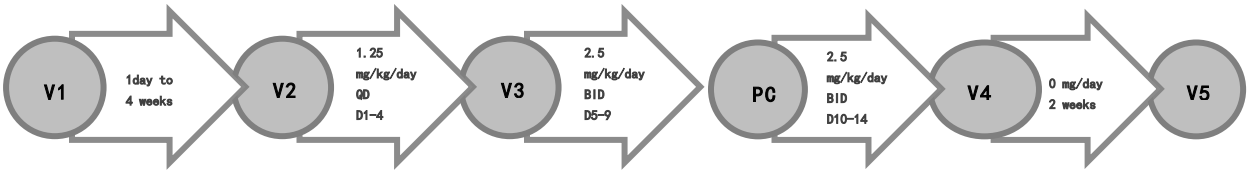
- 30 mL CBD Cannabis extract oral solution filled: Each bottle will have 5055 mg of extract placed in it (3000 mg CBD), filled to 30 mL mark with sesame oil.
- 40 mL CBD Cannabis extract oral solution filled: Each bottle will have 6740 mg of extract placed in it (4000 mg CBD), filled to 40 mL mark with sesame oil.

Dosage Form and Strength

Pre-dilution dosage unit: CBD Cannabis Extract (depending on the subject's weight it will contain either 3 or 4 gms CBD)
Diluted Unit: CBD Cannabis Oral Solution (100mg/ml CBD)

The FDA has approved our IND. The DEA has approved the PI's amended DEA Schedule 1 license. Participants will be given bottles with 30/40 ml of study drug, at concentration of 100 mg/ml CBD or placebo and instructed how to take it. The study drug is best taken fasted, as food will increase Cmax and delay Tmax. The study drug could be taken with a small amount of food as needed if the participants experience nausea. The study drug will be taken orally, started at 1.25 mg/kg/day of CBD, once daily in the morning for four days, then increased to 2.5 mg/kg/day, twice daily at standard times, with a minimum of six hours apart (Figure 2 dosing plan). Participants are instructed to take it before breakfast (30 to 60 minutes) and the same before dinner. Participants are instructed not to drink grapefruit for seven days prior to the first dose of study medication and during the rest of the study.
The study drug is taken as normal on the mornings of assessments. As far as practical, the same assessor carries out assessments at each visit. Assessment data are stored and not made available at subsequent visits.

Figure 2: Dosing plan.



Legend: V: Visit. D: Day. QD: once a day. BID: twice a day. PC: Phone call.
V1: -28 to -1 day. Screening visit.
V2: Day 1, Baseline visit: The first day of CBD 1.25 mg/kg/day. 4 weeks within screening visit.
V3: Day 3/4, 1.25 mg/kg/day dose assessment visit: The third to fourth day of CBD 1.25 mg/kg/day.
PC: Day 7-9, Questionnaire survey reminder phone call. The third to fifth day of CBD 2.5 mg/kg/day.
V4: Day 14, 2.5 mg/kg/day Dose Assessment Visit: The 10^{th} day of CBD 2.5 mg/kg/day.
V5: Day 28, Safety follow up visit, 2 weeks after stopping study drug.

Participants take their routine anti-PD medication on the day of their clinical visit, and when ON (PD medications are working) the testing is done.
CBD and metabolite levels will be measurements: Blood CBD and metabolite levels will be measured at screening visit, each dose assessment visit, and safety follow up visit. Urinary CBD and metabolites levels will be tested at dose assessment visits and safety follow up visit.
Potential drug-drug interactions:
The PI has worked with Jacci Bainbridge, PharmD, to study possible drug interactions. CBD concentrations and adverse events will be monitored in the presence of concomitant medications which are inhibitors of CYP3A4 and 2C19.
There are many possible interactions, but some are more likely and clinically relevant. Thus, the PI will especially monitor for clinical symptoms that may be associated with these particular interactions. The following drugs may increase the level of CBD: fluoxetine, fluvoxamine, fluconazole, ticlopidine, and nefazodone. The following dugs may decrease the level of CBD:

carbamazine, phenytoin, phenobarbital, rifampin, and St. John's Wort. The following drugs may interact with CBD to cause their levels to increase: alprazolam, clonazepam, lorazepam, oxazepam, temazepam, zolpidem, clopidigrel, narcotics (codeine, methadone, oxycodone, hydromorphone, morphine), cyclosporine A, tacrolimus, propranolol, and acetaminophen. Participants will be instructed not to take more than 1 gram per day of acetaminophen.

CBD is a potent inhibitor of CYP2C19. The plasma level of clobazam, which is metabolized by CYP2C19, therefore is expected to increase if CBD is added. Clobazam, per Micromedix, causes somnolence (16-25%). In a recent study, Lancet Neurology 2016;15:270-278, using the a much higher dose of CBD study drug than as in our trial there was approximately twice as much somnolence AEs reported in participants on both CBD and clozabam than in participants on CBD and not clobazam. Thus clobazam will be exclusionary in this study.

The following is additional information relevant to the population of this study, Parkinson disease (PD).
CBD is metabolized by the hepatic CYP450 enzymes 2C19 and 3A4 and an inhibitor of these isoenzymes. Thus the expectation is that selegiline levels could increase. CBD may mildly induce the expression of 1A2, 2B6, and 3A4. Thus the expectation is that levels of rasagiline, ropinirole, and selegiline may decrease.
CBD is a relatively potent inhibitor of UGT1A9 and UGT2B7 and has no significant effect on other UGT isoenzymes. The expectation is that the level of rotigotine may increase.

CBD is highly protein bound, so rasagiline, selegiline, and rotigotine levels may increase transiently. Checking plasma concentration levels of these anti-PD medications is not a routine clinical practice. Thus the PI will monitor participants on these medications for clinical changes. The most important and likely adverse effects of a clinically significant increase in the level of selegiline is anxiety, dyskinesia, agitation, insomnia, and hallucinations. The most important and likely adverse effects of a clinically significant decrease in the levels of rasagiline, ropinirole, and selegiline is an increase in the motor symptoms of Parkinson disease, which are resting tremor, bradykinesia, rigidity, and postural instability. The most important and likely adverse effects of a clinically significant increase in rotigotine is low blood pressure, somnolence, and impulse control disorders.
Instructions to Participants at the End of Each Stage:
We will provide the following instructions about continued marijuana use at the end of the study to facilitate safety:
Cannabis (marijuana) is composed of many substances. Street cannabis is high in tetrahydrocannabinol (THC), which causes the "high" feeling. Street cannabis has lower concentrations of cannabidiol (CBD). The cannabis preparations sold at dispensaries have various concentrations of THC and CBD. The ratio of THC to CBD plays a role in a preparation's beneficial and adverse effects. Studies to date suggest that THC is especially risky in person with PD, because it may worsen thinking and coordination and cause psychiatric symptoms. The precise effects of all the substances in cannabis is unknown. Using marijuana should be under the supervision of your physician, with monitoring the symptoms of PD and other diseases, as well as the interactions of marijuana and other drugs you take.

C.3 Randomization and drug dispensation:

Patients who consent will be stratified by age (40-60 and 61-80) and disease severity (H&Y 1-2.5, 3-5) and divided into blocks of a few patients each, depending on order of recruitment. Equal numbers from each block will be assigned to CBD or placebo group in random order.
Dr. Leehey, the PI, will obtain an amended DEA Schedule 1 license prior to the shipment of the study drug and all procedures of drug handling will be according to DEA specifications and protocol provided by University of Mississippi researchers. Briefly, designated study personnel will receive the study drug, do the formulation procedure, store it, measure and label it. The PI or PharmDs will dispense to the participant.

C.4 Blinding assessment and Un-blinding procedures:

Blinding assessment:

Active drug and placebo will look and taste the same as much as possible. Participants and all study personnel except for Dr. Sillau, Dr. Bainbridge, and her fellow, are blinded.
At the end of treatment phase visits, participants will be asked about the treatment allocation they think they were assigned. The answers are taken in forms with five responses of "strongly believe the treatment is drug," "Somewhat believe the treatment is drug." "Somewhat believe the treatment is placebo," "Strongly believe the treatment is placebo," and "Don't know."

Un-blinding procedures:

The identity of the treatment assigned to individual participants can be revealed in an emergency only. The PI is responsible for ensuring that the instructions on how to request un-blinding of treatment are stored safely, that their location is known, and that access is readily available to the relevant staff in case of an emergency. Dr. Sillau, the statistician will provide the information when un-blinding is requested by the PI. As a back-up, Dr. Sillau will provide a file of sealed envelopes to the PI, which is kept in a locked file in her office. The location is known to the PI, sub-I, and coordinator. A sealed envelope coded with each participant number is provided. In the event that Dr. Sillau is not available to provide break the blind the PI and designated staff can do so.
A participant's treatment assignment should only be un-blinded when knowledge of the treatment is essential for the safety of the participant. Un-blinding for any other reason will be considered a protocol deviation.

C.5 Stopping rules:

Note there are no interim analyses planned.

Participant stopping rules:

- If participant cannot tolerate the study drug at any dose level
- if participant develops a CTCAE criteria grade 3 or 4 adverse event per that the Investigator determines is related the study drug
- Pregnancy or breast-feeding
- Requested by participant to terminate treatment
- Failure by the participant to attend consecutive study visits
- Participant is at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB, Food and Drug Administration (FDA)

If a participant is withdrawn from the study, all efforts will be made to complete the early termination visit that includes efficacy assessments and safety follow-up. In addition, women of childbearing potential will have a post-study pregnancy test performed at the early termination visit.

Withdrawals and the reason for withdrawal will be tabulated by treatment group. The number and percentage of participants who complete the study will be summarized by treatment group. The number and percentage of participants who withdraw from the study will be tabulated by original treatment group and last treatment taken at time of withdrawal. Study medication discontinuations will be summarized in a similar fashion.

Participants will be advised that they are free to withdraw from the study at any time. Reasons that participants may be withdrawn from the study include the following:
Participant discontinued study medication and wishes to withdraw.
Participant consent is withdrawn.

Study stopping rules

- Participants are unable to be recruited
- Study drug becomes unavailable
- Participants are unable to tolerate the study drug at any dose level
- Discovery (from this or other studies) of an unexpected, serious, or unacceptable health hazard to participants, i.e., development of the same adverse event, CTCAE criteria grade ≥3, related to study drug in ≥2 participants
- At the discretion of the IRB, Food and Drug Administration (FDA).

C.6 Adverse events assessments:

Adverse events will be classified according to the grades defined in the Common Terminology Criteria for Adverse Events (CTCAE). Any adverse event or abnormal laboratory test value that is serious (see definition below) and occurs after administration of the investigational product will be documented by the Sponsor-Investigator within 24 hours of discovery of the event.

Severity of Adverse Events

The severity of each AE/SAE will be classified into one of five defined grades. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs. Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.
The severity of the AE will be recorded in the appropriate section on the AE page of the CRF.

Serious Adverse Events (SAEs)

The evaluation of severity will be distinguished from the evaluation of "seriousness." A severe event might not meet the criteria for seriousness and a serious event might be evaluated as mild or moderate. For example, a participant might have a severe headache that does not require hospitalization and is consequently not serious; or a participant might have a mild myocardial infarction that requires hospitalization and is therefore serious.

An SAE is any untoward medical occurrence at any dose that:

- Results in death during the period of protocol-defined surveillance. Death due to PD will not be considered an SAE. However, if a patient requires hospitalization due to an AE related to PD, the specific sign or symptom leading to hospitalization will be reported as an SAE. If death due to PD occurs outside of hospitalization and is considered to be due solely to the patient's PD, no SAE report is required. The death will be recorded as part of PD and patient disposition.
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant, in the view of the Investigator, is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it was more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization*.
- Results in persistent or significant disability or incapacity.
- Results in a congenital anomaly/birth defect.

*Hospitalization: Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it might be (e.g., bronchospasm, laryngeal edema). Hospital admission and/or surgical operations planned before or during a study are not considered SAEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. It should be noted that for this study, participants with planned or anticipated surgery should not be enrolled into the study.

Important Medical Events: Medical and scientific judgment will be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical or surgical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious, and examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Development of drug dependency or drug abuse.

<u>Unanticipated Adverse Events</u>

An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized. An "unexpected" adverse reaction is one in which the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

<u>Relationship to Study Drug</u>

The relationship or association of the AE/SAE to study drug will be characterized as "related" or "not related." An AE/SAE will be considered to be <u>not</u> related to the use of the study drug if any of the following criteria are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related);

- A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug).

Adverse events will be considered "related" to the use of the study drug if none of the "not related" criteria are met. The Investigator will use clinical judgment to determine the relationship of the AE/SAE to study drug. An AE/SAE may be related to the study drug, other concomitant medications, intercurrent illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the Investigator will make a determination based on the most likely causal relationship. Alternative causes, such as the natural history of any underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered. The Investigator will also take into account the Investigator's Brochure in the causality assessment. There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, the Investigator will make an assessment of causality prior to transmission of the SAE report to the Sponsor, as the causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change the causality assessment in light of follow-up information by amending the SAE report accordingly.

SAEs that are considered related (i.e., determined to be possibly, probably, or definitely related) to the investigational product by the Sponsor-Investigator will be followed until the event resolves or stabilizes. Any SAE that occurs after treatment completion, and is considered by the Sponsor-Investigator to be related to the investigational product, will be documented and reported as appropriate.

<u>Reporting Serious Adverse Events to Regulatory Agencies</u>

Events meeting the following criteria will be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report

The Sponsor-Investigator will notify the appropriate review division at the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Sponsor-Investigator to be possibly related to the use of the investigational product. An unexpected adverse event is one that is not already described in the investigational product's Investigator Brochure. Such reports are to be telephoned or faxed to the appropriate review division at FDA and to the manufacturer of the investigational product within seven calendar days of first learning of the event.

15 Calendar Day Written Report

The Sponsor-Investigator will notify the appropriate review division at the FDA, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of the investigational product.

Written IND Safety reports will include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the Sponsor-Investigator with the IND concerning similar events will be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events will be submitted to the appropriate review division at the FDA, and the manufacturer of the investigational product within 15 calendar days of first learning of the event, using FDA Form 3500A.

Written IND Safety Reports will be submitted to the IRB(s) of record per IRB Guidelines.

IND Annual Reports

The Sponsor-Investigator will provide annual reports to the appropriate review division at the FDA within 60 days of the IND's anniversary date, until the IND is withdrawn or terminated.

C.7 Risks of Study Drug:

A review of 25 studies on the safety and efficacy of CBD did not identify significant side effects across a wide range of dosages, including acute and chronic dose regimens, using various modes of administration [Bergamaschi M.M., et al. 2011]. There are no rare but serious side effects reported. The most frequently occurring side effect was somnolence (i.e.drowsiness) (25%). Other side effects, in order of prevalence, include: diarrhea (19%), decreased appetite (19%), fatigue (13%), convulsion (11%), increased appetite (9%), status epilepticus (8%), lethargy (7%), weight increased (7%), and weight loss (6%) [Devinsky O, et al. 2016]. Other side effects include extrapyramidal symptoms, increased prolactin levels, weight gain, increased serum concentrations of antiepileptic drugs, and elevated liver function tests.

Table 6 and 7 show the adverse reactions of pure CBD, i.e., Epidiolex®.

Table 6. Adverse events and treatment-emergent serious adverse events of purified CBD reported in pediatric treatment-resistant epilepsy (an open-label interventional trial, maximum dose 25-50 mg/kg/day of CBD) [Devinsky O, et al. 2016]

Adverse events (reported >5% of patients)	N =162
Somnolence	41 (25%)
Decreased appetite	31 (19%)
Diarrhoea	31 (19%)
Fatigue	21 (13%)
Convulsion	18 (11%)
Increased appetite	14 (9%)
Status epilepticus	13 (8%)
Lethargy	12 (7%)
Weight increased	12 (7%)
Weight decreased	10 (6%)
Drug concentration increased	9 (6%)
Treatment-emergent serious adverse events	
Status epilepticus	9 (6%)
Diarrhoea	3 (2%)
Weight decreased	2 (%)
Convulsion	1 (<1%)
Decreased appetite	1 (<1%)
Drug concentration increased	1 (<1%)
Hepatotoxicity	1 (<1%)
Hyperammonaemia	1 (<1%)
Lethargy	1 (<1%)
Unspecified pneumonia	1 (<1%)
Aspiration pneumonia	1 (<1%)
Bacterial pneumonia	1 (<1%)
Thrombocytopenia	1 (<1%)

Table 7. Adverse events occurring with a frequency of greater than 10% in either trial group (RCT in 120 children and young adults with the Dravet syndrome and drug-resistant seizures, 20 mg/kg/day of CBD) [Devinsky O, et al. 2017]

System Organ Class and Preferred Term	Cannabidiol (n=61)	Placebo (n=59)
Gastrointestinal		
Diarrhea	19 (31%)	6 (10%)
Vomiting	9 (15%)	3 (5%)
General		
Fatigue	12 (20%)	2 (3%)
Pyrexia	9 (15%)	5 (8%)
Infections: upper respiratory tract infection	7 (11%)	5 (8%)
Metabolism: decreased appetite	17 (28%)	3 (5%)
Nervous system		
Convulsion	7 (11%)	3 (5%)
Lethargy	8 (13%)	3 (5%)
Somnolence	22 (36%)	6 (10%)

D. Description, Risks and Justification of Procedures and Data Collection Tools:
Patients could be uncomfortable about their survey of cannabis, drug, alcohol, and tobacco use that is administered during screening in both Stages. However, this information is essential for their safety, to check for history of addiction, and if this is found then the participant could be harmed by participating and thus would be excluded. In addition, this information is needed for scientific rigor. Federal funding sources are likely to want this information to understand the relevance and importance of future cannabis studies. The importance of having the information will be explained and the participant will be reminded that participation is voluntary.

CBD's effect on many aspects of PD are being studied, besides the primary and major secondary outcome measures. This makes the visits longer and may be tiring for some participants. To minimize discomfort participants will be offered sufficient breaks and maximal efforts for efficiency will be made to minimize visit time. The reason for the many assessments is twofold. First, PD is a complex disorder with many different disabling symptoms, and secondly, it is prudent to maximize the information from this study. Studies on cannabis are sorely needed, since many PD patients are taking this potentially dangerous drug as it becomes more available. Access is becoming more available throughout the US as more states are considering legalizing use of medical and recreational marijuana. Besides this lack of vital information, obtaining funding and getting through all the regulatory steps required for study of cannabis is very hard, thus we want to obtain maximal information when such a study (as this one) can be done. This information is vital to guide future studies.
To minimize the risk in the study, the following procedures will be complied with:

1. The study will be conducted in compliance with the COMIRB approved protocol, GCP, and the applicable regulatory requirements.
2. The study will be overseen by COMIRB and a Data Safety Monitoring Board (DSMB) at University of Colorado.
3. Each patient will be closely monitored by frequent clinic visits during study drug treatment phases and the 7th day following discontinuation of study drug as described in Section C to

monitor for adverse effects or withdrawal, as well as changes of medical history and concomitant medications.

4. Adverse events and serious adverse events will be reported from the time of study drug administration until the last study visit or death, whichever occurs first, according to mandated guidelines.
5. All adverse events and serious adverse events will be followed until resolution (or return to baseline status), or until the condition stabilizes or is otherwise explained, or until participant dies or is lost to follow-up.
6. Safety assessments are comprehensive and include vital signs, history and physical examination, concomitant medications collection, EKGs, safety labs (Hematology, Hemoglobin A1C, Complete Metabolic Profile and Liver Function Tests), blood and urinary cannabis and metabolites analysis, MoCA, QUIP-RS, C-SSRS, NPI, SCOPA-sleep, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, Fatigue Severity Scale, Pain Intensity and Interference short form, study drug compliance check, adverse event check, and urine and blood pregnancy testing.

We will follow the FDA's Guidance for evaluating and monitoring potential drug-induced hepatotoxicity. Participants with stable liver disease can be included if they have a normal total bilirubin and prothrombin time/INR at baseline. Liver function tests (ALT, AST, ALP and bilirubin) will be drawn at baseline and at each visit while participants are on the study drug. In addition, if these labs are abnormal at the end of the study visit they will be repeated at the safety follow up visit two weeks later and repeated until back to baseline values. During each visit that assesses the effects of the study drug, nonspecific symptoms of Drug Induced Liver Injury (DILI) will be checked, e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, and vomiting. If symptoms indicative of DILI occur, the participant will return to clinic immediately for measurement of laboratory signs of hepatic injury, regardless of when the next visit or monitoring interval is scheduled. At any time if aminotransferase enzymes are greater than three times the upper limit of normal (ULN), we will repeat ALT, AST, ALP, and bilirubin within 48-72 hours. If symptoms persist or repeat testing shows aminotransferase >3xULN for participants with normal baseline measures or twofold increases above baseline values for participants with elevated values before drug exposure, we will initiate close observation to determine whether the abnormalities are improving or worsening. Per the FDA, close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the participant is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

We will gather further history as recommended. Unless we find that the repeat testing shows the aminotransferase levels decline to baseline, we will consult the UCH Hepatology team to determine further management.

The FDA advises that since transient fluctuations of ALT or AST are common and progression to severe liver injury or failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. The decision of whether to stop the study drug will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors. We will consult the UCH hepatology service and keep the following FDA guidance in mind. The FDA states that discontinuation of treatment should be considered if:
ALT or AST >8xULN
ALT or AST >5xULN for more than two weeks
ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Data collection tools:
To protect the privacy of patients, the data collected in the study is stored completely de-identified. A code will be linked to the information provided, and answers are entered into a computer database using this code. No personal identifiers will be linked to the participant's information in the database. All of this information in the computer is password protected. The code will be linked to the participant's University of Colorado Hospital medical record number in a separate computer database. The PI will keep the surveys completed on paper in a locked cabinet.

E. Potential Scientific Problems:
To maximize scientific integrity this study was peer reviewed by the Colorado Department of Health and Safety (CDPHE) before receiving funding. We do not expect problems with recruitment because of the high level of interest and publicity regarding cannabis research, especially the CDPHE funded studies. In addition, we have a large population of PD patients, since we see over 2000 PD patients in our Movement Disorders clinics annually, including UCH, VAMC, and Denver Health, and will have 14 movement disorders providers assisting recruitment.

F. Data Analysis Plan:
Intention to treat concept is followed. In order to minimize data entry errors a double data entry system will be used.
If study participant agrees, the de-identified data would be shared within CDPHE Marijuana grantee consortium for future research.
The analysis will be performed in accordance with the analysis plan devised prior to unblinding. Baseline variables will be examined for equality between the two sequence groups. The primary, secondary and exploratory outcomes will be analyzed as below from baseline to the end of 2.5 mg/kg/day.

Primary Specific Aim: To evaluate the efficacy of CBD on motor symptoms in PD.
The data will be analyzed to compare two randomized independent samples, CBD and placebo. Means and confidence intervals will be presented for the pre and post outcome values by treatment,

and for the change scores between pre and post treatment within treatment group. A two independent sample T-test will compare the means of the change scores between the treatment groups. We will test the null hypothesis of no treatment effect. Longitudinal regression models will be fit for further analysis, including adjusting for covariates if necessary.
Secondary Specific Aim is to examine safety and tolerability of CBD and the effect of CBD on severity and duration of intractable tremor and other symptoms in PD.

Safety and tolerability and will be assessed in five ways:

1. Frequency of study-related adverse events at each dose level collected at study visits. Analysis (frequency of study-related adverse events at each dose level in the two groups, treatment vs. placebo) will be mostly descriptive and proportions and confidence intervals will be calculated. Contrasts involving repeated measures on the same participants can be tested with McNemar's test (for two correlated proportions) or GEE models/GLMMs. Contrasts for independent data can be tested with standard two sample proportions test and with GLMs. Proportions, logistic regression, and relative risk regression can be applied to binary outcomes over a fixed period of time, and Poisson models can be applied to counts or events over time.
2. Vital signs, orthostatic blood pressures, physical exam, EKG, and labs (hematology, complete metabolic profile, urinalysis) will be done during study visits. For vital signs and labs, data will be analyzed as a simple two-period trial. Means and confidence intervals will be presented pre and post treatment by treatment group, and for the change scores by treatment group. A two independent sample T-test will compare the means of the change scores between the treatment groups. More complex situations can be analyzed with longitudinal regression models.
3. Standardized assessment tools (MoCA, Cognition assessment battery, Anxiety short form, NPI, SCOPA-Sleep, ISI, DBAS-16, Pittsburgh Sleep Quality Index, RBDSQ, QUIP-RS, C-SSRS, Depression short form, Emotional Behavioral dyscontrol short form, Fatigue severity scale, MDS UPDRS, UDysRS, Pain Intensity 3a short form and Pain Intensity 4a short form, IRLS, PDQ-39 and EQ-5D-5L) and lab tests, the data will be analyzed as a simple two-period trial. Means and confidence intervals will be presented pre and post treatment by treatment group and for the change scores by treatment. A two independent sample T-test will compare the means of the change scores between the treatment groups. More complex situations can be analyzed with longitudinal regression models.
4. Proportion of participants who drop out of the study due to study drug intolerance. Analysis (proportions of participants who drop out of the study due to study drug intolerance in the two treatment groups) will be mostly descriptive, and proportions and confidence intervals will be calculated. Proportion differences between groups can be compared with the standard test.

Exploratory Outcome Measures: The efficacy of CBD on cognition, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder, quality of life, and plasma levels of cytokine are evaluated using the aforementioned assessment tools. The change from baseline to end of 2.5 mg/kg/day is compared.

Exploratory analyses: To study the efficacy of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder, plasma levels of cytokine, and seborrheic dermatitis.

Exploratory outcomes include assessments of cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder, and plasma levels of cytokine. Continuous outcomes will be analyzed in the same way as tremor. Transforms or non-parametric methods will be applied as necessary. Non-continuous outcomes will be analyzed with generalized estimating equations models, generalized mixed models, and McNemar's test for binary outcomes.

Sample Size Justification

Using preliminary data we estimate a standard deviation for the within treatment UPDRS Motor change scores, post treatment compared to baseline, of 6.72, and a correlation between the paired observations of the change score of 0.75. Consistent with the preliminary data we anticipate a mean baseline UPDRS Motor score of 23, so a 25% treatment effect would have a magnitude of 5.75, less than the within treatment mean change score of magnitude 6.10 observed in the preliminary data. The estimated standardized effect size is 0.856. Therefore, the two independent samples T-test, testing for a between treatment difference on the within treatment UPDRS Motor change scores, at alpha = 0.05, would require a total sample size of 46 patients for 80% power, and 60 patients for 90% power. Compensating for the possibility of 20% drop out, we would need to recruit 58 patients for 80% power, and 75 patients for 90% power. Thus we plan to recruit 75 patients with a goal of having at least 60 patients complete the study.

Since other outcomes are either descriptive and/or exploratory, and sample size is limited, adjustment for multiple testing adjustments are not planned across different outcome variables.

G. Summarize Knowledge to be Gained:

Marijuana is one of the most used alternative medications. Since it became legal and readily available in Colorado, Parkinson disease (PD) and other movement disorders patients have been trying it, usually without the knowledge of or supervision of their neurologist. This study will promote the safety of our patients and provide data useful in evaluating the effect and safety of CBD on tremor, cognition, anxiety, psychosis, and other symptoms, including sleep, impulsivity, suicidality, mood, fatigue, restless legs syndrome, pain, bradykinesia, rigidity, balance, and dyskinesia in PD patients. Data from this study are essential to aid in designing future marijuana research.

H. References

Aarsland D, Tandberg E, Larsen JP, Cummings JL. 1996. Frequency of dementia in Parkinson disease. Arch Neurol. 53(6): 538-42.
Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. 1999. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. Int J Geriatr Psychiatry. 14(10):866-74.
Aarsland D, Marsh L, Schrag A. 2009. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord. 24(15):2175-86.

Agurell, S.; Halldin, M.; Lindgren, J.E.; Ohlsson, A.; Widman, M.; Gillespie, H.; Hollister, L. 1986. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol. Rev. 38, 21–43.
Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012 Dec;2(6):241-54.
Battistella G, Fornari E, Annoni JM, Chtioui H, Dao K, Fabritius M, Favrat B, Mall JF, Maeder P, Giroud C. 2014. Long-term effects of cannabis on brain structure. Neuropsychopharmacology. 39(9):2041-8.
Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. 2011. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 6(4):237-49.
Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. 2010. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 35(3):764-74.
Bohannon RW. 2006. Reference values for the Timed Up and Go Test: A Descriptive Meta-Analysis. Journal of Geriatric Physical Therapy;29(2):64-8.
Bornheim LM, Everhart ET, Li J, Correia MA. 1994. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. Biochem Pharmacol 48(1): 161-171.
Carroll CB; Bain PG; Teare L; Liu X; Joint C;Wroath C; Parkin SG; Fox P; Wright D; Hobart J; and Zajicek JP. 2004. Cannabis for dyskinesia in Parkinson disease A randomized double-blind crossover study. Neurology 63;1245-1250.
Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, dos Santos AC, Teixeira AL, Hallak JE, Crippa JA. 2014. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 28(11):1088-98.
Colorado Department of Revenue, 2015. Marijuana equivalency in portion and dosage
An assessment of physical and pharmacokinetic relationships in marijuana production and consumption in Colorado
Consroe P, Sandyk R, Snider SR. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. Int J Neurosci.30(4):277-82.
Consroe, P.; Laguna, J.; Allender, J.; Snider, S.; Stern, L.; Sandyk, R.; Kennedy, K.; Schram, K. 1991. Controlled clinical trial of cannabidiol in Huntington’s disease. Pharmacol. Biochem. Behav. 40, 701–708.
Crippa, J.A.; Derenusson, G.N.; Ferrari, T.B.; Wichert-Ana, L.; Duran, F.L.; Martin-Santos, R.; Simões, M.V.; Bhattacharyya, S.; Fusar-Poli, P.; Atakan, Z.; et al. 2011. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. J. Psychopharmacol. 25, 121–130.
Dalterio S, Steger R, Mayfield D, Bartke A. 1984. Early cannabinoid exposure influences neuroendocrine and reproductive functions in mice: II. Postnatal effects. Pharmacol Biochem Behav. 20(1):115-23.
de Lau LM, Breteler MM. 2006. Epidemiology of Parkinson's disease. Lancet Neurol. 5(6):525-35.
Devinsky O, Marsh E, Friedman D, et al. 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 15 (3): 270-8.
Devinsky O, Cross JH, Laux L, et al. 2017. Trial of Cannabidiol for drug-resistant seizures in the Dravet Syndrome. N Engl J Med. 376 (21): 2011-2020.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D, Feilding A, Walker L, Murray RM, Kapur S. 2013. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 27(1):19-27.
Findley LJ. 2007. The economic impact of Parkinson's disease. Parkinsonism Relat Disord. 13 Suppl:S8-S12.
Finseth TA, Hedeman JL, Brown RP 2nd, Johnson KI, Binder MS, Kluger BM. 2015. Self-reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado. Evid Based Complement Alternat Med. 2015:874849.
Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. 2007. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. Brain Res. 1134(1):162-70.
Grotenhermen F. 2003. Pharmacokinetics and Pharmacodynamics of Cannabinoids, Clin Pharmacokinetics 42;n327-260.
Frankel JP, Hughes A, Lees AJ, Stern GM. 1990. Marijuana for parkinsonian tremor. J Neurol Neurosurg Psychiatry. 53(5):436.
Gruber SA, Yurgelun-Todd DA. 2005. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. Brain Res Cogn Brain Res. 23(1):107-18.
Gomes FV, Del Bel EA, Guimarães FS. 2013. Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT1A receptor activation in mice. Prog Neuropsychopharmacol Biol Psychiatry. 46:43-7.
Guy, G.W.; Whittle, B.A.; Robson, P. 2004. The Medicinal Uses of Cannabis and Cannabinoids; TJ International: Cornwall, UK, 2004.
Hall W., Solowij N. 1998. Adverse effects of cannabis. Lancet. 352(9140): 1611-6.
Harvey, D.J.; Mechoulam, R. 1990. Metabolites of cannabidiol identified in human urine. Xenobiotica 20: 303–320.
Hayakawa K, Mishima K, Nozako M, Ogata A, Hazekawa M, Liu AX, Fujioka M, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. 2007. Repeated treatment with cannabidiol but not Delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance. Neuropharmacology. 52(4):1079-87.
Hayakawa K, Mishima K, Hazekawa M, Sano K, Irie K, Orito K, Egawa T, Kitamura Y, Uchida N, Nishimura R, Egashira N, Iwasaki K, Fujiwara M. 2008. Cannabidiol potentiates pharmacological effects of Delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. Brain Res. 1188:157-64.
Hindocha C., Freeman TP., Xia JX, et al. 2017. Acute memory and psychotomimetic effects of cannabis and tobacco both joint and individually a placebo-controlled trial. Psychological Medicine. 47: 2708-2719.
Hobson P, Meara J. 2004. Risk and incidence of dementia in a cohort of older participants with Parkinson's disease in the United Kingdom. Mov Disord. 19(9):1043-9.
Hoddes E., Dement W. and Zarcone V. 1972. The development and use of the Stanford Sleepiness Scale (SSS). Psychophysiol., 9:150.
Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. 2009. Cannabidiol: a promising drug for neurodegenerative disorders? CNS Neurosci Ther. 15(1):65-75.
L.E. Hollister, et al. Do Plasma Concentrations of Delta 9-THC reflect the degree of intoxication? J Clin Pharmacol. 1981; 21:171s-177s

Jager G, Block RI, Luijten M, Ramsey NF. 2010. Cannabis use and memory brain function in adolescent boys: a cross-sectional multicenter functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry. 49(6):561-72, 572.e1-3.
James A, Hough M, James S, Winmill L, Burge L, Nijhawan S, Matthews PM, Zarei M. 2011. Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia(AOS). Schizophr Res. 128(1-3):91-7.
Kindred JH, Li K, Ketelhut NB, et al. 2017. Cannabis use in people with Parkinson's disease and multiple sclerosis"
Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. 2014. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 82(17):1556-63.
Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. 2005. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. Neurobiol Dis. 19(1-2):96-107.
Lauterbach EC. 2004. The neuropsychiatry of Parkinson's disease and related disorders. Psychiatr Clin North Am. 27(4):801-25. Review.
Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, Weintraub D, Sampaio C, Poewe W, Rascol O, Stebbins GT, Goetz CG. 2008. Anxiety rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 23(14):2015-25.
Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D. 2012. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry. 2:e94.
Lotan I, Treves TA, Roditi Y, Djaldetti R. 2014. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clin Neuropharmacol. 37(2):41-4.
Maclean AW, Fekken GC, Saskin P, et al. 1992. Psychometric evaluation of the Stanford Sleepiness Scale. J. Sleep Res, 1:35-39.
Marttila RJ, Rinne UK. 1976. Dementia in Parkinson's disease. Acta Neurol Scand. 54(5):431-41.
Matochik JA, Eldreth DA, Cadet JL, Bolla KI. 2005. Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend. 77(1):23-30.
Matsuyama SS, Fu TK. 1981. In vivo cytogenetic effects of cannabinoids. J Clin Psychopharmacol. 1(3):135-40.
Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y. 1992. A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. Arch Neurol. 49(5):492-7.
Mecha M, Feliú A, Iñigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C. 2013. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. Neurobiol Dis. 59:141-50.
Menza MA, Robertson-Hoffman DE, Bonapace AS. 1993. Parkinson's disease and anxiety: comorbidity with depression. Biol Psychiatry. 34(7):465-70.
Nadulski, T.; Pragst, F.; Weinberg, G.; Roser, P.; Schnelle, M.; Fronk, E.M.; Stadelmann, A.M. 2005. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of delta-9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. Ther. Drug Monit. 27: 799–810.

Nadulski, T.; Sporkert, F.; Schnelle, M.; Stadelmann, A.M.; Roser, P.; Schefter, T.; Pragst, F. 2005b. Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract. J. Anal. Toxicol. 29: 782–789.
Nagatsu T, Mogi M, Ichinose H, Togari A. 2000. Cytokines in Parkinson's disease. J Neural Transm Supply. 58:143-151.
Narimatsu S, Watanabe K, Yamamoto I, Yoshimura H. 1990. Inhibition of hepatic microsomal cytochrome P450 by cannabidiol in adult male rats. Chem Pharm Bull; 38(5): 1365-8.
Nussbaum M, Treves TA, Inzelberg R, Rabey JM, Korczyn AD. 1998. Survival in Parkinson's disease: the effect of dementia. Parkinsonism Relat Disord. 4(4):179-81.
Nuti A, Ceravolo R, Piccinni A, Dell'Agnello G, Bellini G, Gambaccini G, Rossi C, Logi C, Dell'Osso L, Bonuccelli U. 2004. Psychiatric comorbidity in a population of Parkinson's disease patients. Eur J Neurol. 11(5):315-20.
Ohlsson, A.; Lindgren, J.E.; Andersson, S.; Agurell, S.; Gillespie, H.; Hollister, L.E. 1986. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. Biomed. Environ. Mass Spectrom. 13: 77–83.
Oviedo A, Glowa J, Herkenham M. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. Brain Res. 1993. 616(1-2): 293-302.
Poewe W. 2006. The natural history of Parkinson's disease. J Neurol. 253 Suppl 7:VII2-6.
Niesink RJ, et al. 2013. Does cannabidiol protect against adverse psychological effects of THC? Front Psychiatry. 4:130.
Richard IH. 2005. Anxiety disorders in Parkinson's disease. Adv Neurol. 96:42-55. Review.
Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. 2009. Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. Br J Pharmacol. 156(7):1154-66.
Rosenkrantz H, Fleischman RW, Grant RJ. 1981. Toxicity of short-term administration of cannabinoids to rhesus monkeys. Toxicol Appl Pharmacol. 58(1): 118-31.
Sawada M, Imamural K, Nagatsu T. 2006. Rold of cytokines in inflammatory process in Parkinson's disease. J Neurol Transm Supply. 70: 373-381.
Schrag A, Jahanshahi M, Quinn N. 2000. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 69(3):308-12.
Scopinho AA, Guimarães FS, Corrêa FM, Resstel LB. 2011. Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists. Pharmacol Biochem Behav. 98(2):268-72.
Sneider JT, Mashhoon Y, Silveri MM. 2013. A Review of Magnetic Resonance Spectroscopy Studies in Marijuana using Adolescents and Adults. J Addict Res Ther. Suppl 4.
Soulas T, Gurruchaga JM, Palfi S, Cesaro P, Nguyen JP, Fénelon G. 2008. Attempted and completed suicides after subthalamic nucleus stimulation for Parkinson's disease. J Neurol Neurosurg Psychiatry. 79(8):952-4.
Stein MB, Heuser IJ, Juncos JL, Uhde TW. 1990. Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry. 147(2):217-20.
Stone JM, Bhattacharyya S, Barker GJ, McGuire PK. 2012. Substance use and regional gray matter volume in individuals at high risk of psychosis. Eur Neuropsychopharmacol. 22(2):114-22.
Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. 2012. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Mov Disord. 27(2):242-7.

Venderová K, Růzicka E, Vorísek V, Visnovský P. 2004. Survey on cannabis use in Parkinson's disease: participantive improvement of motor symptoms. Mov Disord. 19(9):1102-6.
Vuolo F, Petronilho F, Sonai F, et al. 2015. Evaluation of serum cytokines levels and the role of cannabidiol treatment in animal model of asthma. Medicators of Inflammation. 2015: 538670.
Yao SC, Hart AD, Terzella MJ. 2013. An evidence-based osteopathic approach to Parkinson disease. Osteopathic Family Physician. 5(3): 96–101.
Zhornitsky S, Potvin S. 2012. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). (5):529-52.
Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA. 2006. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol. 20(5):683-686.
Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, Dursun SM, Tumas V. 2009. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Paychopharmacol. 23(8):979-83.
Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. 1995. Antipsychotic effect of cannabidiol. J Clin Psychiatry. 56(10):485-486.

Appendix 1: Schedule of Events														
schedule of events														
	screening		baseline	Treatment Period							Safety Followup			
week (number of days)			1	1-2 (14 days)							3	3	3 to 4 (10 days)	4
Days	< negative 28	negative 14-3	1 (s)	1-3(i)	4	5-8(i)	9*	10 - 12	13(i)(s)	14 (+4) (l)	15-17	18 - 21	22-27 (i)	28 (+/- 4)
Dosage of CBD or placebo mg/kg/day	0		1.25 (take the first dose in clinic)	1.25	1.25	2.5	2.5	2.5	2.5	2.5 (take the study drug upon arrival at clinic)	0	0	0	0
clinical visit	1		2		3					4				5
telephone call							1				2 (j)	3 (j)		
Informed consent	√													
Eligibility Criteria	√		√ (y)											
Demographics	√ (r)													
Medical History (a)	√(r)													
Medical History			√(y)		√					√	√	√		√(z)
Family medical history	√ (r)													
Concomitant Medications	√ (r)		√(y)		√					√	√	√		√(z)
Randomization			√											
Blinding assessment					√					√				

Study drug compliance check					√					√				
Dispense study drug and instruction			√											
Adverse Events (b)			√		√					√	√	√		√(z)
Abuse-related Aes	√(r)				√					√	√	√		√
Formal drug interaction assessment			√											
Vital Signs (c)	√		√ (n)		√ (n)					√(p)				√
Orthostatic Blood Pressures check	√		√ (n)		√ (n)					√(p)				√
Height and Weight	√		√		√					√				
Complete Physical Exam (d)	√				√					√				√
Neurological exam (e)	√				√					✓				
Brief physical exam (heart and lung auscultation)			√											
Hematology (f)	√				√					√				√ (m)
Hemoglobin A1C	√													
Complete metabolic profile + LFTs (g)	√				√					√				√ (m)
Plasma cytokines test	√									√				
Blood cannabis analysis	√				√ (o)					√ (o)				√
Urinalysis (h)	√				√					√				√ (m)
Urine drug (THC) test			√											
Urinary CBD and metabolites levels test (q)					√					√				√
Urine cups dispense and urine collection instruction			√		√					√				

ECG (12-LEAD)	√				√					√				√ (m)
Serum Pregnancy Test (for women childbearing potential)	√													
Urine Pregnancy Test (for women childbearing potential)			√		√					√				√
Assessment of past marijuana use	√													
Drug, alcohol and tobacco abuse screening test	√													
MOCA	√				√					√				
Cognitive assessment battery			√							√				
Alertness test (Stanford Sleepiness Scale SSS)			√(t) (y)											
MDS-UPDRS part III	√													
MDS-UPDRS (all 4 parts)			√		√					√				√
H & Y rating	√		√		√					√				√
Schwab & England Daily Activities Scale	√		√		√					√				√
TUG			√		√					√				
QUIP-RS	√				√					√				√
C-SSRS	√(r)		√(y)		√		√			√				√(z)
RBDSQ			√(y)		√					√				√(z)
NPI	√(r)				√					√				√(z)
Anxiety short form			✓(y)		√		√			√				√(z)
Depression short form			✓(y)		√		√			√				√(z)
Emotional and behavioral dyscontrol short form	√(r)				√		√			√				√(z)
SCOPA-sleep			✓(y)		√		√			√				√(z)
IRLS			√(y)		√					√				√(z)

Fatigue severity scale			✓(y)		√					√				√(z)
Pain intensity and interference short form			✓(y)		√					√				√(z)
Bladder function-OABSS			√(y)		√					√				√(z)
PDQ-39			√(y)		√					√				√(z)
EQ-5D			√(y)		√		√			√				√(z)
CGI			√		√					√				
PGI-I			√		√					√				
PGI-C					√					√				
Unified Dyskinesia Rating Scale (UDysRS)			√		√					√				√
NMSS			√(y)		√					√				√(z)
Dermatology Intake Form			√(y)											
DLQI			√(y)							√				
Insomnia Severity Index (ISI)			√(y)		√					√				
Modified Dysfunctional Beliefs and Attitudes about Sleep Questionnaire (DBAS-16)			√(y)		√					√				
Pittsburgh Sleep Quality Index			√(y)		√					√				
Home diary dispense & instruction			√											
Home diary collection & review					√					√				
Tremor constancy and amplitude measure (k)	√		√		√			√		√				
Tremor measure device dispatched and instruction	√		√											
PSG equipment set up and instruction		√ (x)							√ (u)					

Patient Instruction sheet for At-Home Sleep Monitoring Test dispense		√ (x)							√ (u)					
Morning Daytime Dysfunction Questionnaire (v)		√							√					
Sleep Diary (v)		√							√					
PSG equipment and data collected (w)			√							√				
skin evaluation (photo of central face)			√							√				
* Questionnaire reminder phone call on the 3rd to 5th day of 1.25 mg/kg BID.														
Note: regarding the rows of days and weeks, it is variable, because of note (l).														
a. A complete medical history (including PD history, mental health history, alcohol and drug use) will be obtained from the subject at the Screening Visit and recorded on the appropriate CRF. The medical history and other enrollment criteria will be reviewed and updated at the Baseline/Day 1 visit to determine continued eligibility for the study.														
b. Adverse events will be recorded from the time that the study subject signs the consent form. Any subject with an ongoing AE will be followed until the AE is resolved, returns to baseline or deemed stable by the investigator.														
c. Vital signs obtained after the subject has been sitting for at least 5 minutes.														
d. Complete PE to include: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.														
e. Neurological exam.														
f. Hematology consists of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red blood cell count (RBC), white blood cell (WBC) count, WBC differential (absolute), and numerical platelet count.														
g. Serum chemistry (fasting not required) consists of alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine (MDRD formula for eGFR, to be done by the central laboratory), glucose, potassium, alanine aminotransferase, aspartate aminotransferase, sodium, total bilirubin, and total protein, GGT.														
h. Urinalysis dipsticks including leukocytes, specific gravity, pH, protein, ketones, glucose, nitrite, blood, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed at the central laboratory.														
i. Call patient to remind them the clinical visit next day														
j. Call patient to collect adverse events and information of signs of withdrawal														

k. Tremor time percentage and amplitude will be measured by a portable device and laptop. Subject will measure it at home 2 days after screening visit, 3 days before baseline visit, 3 days prior to each dose assessment visit, twice a day (2 hours after breakfast dose and 2 hours after dinner dose), 90 seconds each measurement. Tremor will also be measured at clinic, twice at screening visit, 2 hours after taking study drug at baseline and each dose assessment visit.
l. Treatment assessment visit can occur on 10 (+4) days for each dose.
m. Hematology, chemistry, urinalysis and EKG will be done if there was a clinically significant change at the high dose evaluation visit compared to baseline visit.
n. Subject will be monitored and vital signs will be checked again at before and 1 hour after taking the study drug.
o. Blood drawn will be performed 3 hours after taking the study drug of the clinical visit day.
p. Subject will be monitored and vital signs will be checked at before and 1 and 3 hours after taking the study drug.
q. Clean catch urine collection after taking the study drug. Urine is collected in a 500 mL container and stored in 3-4 small cups (120 mL, fill up to 3/4).
r. Procedures can be done remotely after onsite screening visit
s. Phone call to remind patient to measure tremors at home for consecutive 3 days before the next clinic visit.
t. Alertness test will be done before and 3 hours after taking study drug.
u. Home sleep test will be done after at least 7 days on the max dose and until (including) the 3rd night before 2.5 mg/kg/day dose assessment visit.
v. Morning Daytime Dysfunction Questionnaire and Sleep diary will be done within the first 30 minutes of waking after home sleep test.
w. PSG equipment and data collected on the next day of home sleep test or at baseline or 2.5 mg/kg/day dose assessment visit
x. The sleep study before the baseline visit is to be done from 14 to 3 nights before baseline visit.
y. Procedures can be done remotely , between screening and onsite baseline visit
z. procedures can be done remotely 1-3 days prior to or after safety follow up visit

Appendix 2: Myo tremor measurement guide

RESTING STATE TREMOR DETECTION

Procedures:

1. Plug the USB cable into laptop.
2. Strap the device to your hand (tremor dominant), with device on top of hand and cable protruding from the front of the device.
3. When it is connected, click the Icon “tremor” to run the program.
5. Use the dropdown menus to specify the time of your last dose. Provide the hour, minute, and AM/PM. Then click “Okay” to accept this entry and move on to the main program.
6. Click start to begin collecting data.
7. You will be shown an example of the hand movement to mimic: 1) finger tapping, 2) supination/pronation, and 3) ‘screwing in a lightbulb’. For each sequence you be told to ‘START’ and ‘STOP’. When the last sequence has run the program will indicate ‘COMPLETE’.
8. Close the program (click the X button on the upper right corner) to finish.

Integrator Guide

Contents

1 Introduction

This Integrator Guide is the main technical reference for the recipients of the TremorGUI MATLAB package. This guide will walk through the

2 Prerequisites

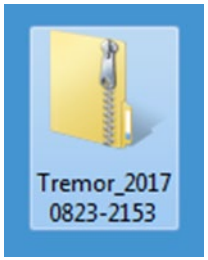
The recommended system configuration for this package is a computer that is no more than 2 years old running Windows 7/8/10. Older machines might work as well, but it's possible that the hardware may not support some required features. This package will not work with operating systems that are not 64 bit Windows (e.g. Mac OS or Linux).

3 Setup and Installation

Begin this setup locating the provided package archive named Tremor_YYYYMMDD_hhmm.zip.

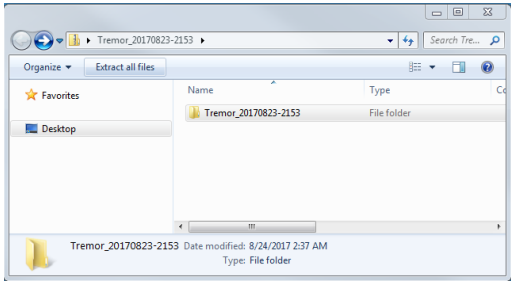
1. Move this ZIP archive to a convenient location in your user profile such as the Desktop:

C:\Users\<username>\Desktop\

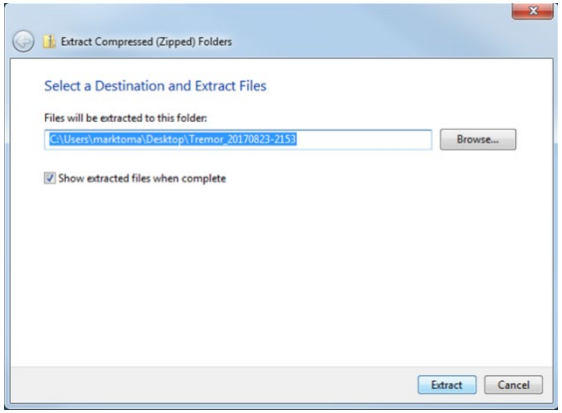


2. Extract the ZIP archive here. This is described in detail for the default Windows Explorer extractor in Windows 7. If you have a different archive manager program, the steps may differ slightly.

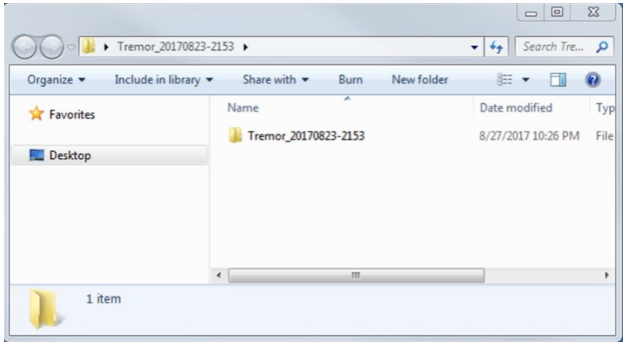
First double click the desktop icon. Then click on "Extract all files"



Next click "Extract" to extraxt the archive to the standard location and show the files when the operation completes.



Finally, you'll see the resulting folder.

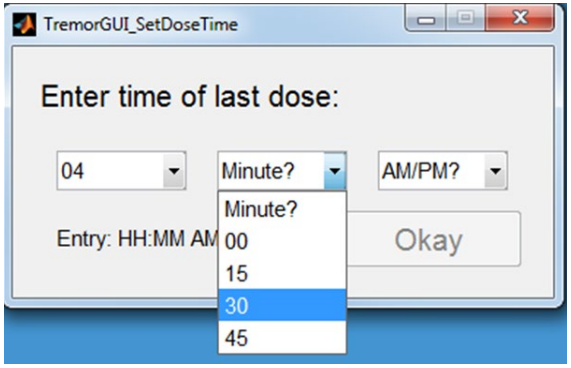


Important: The Tremor directory contents and the Tremor shortcut place on the desktop are written without checking for existing files of the same name. Verify that conflicts do not exist before performing this step!

Note: If the above steps [partially] fail, the user may need to perform them manually and/or request support to repair the installation.

1. Launch \Tremor.exe by double clicking its shortcut icon on the Desktop

2. Use the dropdown menus to specify the time of your last dose. Provide the hour, minute, and time of day (AM/PM). Then click "Okay" to accept this entry and move on to the main program.



3. Click start to begin collecting data

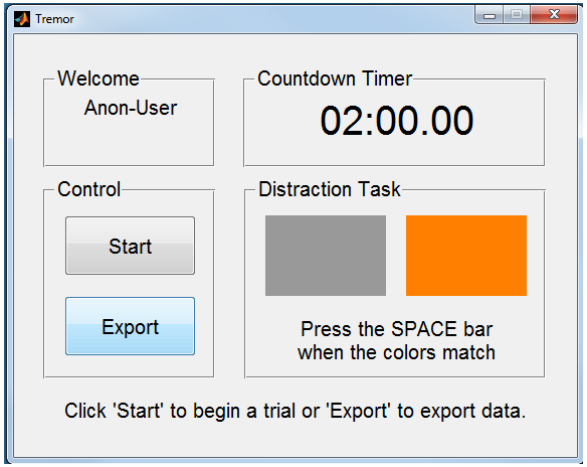
Note: The current dataset can be discarded by clicking the same button again to "Restart" the current trial.

Note: There is no option to cancel collection. If this is desired, then close the program and begin again.

4. Perform the distraction task as instructed.

Note: Upon completion of a trial, the program will automatically save the data in multiple CSV files within the \private\data directory.

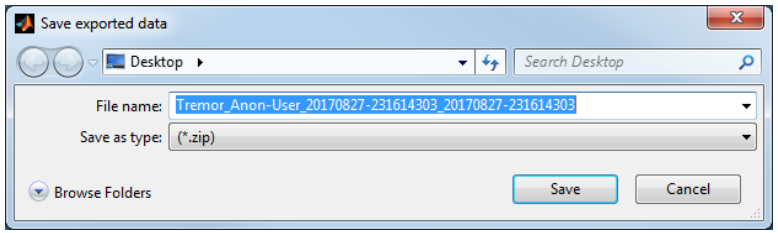
5. Export data by clicking the Export button.



The following occurs:

- All individual CSV files from \private\data are added to a new ZIP archive stored at the same location.
- The ZIP archive is named with time/date stamp range indicated the earliest and latest data files it contains. The application name and user tag from one of the data files is prepended to the ZIP archive name.
- The ZIP archive is saved primarily in the \private\data direcrory
- The user is then prompted to select a location on the computer where a copy of the ZIP is also saved. The default location is the user's Desktop directory. This can be reconfigured using TremorOpts.txt

When prompted, select a location to save the exported data archive. The default location is the Desktop. Click Save to save the data.



6. Close the program to finish.

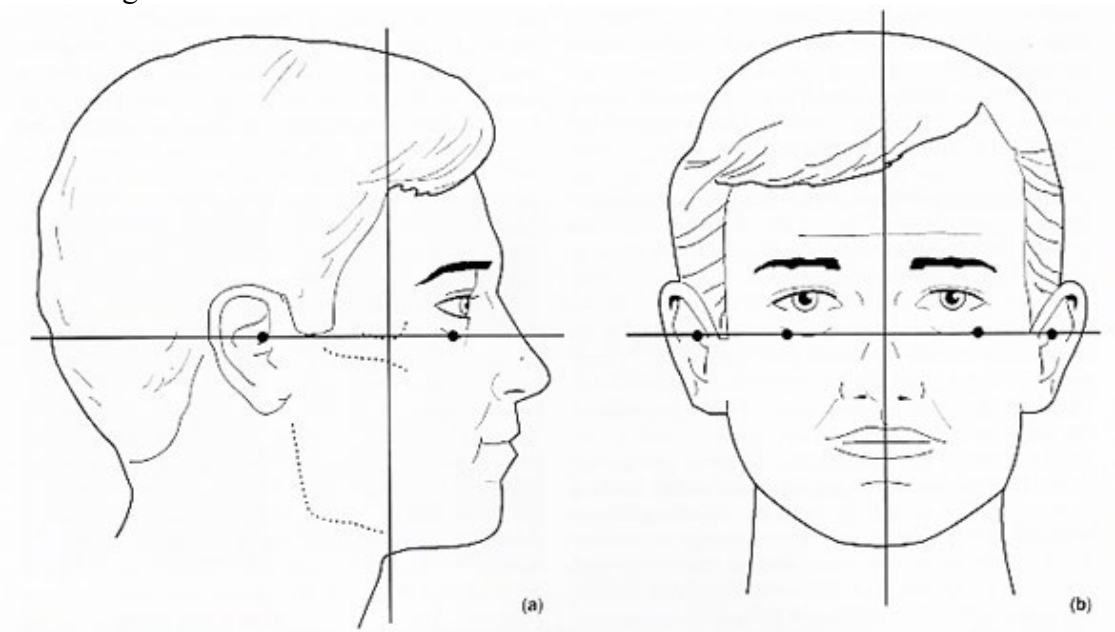
5 Options File

Tremor test:
Device: recording device, USB charging cable, USB hard lock, a connector allows you to transfer information from the device to the computer.

Appendix 3: Dermatology Photography Protocol

1. Ensure the patient did not apply make-up prior to having their picture taken. If the patient is wearing make-up, please make a note of this and have the patient remove make-up from the nasolabial folds (eye make-up is ok).
2. Have patient remove any jewelry including necklace, scarves, glasses, hat.
3. If needed, place headband to pull hair away from forehead
4. Position patient away from a direct light source and standing against a wall of neutral color
5. Instruct patient to have a relaxed facial expression with closed eyes and neutral lips
6. Stand approximately 1.5m from the patient with the camera in portrait position
7. Confirm camera settings- flash on, portrait orientation, and position camera in the same plane as the participants face.
8. Give instructions like, “slowly move your chin down” or “slowly turn your nose to the left” to achieve the desired pose.
9. Take 3 photos. Photos of the left and right side of the patient’s face should span from the ear to nose in horizontal plane, and from the forehead to chin in the vertical plane. From center, include both patient’s ears, forehead and chin. (see figure below)
10. Take additional photos of the ears and if one or more is out of focus
11. Upload photos to drive

Figure:



(a) right side
(b) center
(c) left side- not shown

Appendix 4: CBD Cannabis Extract Certification of Analysis

NATIONAL CENTER FOR NATURAL PRODUCTS RESEARCH
School of Pharmacy
806 Hathorn Road
135 Coy Waller Complex
P. O. Box 1848
The University of Mississippi
University, MS 38677-1848

Telephone: 662-915-5928

THE UNIVERSITY OF MISSISSIPPI
School of Pharmacy

CERTIFICATE OF ANALYSIS

Product: **CBD Cannabis Extract**
Product Code: **1102**
Lot Number: **1102 – 1507 – 03**

TEST	SPECIFICATION	RESULT
Potency (by GC)		
Cannabidiol (CBD)	≥25% w/w	59.34 %
Other Cannabinoids (by GC)		
Tetrahydrocannabivarin (THCV)	≤0.3% w/w	< 0.01 %
Δ^9-tetrahydrocannabinol (THC)	≤5% w/w	1.96 %
Cannabichromene (CBC)	≤5% w/w	2.10 %
Cannabigerol (CBG)	≤5% w/w	1.10 %
Cannabinol (CBN)	≤5% w/w	< 0.01 %
CBD:THC ratio	≥ 15:1	30 : 1
Residual Solvent (by GC)		
Hexane	≤1% w/w	< 0.5 %
Loss on Drying (by IR radiation)		
Total Moisture & Volatile Impurities	≤6% w/w	0.32 %
Heavy Metals (by ICP-MS)		
Lead (Pb)	≤ 0.5 ppm	N D
Mercury (Hg)	≤ 1.5 ppm	N D
Cadmium (Cd)	≤ 0.5 ppm	N D
Arsenic (As)	≤ 1.5 ppm	N D
Aflatoxins		
AFB_1	≤ 5 ppb	< 5 ppb
AFB_1, AFB_2, AGF_1, AFG_2	≤ 20 ppb	N D
Store in freezer.		
Expires: July, 2020.		
Certified by: Date: 09-18-2015		

F93A

Appendix 5

If subject is on this & CBD (which is metabolized by this enzyme) is added, the CBD level may be reduced	If subject is on this & CBD (which is metabloized by this enzyme) is added then the CBD level may be higher	If subject is on this & CBD (which is metabolized by this enzyme) is added, the CBD level may be reduced	If subject is on this & CBD (which is metabloized by this enzyme) is added then the CBD level may be higher	Add CBD (which inhibits this enzyme) and the drug level may be increased	Add CBD (which inhibits this enzyme) and the drug level may be increased	Add CBD (which inhibits this enzyme) and the drug level may be increased	Add CBD (which inhibits this enzyme) and the drug level may be increased	If subject is on this & CBD (which is glucurondated by this enzyme) is added then the CBD level may be higher	If subject is on this & CBD (which is glucurondated by this enzyme) is added then the CBD level may be higher	If subject is on this & CBD (which is glucurondated by this enzyme) is added then the CBD level may be higher	If subject in on CBD and starts any of these medications, CBD levels may decrease (CBD is glucurondated by this enzyme)	If subject in on CBD and starts any of these medications, CBD levels may decrease (CBD is glucurondated by this enzyme)	Highly Protein Boud drugs (serum concentrations can fluctuate between both drugs)
CYP 3a4 inducers	**CYP 3a4 inhibitors**	**CYP 2c19 inducers**	**CYP 2c19 inhibitors**	**CYP 3a4 substrates**	**CYP 2c19 substrates**	**UGT1A9 substrates**	**UGT2B7 substrates**	**UGT1A7 inhibitors**	**UGT1A9 inhibitor**	**UGT2B7 inhibitor**	**UGT1A9 Inducers**	**UGT2B7 Inducers**	**Highly Protein Bound**
Carbamazepine	Amiodarone	Aminoglutethimide	Chloramphenicol	Alfentanil (Alfenta)	Aripiprazole (abilify)	Acetaminophen	Azidothymidine	--	Cyclosporin A	ketoconazole	--	Gancyclovir	Phenobarbital
armodafinil	alprazolam	Artemisinin	amitriptyline	Alfuzosin (Uroxatral)	Carisoprodol (Soma)	diclofenac	clofibrate		Milk Thistle (Silymarin)	valproic acid		Phenobarbital	Phenytoin
bosentan	amlodipine	phenobarbital	armodafinil	Almotriptan (Axert)	Citalopram (Celexa)	ethinyl estidol	clorampehnicol		Niflumic acid	spironaldactone		Rifampin	Rasagiline
cisplatin	amprenavir	Carbamazepine (eg. Tegretol)	carbamazine	Alprazolam (Xanax)	Clobazam (Onfi)	flavipirido	Codeine		Tacromlimus (Prograf)	canreone		Tobacco Smoking	Rotigptine
cyclophosphamide	Anastrozole	Phenytoin (eg. Dilantin)	Cimetidine (Tagamet)	Amiodarone (Cordarone)	Clomipramine (Anafranil)	ibuprofen	Cyclosporin A			Amitryptline			Selegiline
Dexamethasone	aprepitant	Primidone	Clopidogrel (Plavix)	Amlodipine (Norvasc)	Clopidogrel (Plavix)	kampferol	Cyclosporin A			Ketoconazole			Valproic Acid
efavirenz	atanazanavir	Rifampin (eg. Rifadin)	Delavirdine (Rescriptor)	Aprepitant (Emend)	Clozapine (Clozaril)	ketoprofen	diclofenac (Voltaren)			chloramphenicol			
Ethosuximide	atorvastatin	Rifapentine	Efavirenz (Sustiva)	Atazanavir (Reyataz)	Desipramine (Norpramin)	labetolol	Entacapone			clofibrate			
etravirine	Azithromzcin	ST. John's wort	Esomeprazole (Nexium)	Atorvastatin (Lipitor)	Diazepam (Valium)	naproxen	Hydromorphone (Dilaudid)			codeine			
felbamate	bicalutimde	prednisone	esomeprazole (Nexium)	Bepridil (Vascor)	Diphenhydramine (Benadryl)	Propranolol	ibuprofen			diazepam			
Glucocorticoids	boceprevir	ritonavir	etravirine	Bexarotene (Targretin)	Doxepin (Sinequan)	Propofol	ketoconazole?			dicofenac			
Griseofulvin	bromocriptine	valproic acid	Felbamate (Felbatol)	Bosentan (Tracleer)	Escitalopram (Lexapro)	phenylbutazone	ketoprofen			ibuprofen			
ifsofamide	Cannabinoids		Fluconazole (Diflucan)	Bromocriptine (Parlodel)	Fluoxetine (Prozac)	quercetin	Lorazepam (Ativan)			fluconazole			
lopinavir	chloroquine		Fluoxetime (Prozac)	Budesonide (Entocort)	Lansoprazole (Prevacid)	valproic acid	losartan			guanfacine			
methadone	cilostazol		Fluvoxamine	Buprenorphine (Subutex)	Lmipramine (Tofranil)		morphine			ketoprofen			
methlyprednisolone	Cimetidine		imipramine	Bupropion (Zyban, Wellbutrin, V	Mephenytoin (Mesantoin)		morphine			methadone			
Modafinil	ciprofloxin		indomethacin	Carbamazepine (eg, Tegretol)	Methadone		nalaxone			morphine			
Nafcillin	ciprofloxin		Isoniazid	Cevimeline (Evoxac)	Moclobemide (Manerix)		nalorphin			naproxen			
Nelfinavir	Clarithromycin		ketoconazole	Cilostazol (Pletal)	Nelfinavir (Viracept)		naltrexone			oxazepam			
Nevirapine	Clotrimazole		lansoprazole	Cisapride (Propulsid)	Olanzapine (Zyprexa)		naproxen			probenacid			
Oxcarbazepine	conavapin		Moclobemide (Manerix)	Clarithromycin (Biaxin)	Omeprazole (Prilosec)		Oxazepam			propofol			
Phenobarbital	conivaptan		Modafinil (Provigil)	Clonazepam (Klonopin)	Pantoprazole(Protonix)		Oxycodone			ranitidine			
Phenylbutazone	crizotinib		norfluoxetine	Clopidogrel (Plavix)	Pentamidine		Tacrolimus (Prograf)			temazepam			
Phenytoin	crizotinib		Omeprazole (Prilosec)	Colchicine	Phenobarbital		temazepam			trimethoprim			
pioglitazone	Cyclosporine		oral contraceptives	Cyclophosphamide (Cytoxan)	Phenytoin (eg. Dilantin)		Tolcopone						
prednisone	Danazol		Oxcarbazepine (Trileptal)	Cyclosporine (Neoral)	Proguanil		zidovudine						
prednisone	darunavir		paroxetine	Dapsone (Avlosulfon)	Propranolol (Inderal)								
Primidone	Delavirdine		ranitidine	Darunavir (Prezista)	R-warfarin (less active isomer)								
primidone	Dexamethasone		ritonavir	Dasatinib (Sprycel)	Rabeprazole (Aciphex)								
Progesterone	Diethyldithiocarbamate		Ticlopidine (Ticlid)	Delavirdine (Rescriptor)	Sertraline (Zoloft)			our PD patients are more likely to be taking these					
Rifabutin	Diltiazem		topiramate	Dexamethasone (Decadron)	Thalidomide								
Rifampin	Dirithyromycin		Voriconazole (Vfend)	Dihydroergotamine	Voriconazole (Vfend)			strong					
rifapentine	Disulfiram			Diltiazem (Cardizem)				moderate					
ritonavir	efavarinz			Disopyramide (Norpace)				weak					
ritonavir	Entacapone (high dose)			Docetaxel (Taxotere)									
Rofecoxib (mild)	Erythromycin			Donepezil (Aricept)									
St John's wort	Ethinyl estradiol			Doxorubicin (Adriamycin)									
Sulfadimidine	fasoamprinavir			Droperidol									
Sulfinpyrazone	Fluconazole			Dutasteride (Avodart)									
Troglitazone	Fluoxetine			Ebastine (Kestine)									
	Fluvoaxamine			Efavirenz (Sustiva)									
	Gestodene			Eletriptan (Relpax)									
	ginkgo			Eplerenone (Inspra)									
	goldenseal			Ergotamine (Ergomar)									
	Grapefruit juice			Erlotinib (Tarceva)									
	haloperidol			Erythromycin									
	imitinib			Estazolam (ProSom)									
	Indinavir			Eszopiclone (Lunesta)									
	Isoniazid			Ethinyl Estradiol									
	itraconazole			Ethosuximide (Zarontin)									
	itraconazole			Etoposide (Vepesid)									
	Ketoconazole			Exemestane (Aromasin)									
	lapatinib			Felodipine (Plendil)									
	lopinavir			Fentanyl (Sublimaze)									
	methadone			Finasteride (Proscar)									
	methlyprednisolone			Flurazepam (Dalmane)									
	Metronidazole			Fosamprenavir (Lexiva)									
	Mibefradil			Galantamine (Reminyl)									
	Miconazole			Gefitinib (Iressa)									
	most ***ivir meds			Granisetron (Kytril)									
	Nefazodone			Halofantrine (Halfan)									
	Nelfinavir			Ifosfamide (Ifex)									
	Nevirapine			Imatinib (Gleevec)									
	nifedipine			Indinavir (Crixivan)									
	nilobinib			Irinotecan (Camptosar)									
	Norfloxacin			Isradipine (DynaCirc)									
	Norfluoxetine			Itraconazole (Sporanox)									
	Omeprazole			Ixabepilone (Ixempra)									
	oral contraceptives			Ketoconazole (Nizoral)									
	Oxiconazole			Lapatinib (Tykerb)									
	Paroxetine (weak)			Levomethadyl (Orlaam)									
	pazopanib			Loperamide (Imodium)									
	phenobarbital			Lopinavir (Kaletra)									
	posaconazole			Loratadine (Claritin)									
	primaquine			Lovastatin (Mevacor)									
	Propoxyphene			Maraviroc (Selzentry)									
	prosaconazole			Mefloquine (Lariam)									
	Quinidine			Methylprednisolone									
	Quinine			Midazolam (Versed)									
	Quinupristine and dalfopristin			Mifepristone (Mifeprex)									
	Ranitidine			Modafinil (Provigil)									
	ranolazine			Nefazodone									
	riton			Nevirapine (Viramune)									
	Ritonavir			Nicardipine (Cardene)									
	ritonavir			Nifedipine (Adalat)									

	Saquinavir			Nimodipine (Nimotop)										
	saquinavir			Nisoldipine (Sular)										
	Sertindole			Nitrendipine (Baypress)										
	Sertraline			Oxybutynin (Ditropan)										
	tacrolimus			Oxycodone (Percodan)										
	tamoxifen			Paclitaxel (Taxol)										
	telaprevir			Paricalcitol (Zemplar)										
	telithromycin			Pimozide (Orap)										
	ticagrelor			Pioglitazone										
	tipranavir			Praziquantel (Biltricide)										
	Troglitazone			Prednisolone										
	Troleandomycin			Prednisone										
	Valproic acid			Propoxyphene (Darvon)										
	verapamil			Quazepam (Doral)										
	voriconizole			Quetiapine (Seroquel)										
	zafirlukast			Quinacrine										
	zileuton			Quinidine										
				Quinine										
				Ranolazine (Ranexa)										
				Repaglinide (Prandin)										
				Rifabutin (Rimactane)										
				Ritonavir (Norvir)										
				Saquinavir (Invirase)										
				Sibutramine (Meridia)										
				Sildenafil (Viagra)										
				Simvastatin (Zocor)										
				Sirolimus (Rapamune)										
				Solifenacin (Vesicare)										
				Sufentanil (Sufenta)										
				Sunitinib (Sutent)										
				Tacrolimus (Prograf)										
				Tadalafil (Cialis)										
				Tamoxifen (Nolvadex)										
				Tamsulosin (Flomax)										
				Teniposide (Vumon)										
				Testosterone										
				Tiagabine (Gabitril)										
				Tinidazole (Tindamax)										
				Tipranavir (Aptivus)										
				Topiramate (Topamax)										
				Triazolam (Halcion)										
				Vardenafil (Levitra)										
				Verapamil (Calan)										
				Vinblastine (Velbane)										
				Vincristine (Oncovin)										
				Ziprasidone (Geodon)										
				Zolpidem (Ambien)										
				Zonisamide (Zonegran)										
				Zopiclone (Imovane)										

Appendix 6: Clinic visits procedures and duration

During each clinic visit, participants will be given breaks every 1.5 hours and will be given lunch vouchers.

1. Screening visit

Screening visit	Time (min)	Note
Informed consent	45	PRA, PI
Eligibility Criteria	2	PRA, PI
Demographics	3	PRA
Medical History	10	PRA, PI
Family medical history	2	PRA
Concomitant Medications	10	PRA, PI
Assessment of past marijuana use	3	PRA
Drug, alcohol and tobacco abuse screening test	3	PRA
Drug Abuse-related AEs collection	2	PRA
MOCA	7	PRA
C-SSRS	2	PRA
Vital Signs , orthostatic BP, weight, height	10	PRA
Formal drug interaction assessment	3	PI
QUIP-RS	5	PI
Complete Physical Exam	10	PI
Neurological exam	10	PI
MDS-UPDRS part III, H&Y staging, Schwab & England Activities of Daily Living Scale	10	PI
Urinalysis	5	PRA
Blood draw for Hematology, hemoglobin A1C, CMP, cannabis test, serum pregnancy test if applicable	10	CTRC
ECG (12-LEAD)	10	CTRC
NPI	5	
Emotional and behavioral dyscontrol short form	2	Study subject
Tremor constancy and amplitude measure	5	PRA
Tremor measure device dispatched and instruction	10	PRA
Total visiting	184	Estimated visiting time-3 hours

2. Baseline visit

Baseline visit	Time	Note
Eligibility Criteria	1	PRA, PI
Medical History	2	PRA, PI
Concomitant Medications	2	PRA, PI
Randomization	1	PRA, PI
Alertness test	3	Study subject, before taking study drug
Vital Signs, orthostatic BP, height, weight	10	PRA, before taking study drug
Taking study drug	2	Study subject
Dispense study drug and instruction	10	PI
Adverse Events (b)	2	PRA, PI
Brief physcial exam (heart and lung ausculation)	5	PI
CGI	1	PI
MDS-UPDRS (all 4 parts), H&Y, Schwab & England Activities of Daily Living Scale	30	PI, Study subject
Unified Dyskinesia Rating Scale (UDysRS)	5	PI, Study subject
Vital Signs, orthostatic BP	10	PRA, one hour after taking study drug
Cognitive assessment battery	60	PRA
C-SSRS	2	PRA
NMSS	10	PRA
Home diary dispense and instruction	3	PRA
Tremor measure device dispatched and instruction	5	PRA
RBDSQ	2	Study subject
Anxiety short form	2	Study subject
Depression short form	2	Study subject
SCOPA-sleep	5	Study subject
Insomnia Severity Index (ISI)	2	Study subject
Modified Dysfunctional Beliefs and Attitudes about Sleep Questionnaire (DBAS-16)	3	Study subject
Pittsburgh Sleep Quality Index	3	Study subject
IRLS	2	Study subject
Fatigue severity scale	3	Study subject
Pain intensity and interference short form	2	Study subject
Bladder function-OABSS	3	Study subject
PDQ-39	7	Study subject
EQ-5D	2	Study subject

PGI-I	1	Study subject
Take picture of central face	5	PRA, Study subject
TUG	5	PRA, Study subject
Urine drug (THC) test, urine pregnancy test if applicable	5	PRA
Urine cups dispense and urine collection instruction	2	PRA
Tremor constancy and amplitude measure	5	PRA, 2 hours after taking study drug
Alertness test	3	Study subject, 3 hours after taking study drug
PSG equipment and data collected	2	PRA
Total time	230	estimated visiting time-3.5 hours

3. 1.25 mg/kg/day dose assessment visit

1.25 mg/kg/day Dose assessment visit	Time	Note
Vital Signs, orthostatic BP	10	PRA, Begore taking study drug
Taking study drug in clinic	2	Study subject
Vital Signs, orthostatic BP	10	PRA, one hours after taking study drug
Medical History	2	PI, PRA
Concomitant Medications	2	PI, PRA
Adverse Events and drug abuse related AEs Withdrawal AEs, Liver function related AEs	3	PI, PRA
Complete Physical Exam	10	PI
Neurological exam	10	PI
QUIP-RS	5	PI
CGI	1	PI
MDS-UPDRS (all 4 parts), H&Y, Schwab & England Activities of Daily Living Scale	30	PI, Study subject
Unified Dyskinesia Rating Scale (UDysRS)	5	PI, Study subject
MOCA	10	PRA
TUG	5	PRA
NMSS	10	PRA
Home diary collection and review	2	PRA
Tremor constancy and amplitude measure (k)	5	PRA, 2 hours after taking study drug
Blinding assessment	1	PRA
Study drug compliance check	2	PRA
C-SSRS	2	PRA
RBDSQ	2	PRA
NPI	5	Signifant others
Anxiety short form	2	Study subject
Depression short form	2	Study subject
Emotional and behavioral dyscontrol short form	2	Study subject
SCOPA-sleep	5	Study subject
Insomnia Severity Index (ISI)	2	Study subject
Modified Dysfunctional Beliefs and Attitudes about Sleep Questionnaire (DBAS-16)	3	Study subject
Pittsburgh Sleep Quality Index	3	Study subject
IRLS	2	Study subject
Fatigue severity scale	3	Study subject
Pain intensity and interference short form	2	Study subject
Bladder function-OABSS	3	Study subject
PDQ-39	5	Study subject
EQ-5D	2	Study subject
PGI-I	1	Study subject

PGI-C	1	Study subject
Urinalysis, pregnancy test if applicable	5	PRA
Urinary collected for CBD and metabolites levels test	2	PRA
ECG (12-LEAD)	10	CTRC
Blood draw for Hematology, CMP, cannabis test	10	CTRC, 3 hours after taking study drug
Total visiting time	200	3.5 hours

4. Liver function monitoring visit

Liver Function monitoring visit	Time	Note
Medical History	2	PRA
Concomitant Medications	2	PRA
Adverse Events (b) and drug abuse related AEs	3	PRA
Anxiety short form	2	Study subject
Depression short form	2	Study subject
Emotional and behavioral dyscontrol short form	2	Study subject
SCOPA-sleep	4	Study subject
EQ-5D	2	Study subject
C-SSRS	2	PRA
Vitals	5	PRA
Blood draw for liver function tests	10	CTRC
Total visiting time	36	0.5 hours

5. 2.5 mg/kg/day Dose assessment visit

2.5 mg/kg/day Dose assessment visit	Time	Note
Vital Signs, orthostatic BP	10	PRA, Begore taking study drug
Taking study drug in clinic	2	Study subject
Cognitive assessment battery	60	PRA
Vital Signs, orthostatic BP	10	PRA, one hours after taking study drug
Medical History	2	PI, PRA
Concomitant Medications	2	PI, PRA
Adverse Events and drug abuse related AEs Withdrawal AEs and liver function related AEs	3	PI, PRA
Complete Physical Exam	10	PI
Neurological exam	10	PI
QUIP-RS	5	PI
CGI	1	PI
MDS-UPDRS (all 4 parts), H&Y, Schwab & England Activities of Daily Living Scale	30	PI, Study subject
Unified Dyskinesia Rating Scale (UDysRS)	5	PI, Study subject
MOCA	10	PRA
TUG	5	PRA
NMSS	10	PRA
Home diary collection and review	2	PRA
Tremor constancy and amplitude measure (k)	5	PRA, 2 hours after taking study drug
PSG equipment and data collected (u)	2	PRA
Blinding assessment	1	PRA
Study drug compliance check	2	PRA
C-SSRS	2	PRA
RBDSQ	2	PRA
NPI	5	
Anxiety short form	2	Study subject
Depression short form	2	Study subject
Emotional and behavioral dyscontrol short form	2	Study subject
SCOPA-sleep	5	Study subject
Insomnia Severity Index (ISI)	2	Study subject
Modified Dysfunctional Beliefs and Attitudes about Sleep Questionnaire (DBAS-16)	3	Study subject
Pittsburgh Sleep Quality Index	3	Study subject
IRLS	2	Study subject
Fatigue severity scale	3	Study subject

Pain intensity and interference short form	2	Study subject
Bladder function-OABSS	3	Study subject
PDQ-39	5	Study subject
EQ-5D	2	Study subject
PGI-I	1	Study subject
PGI-C	1	Study subject
Urinalysis, pregnancy test if applicable	5	PRA
Urinary collected for CBD and metabolites levels test	2	PRA
Take picture of central face	5	PRA, Study subject
ECG (12-LEAD)	10	CTRC
Blood draw for Hematology, CMP, cannabis test	10	CTRC, 3 hours after taking study drug
Vital Signs, orthostatic BP	10	PRA, 3 hours after taking study drug
Total visiting time	275	4 hours

6.Safety follow up visit

Safety follow up visit	Time	Note
Medical History	2	PI, PRA
Concomitant Medications	2	PI, PRA
Adverse Events and drug abuse related AEs Withdrawal AEs, and liver function related AEs	3	PI, PRA
QUIP-RS	10	PI
Complete Physical Exam	10	PI
Unified Dyskinesia Rating Scale (UDysRS)	5	PI, Study subject
MDS-UPDRS (all 4 parts), H&Y, Schwab & England Activities of Daily Living Scale	30	PI, Study subject
Vital Signs, orthostatic BP	10	PRA
Urinalysis if applicable	5	PRA
Urinary CBD and metabolites levels test	5	PRA
NMSS	10	PRA
Urine Pregnancy Test (for women childbearing potential)	5	PRA
MOCA	7	PRA
C-SSRS	2	PRA
RBDSQ	2	Study subject
NPI	5	
Anxiety short form	2	Study subject
Depression short form	2	Study subject
Emotional and behavioral dyscontrol short form	2	Study subject
SCOPA-sleep	5	Study subject
IRLS	2	Study subject
Fatigue severity scale	5	Study subject
Pain intensity and interference short form	2	Study subject
Bladder function-OABSS	3	Study subject
PDQ-39	5	Study subject
EQ-5D	2	Study subject
Blood draw for Hematology, CMP, Cannabis test	10	CTRC
ECG (12-LEAD)	10	CTRC
Total visiting time	165	3 hours

Appendix 7: Chemotherapeutic, antihistaminic and Anti0inflammatory medications, including, but not limited to:

Alemtuzumab (Lemtrada)
Aspirin
Celecoxib (Celebrex)
Daclizumab (Zinbryta)
Diclofenac (Cambia, Cataflam, Voltaren-SR, Zipsor, Zorvolex)
Diflunisal (Dolobid)
Dimethyl fumarate (Tecfidera)
Etodolac (Lodine)
Fingolimod (Gilenya)
Glatiramer acetate (Copaxone)
Ibuprofen (Motrin, Advil)
Indomethacin (Indocin)
Interferon beta-1a (Avonex, Rebif)
Interferon beta-1b (Betaseron, Extavia)
Ketoprofen (Active-Ketoprofen)
Ketorolac (Toradol)
Mitoxantrone
Nabumetone (Relafen)
Naproxen (Aleve, Anaprox, Naprelan, Naprosyn)
Natalizumab (Tysabril)
Ocrelizumab
Oxaprozin (Daypro)
Peginterferon beta-1a (Plegridy)
Piroxicam (Feldene)
Rituximab (Rituxab)
Salsalate (Disalsate)
Sulindac (Clinoril)
Teriflunomide (Aubagio)
Tolmetin (Tolectin)
Other chemotherapeutic, antihistaminic and anit-inflammatory medications per PI discretion

Appendix 8: Inflammatory and atopic disease, including, but not limited to:

Inflammatory Diseases	Cryoglobulinemia
Gout	Allergic asthma
Lupus	Anaphylaxis
Asthma	Angioedema
Crohn's disease	Urticaria
Eczema	Latex allergies
Ulcerative colitis	Systemic lupus erythematosus
Hepatitis	Acute hypersensitivity pneumonitis
Nephritis, Glomerulonephritis	Leukocytoclastic vasculitis
Psoriasis	
Vasculitis	Other inflammatory and atopic disease per PI discretion
Thyroiditis	
Sarcoidosis	
Multiple Sclerosis	
Rheumatoid and other inflammatory arthritides	
Seborrheic dermatitis	
Wegener's granulomatosis	