COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD

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Protocol #:15-0929

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

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I. Hypotheses and Specific Aims:

Parkinson disease (PD) is a relatively common, progressive, disabiling 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. According to published and anecdotal reports cannabidiol (CBD), is a component of cannabis, has potential beneficial medical uses. However, the safety, tolerability, dose and benefits are unknown.

There are many forms of CBD being marketed. In this study we are using Epidiolex, because it is >99% pure CBD with only a trace amount of THC (<0.15%) and because it has more data on it regarding safety, tolerability, dosing and efficacy than most other forms. It is manufactured by GW Pharmaceuticals and currently it is being used in four FDA approved epilepsy studies. GW has determined a dose range that is best tolerated and effective in psychosis and seizure disorders. These studies are described in the Investigational Brochure (IB) Edition 8, Section 7.3.1. The largest cohort of subjects have been in epilepsy studies, and the majority of them were pediatric. Because there is no definitive published data on what dose of Epidiolex is best tolerated and effective in an adult population with a neurodegenerative disease, PD, this study is conducted in two stages.

- The major purpose of the Stage 1 is to study the safety and tolerability of the proposed dosage regimen, which is based on GW Pharmaceutical's experience. This is an open label study in 10 subjects, during which the dose is gradually increased to the manufacturers recommended target dose, with tolerability being evaluated at each dose level. Based on the response of subjects in the Stage 1, a target dose is determined for the next stage. Standardized tools will be administered to study both tolerability and efficacy. Efficacy assessments are simply explorative, and are done to look for an effect that warrants specific or different evaluation in the next stage.
- The major purpose of Stage 2 is to assess the safety and tolerability of the Epidiolex at the determined dose, and secondarily to study efficacy, particularly regarding tremor. Stage 2 is a crossover, double-blind, randomized controlled trial (RCT) with 50 subjects.

Our **Hypotheses** are:

Stage 1: Open Label Dose Escalation Tolerability Study

(1) Epidiolex, a purified form of cannabidiol (CBD) manufactured by GW Pharmaceuticals, is safe and tolerated in Parkinson disease (PD) patients using the dosing regimen recommended by GW.

(2) Epidiolex has some beneficial effect on PD tremor and other conditions that occur in PD.

Stage 2: Randomized, Controlled Trial

(1) CBD, in the form of Epidiolex, is safe and tolerated in PD.

(2) CBD has a significant treatment effect on PD tremor.

(3) CBD has a some beneficial effect on other conditions that occur in PD - cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder.

(4) CBD has some beneficial effect on these same conditions, particularly on anxiety, at a low dose.

Our **Specific Aims** are:

Stage 1: Open Label Dose Escalation Tolerability Study

Primary Specific Aim: To confirm that the dosage regimen of CBD, in the form of Epidiolex recommended by the study drug manufacturer is safe and tolerated in 10 subjects with PD. Epidiolex is started at 5 mg/kg/day and is increased every 3 days by 2.5 mg/kg/day to 10 mg/kg/day. Then increase the dosage every 5 days by 5 mg/kg/day to a target dose of 20 mg/kg/day.

Secondary Specific Aim: To examine the effect of CBD on severity & duration of tremor and other conditions that occur in PD.

Stage 2: Randomized, Controlled Trial

Primary Specific Aim: To evaluate the safety and tolerability of CBD, in the form of Epidiolex, in PD.

Secondary Specific Aim: To examine the effect of CBD on severity & duration of intractable tremor in PD.

Exploratory Analyses:

(1) To study the effects of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder.

(2) To evaluate the effects of CBD on these same conditions at a low dose.

II. **Background and Significance**:

Persons with Parkinson's disease (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, are associated with increased carer 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 identify these symptoms in order to optimize the management of PD patients.

Current therapies are inadequate. Medications have improved the prognosis of PD, but also have problematic adverse effects [Poewe W. 2006]. Since treatment of PD is often unsatisfactory and since marijuana 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 Movement Disorders Center (UCMDC) clinic about 5% of 207 PD patients, average age 69, reported using marijuana [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 UCMDC, about 30% of the PD patients have asked doctors during their clinic visits over the past 6 months about marijuana.

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, 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.

Cannabis is composed of many cannabinoid compounds and other substances. Cannabidiol (CBD) is a cannabinoid that is present to a lesser extent in street marijuana, and limits Delta-9-tetrahydrocannabinol (THC)'s psychoactive effect [Bhattacharryya S et al, 2010; Hayakawa K, et al. 2008; Atakan Z. 2012]. 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]. 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].

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]. 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].

Many clinicians who suspect cannabis may have a positive effective upon a particular patient group have no idea of 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 utilised.

Given the current literature regarding CBD: possible neuroprotective effect, good tolerability, anxiolytic and antipsychotic effects and general lack of information in PD, including its effect on tremor, we hypothesize that CBD would reduce tremor, anxiety and psychosis, stabilize cognitive decline and would be well tolerated in PD. This is a randomized, double-blind, placebo-controlled crossover study to evaluate the efficacy and tolerability of oral CBD on tremor and other important aspects of PD. A strength of the study is that it uses well defined form or CBD.

III. Preliminary Studies/Progress Report:

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.

CBD is a cannabinoid that is present to a lesser extent in street marijuana, and limits THC's psychoactive effect [Bhattacharryya S et al, 2010; Hayakawa K, et al. 2008; Atakan Z. 2012]. 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]. 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].

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 18–33 hours following intravenous administration, 27–35 hours following smoking, and 2–5 days following oral administration. Bioavailability of oral and smoked CBD in humans was found to be around 6% and 31%, respectively, providing further support for a substantial first-pass effect [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]. Oral cannabis extract (10 mg ∆9-THC; 10 mg CBD) produced markedly lower levels of CBD (range = 0–2.6 ng/mL) at 30–120 minutes after administration and absorption was increased with food [Nadulski, T. et al. 2005a; Nadulski, T. et al. 2005b].

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 may improve motor and non-motor symptoms and alleviate levodopa-induced dyskinesia in PD [KaterˇinaVenderova´, et al. 2004; Lotan I, et al. 2014; Chaqas MH, et al. 2014; Zuardi AW, et al. 2008]. 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].

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, 5 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 subjects each who were treated with placebo, CBD 75 mg/day or CBD 300 mg/day for 6 weeks. The study found that 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 3 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 dose (start with an oral dose of 150 mg/day) for 4 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].

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.

In this study we are using Epidiolex, which is >99% pure CBD with only a trace amount of THC (<0.15%). GW conducted a single ascending dose study in which four groups of six healthy volunteers received single oral doses of either 1500mg, 3000mg, 4500mg or 6000mg purified CBD oral solution (Ref: GWEP1544 safety assessment following dose administration of cannabidiol to healthy volunteers, 2015). Each single oral dose was well tolerated. In a 70kg individual these doses are equivalent from 21 mg/kg to 85mg/kg in a single daily dose. Currently Epidiolex is being used in four FDA approved epilepsy studies. GW has determined a dose range that is best tolerated and effective in psychosis and seizure disorders. These studies are described in the Investigational Brochure (IB) Edition 8, Section 7.3.1. Open label study results have recently been published and are described in section C.1.

IV. Research Methods

A. Outcome Measure(s):

Stage 1: Open Label Dose Escalation Tolerability Study

Primary Specific Aim: To confirm that the dosage regimen of CBD, in the form of Epidiolex recommended by the study drug manufacturer is safe and tolerated in 10 subjects with PD. Epidiolex is started at 5 mg/kg/day and is increased every 3 days by 2.5 mg/kg/day to 10 mg/kg/day. Then increase the dosage every 5 days by 5 mg/kg/day to a target dose of 20 mg/kg/day.

Primary Outcome Measures: The safety and tolerability of Epidiolex is measured in 4 ways:

1. By examining the frequency of study-related adverse events at each dose level.
   Adverse events are measured primarily by a standardized phone script administered at each dose level. The phone script starts 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 advere effects (including previously reported adverse effects of CBD and general common adverse effects of medications), 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 addtition, since a major dose limiting effect, per GW, is somnolence, the daytime sleepiness part of the SCOPA-sleep is included in the phone script.

   The phone script is administered before each dose increase. This phone call is done by a RN, MD or an advanced practice practitioner (APP). Tolerability is judged by the appropriate clinical staff (APP, neurologist) under the supervision of the PI and sub-I (who are MDs), based on their clinical expertise.

2. By monitoring vital signs, orthostatic blood pressures, physical exam, EKG and labs (hematology, complete metabolic profile, and urinalysis) during study visits.

3. By conducting standardized assessment tools on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, suicidality, and motor and non-motor PD signs during study visits. In addition, since many patients with PD also have restless legs syndrome and REM sleep behavior disorder, assessments for these are also done. The assessment tools are:

   Cognition:

   - 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].

   Anxiety:

- 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 8 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 5 questions per minute.

Psychosis:

- 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 subject's behavior.

Sleep & daytime sleepiness:

- 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. Subjects 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). Subjects 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.

Mood:

- Depression 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 8 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 5 questions per minute.
- Emotional and behavioral dyscontrol short form - is 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 8 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 5 questions per minute.

Fatigue:

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

Pain:

- 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 4 primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the 4 ICDs (compulsive gambling, buying, eating, and sexual behavior) and 3 related disorders (medication use, punding, and hobbyism). It uses a 5-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 4 weeks (or any 4-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 symtoms. 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 & 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. Rater involvement time for administering the MDS-UPDRS is estimated to require less than 10 min for the interview items of Part I, 15 min for Part III, and 5 min for Part IV, resulting in an equivalent rater time investment to the original scale and meeting the 30-min goal.

- 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.

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 subjective 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 subject'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.

4. By assessing the proportion of subjects that drop out of the study due to study drug intolerance.

Secondary Specific Aim: To examine the effect of CBD on severity & duration of tremor and other conditons that occur in PD.

Secondary Outcome Measures:

The effect of CBD on tremor is measured by the change from baseline to the end of treatment phase (week 4) change in 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).

The effect of CBD on other conditions that occur in PD, cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder, are measured by the same standardized tools used for safety and tolerability assessments (listed above). The effect of CBD are also measurend by Clincial Global Impression (CGI) and Patient Global Impression-improvement (PGI-I) and Change (PGI-C). CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the mose 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 clinicans. PGI-C is rated on a 7-point scale, evaluating all aspects of patient' health and determining if there has been an improvement or not.

Stage 2: Randomized, Controlled Trial

Primary Specific Aim: To evaluate the safety and tolerability of CBD, in the form of Epidiolex, in PD.

Primary Outcome Measures: The primary objective, to evaluate the safety and tolerability of CBD in PD is assessed in 4 ways:

1. By examining and comparing the frequency of study-related adverse events at each dose level between the two groups (treatment vs. placebo). Adverse events are measured by assessments at study visits and by the standardized phone script administered at each dose level (as in Stage 1).

2. 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.

3. By conducting and comparing standardized assessment tools on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, suicidality, and motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder and quality of life. These are the same tools used in the Stage 1 safety and tolerability evaluation, except that a more detailed cognitive assessment, an additional motor test and measures of quality of life are done. These are collected during study visits. The change from baseline to 10th day of 5 mg/kg/day (low dose analysis) and from baseline to the maximum tolerated or targeted dose is compared. The additional tools that are

   Cognition:

   - 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.

     Visuospatial construction

2) Rey-Osterrieth Complex Figure (ROCF) Test- is a widely used neuropsychological test for the evaluation of visuospatial constructional ability (Copy trial) and visual memory (Immediate Recall, Delayed Recall, and Recognition trials). It consists of three test conditions: Copy, Immediate Recall and Delayed Recall.

Attention/Processing Speed/Executive Functioning

3) Trail making tests – is a neuropsychological test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. It can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning.

4) 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). Subjects are presented with a key at the top of a page pairing unique symbols with single digits. Subjects 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.

5)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 subjects at varying intervals (i.e., 2 seconds, 3 seconds). Subjects 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.

6)Controlled Oral Word Association Test (COWAT) - The COWAT is a measure of speeded verbal fluency and word retrieval in which subjects 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

7)Hopkins Verbal Learning Test-Revised (HVLT-R) - The HVLT-R is a measure of verbal learning and memory in which subjects 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.

Language functioning

8)Semantic Verbal Fluency – Semantic Verbal fluency is a measure of speeded verbal fluency and word retrieval in which subjects 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>Motor testing</u>

- Rapid Paced Walk (RPW) test: The RPW assesses stride length, balance and overall mobility, all of which can be impaired in PD [Crizzle AM, et al. 2013].

<u>Quality of Life</u>

- 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 8 discrete scales: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items), and bodily discomfort (3 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 5 options (likert Scale): never/occasionally/sometimes/often/always or cannot do at all.

- EuroQoL-5 Dimension-5 level (EQ-5D-5L): consists of 2 pages-the EEQ-5D-5L descriptive system and the EQ Visual Analogue Scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 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.

4. By assessing and comparing the proportion of subjects that drop out of the study due to study drug intolerance in the two groups (treatment vs. placebo).

Secondary Specific Aim: To examine the effect of CBD on severity & duration of tremor in PD.

Secondary Outcome Measure: Tremor is measured by the change from baseline to 10th day of 5 mg/kg/day (week 2 and week 12) and the end of each treatment phase (week 7 and week 17) change in 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).

Exploratory Analyses:

(1) To study the effects of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder and global impression of patients and clinicians.

(2) To evaluate the effects of CBD on these conditions at a low dose.

Exploratory Outcome Measures: The effects of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, and motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder and quality of life are evaluated using the aforementioned assessment tools. The change from baseline to 10th day of 5 mg/kg/day (low dose analysis) and from baseline to the maximum tolerated or targeted dose is compared.

Table 1. Measurement tools performed in Stage 1 and Stage 2.

Assessments	Stage 1		Stage 2		
	Primary	Secondary	Primary	Secondary	Exploratory

MoCA	X	X	X		X
Detailed cognitive battery			X		X
Anxiety short form	X	X	X		X
NPI	X	X	X		X
SCOPA-Sleep	X	X	X		X
Depression short form	X	X	X		X
Emotional and Behaviroral dyscontrol short form	X	X	X		X
Fatigue Severity Scale	X	X	X		X
Pain Intensity 3a and Interference 4a short forms	X	X	X		X
QUIP-RS	X	X	X		X
MDS UPDRS total	X	X	X	X*	X
Unified Dyskinesia Rating Scale (UDysRS)	X	X	X		X
Rapid Paced Walk (RPW) test			X		X
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	X	X	X		X
The Columbia-Suicide Severity Rating Scale (C-SSRS)	X		X		
International Restless Legs Syndrome Study Group Rating Scale (IRLS)	X	X	X		X
PDQ-39			X		X
EQ-5D			X		X
CGI		X			X
PGI		X			X

*Specifically items 3.17 and 3.18 in part III

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 and study drug dose determination

The study is conducted in two stages. The major purpose of the Stage 1 is to study the safety and tolerability of the proposed dosage regimen, which is based on GW Pharmaceutical's experience. This is an open label study in 10 subjects, during which the dose is gradually increased to the manufacturers recommended target dose, with tolerability being evaluated at each dose level. Based on the response of subjects in the Stage 1, a target dose is determined for the next stage. Standardized tools will be administered to study both tolerability and efficacy. Efficacy assessments are simply explorative, and are done to look for an effect that warrants specific or different evaluation in the next stage. We will be recruiting up to 20 subjects in Stage 1 to end up with 10.

The major purpose of Stage 2 is to assess the safety and tolerability of the Epidiolex at the determined dose, and secondarily to study efficacy, particularly regarding tremor. The study has been powered to detect a clinically significant reduction in tremor, all other efficacy analyses are exploratory. Stage 2 is a crossover, double-blind, randomized controlled trial (RCT) with 50 subjects. We will be recruiting up to 60 subjects in Stage 2 to end up with 50.

See Appendix 1 Schedule of Events for each Stage for more detail on study design.

The study drug is obtained from GW Pharmaceuticals and is called Epidiolex. How the dose is started and escalated and what target dose is chosen is based on human literature but primarily on recommendations from GW staff. Animal data supports the use of CBD dosing up to 24 mg/kg/day. In human literature CBD has been well tolerated up to 1500 mg/day (~21 mg/kg/day). Studies using Epidiolex are described in GW's Investigational Brochure (IB) Edition 8, Section 7.3.1. Epidiolex has been used in six Phase 2 studies (mostly related to pain). Presently a study of patients with psychosis are taking 1000 mg per day. Also GW has initiated a clinical program of Phase 1-3 studies to investigate its effect in severe forms of epilepsy, i.e., Davet's syndrome and Lenox Gastaut syndrome. Based on their experience, GW has recommended the dose escalation and target used in this study. As noted, the purpose of Stage 1 study, n=10, is to check for tolerability of this dose regimine in PD patients. If Stage 1 shows that the maximal dose tolerated is less than 20 mg/kg/day, then the maximal targeted dose for the RCT study will be reduced accordingly.

A recent publication, Lancet Neurol 2016; 15: 270-78, shows evidence for using this dose. The study reported on the safety (n=128) and efficacy (n=137) of the study drug we are using, but in a pediatric (aged 1-30; mean

10) population with severe epilepsy. Subjects were evaluated after 12 weeks on study drug, mean dose of ~23 mg/kg/day. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). Somnolence and fatigue were not dose related, diarrhea and weight loss occurred more often in subjects taking >15 mg/kg/day. Of note, the concomitant use of clobazam (an anticonvulsant medication) was highly associated with somnolence, meaning somnolence was less in those not on clobazam (21%) compared to those taking it (51%). Most adverse events were moderate and transient. SAEs deemed related to the study drug occurred in 12% of subjects, including 9 who had status epilepticus. However, of note, the study showed a ~50% reduction in seizures on study drug, and status epilepticus is a common problem in the population studied. Five subjects (3%) stopped the study drug due to an adverse event. Please see the article regarding clinically significant changes in safety blood analyses. Hepatotoxicity (< 1%), hyperammonemia (<1%), and thrombocytopenia (<1%) occurred only in subjects also taking valproate.

The maximum tolerated doses, in mg/kg/day, of the 10 subjects will be averaged, and adjusted to the next highest 5 mg/kg/day. That dose will be used as the targeted dose for the RCT. For example if the average of the maximal tolerated doses in Stage 1 subjects is 17.4 mg/kg per day, the targeted dose in the RCT will be 20 mg/kg/day. Or if the average of the maximal tolerated doses in stage 1 subjects is 22.7 mg/kg per day, the targeted dose in the RCT will be 25 mg/kg/day.

C.2 Stage 1: Open Label Dose Escalation Tolerability Study

The dose escalation tolerability study will be conducted in 10 subjects (we will be recruiting up to 20 subjects to end up with 10) as an open label study lasting 4 weeks followed by a 2-week safety follow up. Subjects are closely monitored as the dose is titrated. Subjects will have a screening visit, a baseline visit within the next 4 weeks, a final assessment visit when they have been on the maximal tolerated or the targeted study drug dose for 10-15 days, and a safety visit 2 weeks later. The subject is to be on the maximal tolerated or targeted dose for 10-15 days, and return for the final assessment visit on that dose on any of days 10-15. The reason for a range of 10-15 days instead of exactly 10 days is to allow for some flexibility in getting subjects in for the study visit. Subjects will be called on the 3rd day of each dose between 5-10 mg/kg/day and the fifth day of each dose between 10-20 mg/kg/day. During phone calls subjects are monitored for adverse events, especially excessive daytime sleepiness, symptoms of hepatotoxicity, as well as changes in medical history and concomitant medications. At the final assessment visit, urinary CBD and metabolites will be tested. Subjects are also called 3 days after stopping the study drug to check for signs of withdrawal.

To increase compliance with taking study drug, subjects will be asked to fill out a diary at home. The diary will be a record of the date and time subjects take study drug, adverse and beneficial events, and whether they talked to study staff on the phone that day, and if so what they were told to do with the dose. To make sure the diary is recorded correctly, subjects will be asked to mail, email or fax a copy or image of the diary they filled out within 3 days of increasing from 5 to 7.5 mg/kg/day. This is so that diary errors can be corrected early.

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. Subjects will be given two urine cups, 100 mL each, at the baseline visit. On the phone call before the day of the final assessmen visit, subjects will be reminded to collect urine in the morning of the study visit. They are asked to fill each up at least 3/4 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 & Development.

Inclusion & Exclusion criteria

Inclusion criteria:

- Male or female subjects between 45 and 78 years of age inclusive.
- Willing and able to give informed consent.
- Idiopathic PD, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria
- Rest tremor amplitude score of ≥2 in any limb on question 3.17 of the MDS-UPDRS (ON state).
- Anti-parkinsonian medication is fixed for at least 1 month prior to the day the subject starts study drug treatment.
- If MoCA<22 subject must have a legally authorized representative (LAR) sign the consent, and 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 to drive them to and from study visits
- Has a significant other (someone who knows the subject 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 (required for those with MOCA<22), caregiver (required for those with MOCA<22), and significant other (required for all subjects) 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 subject 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 subject 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 amphetamine, 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 2 years post-menopausal, or does not agree to utilize an effective method of contraception from screening through at least 4 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.

Dose escalation strategy

Study product will be started at 5 mg/kg/day and increased every 3 days by 2.5 mg/kg/day to 10 mg/kg/day. Then increase the dosage every 5 days by 5 mg/kg/day until the subject reaches a maximum targeted dose (20 mg/kg/day) or experiences intolerable adverse effects, in which case the dose will be dropped to the last tolerated dose, for 10-15 days. Tolerability will be assessed on the third day of each dose between 5-10 mg/kg/day and the fifth day of each dose between 10-20 mg/kg/day and the subject is instructed whether or not to change the dose starting the next day. Once a subject has been on a specific dose for at least 3 days (5-10 mg/kg/day) or 5 days (10-20 mg/kg/day), that dose can be changed for less or more than 3 (5-10 mg/kg/day) or 5 days (10-20 mg/kg/day) and can be changed by a smaller increment (2.5-5 mg/kg/day) as needed for tolerability. The maximal tolerated dose is determined by the PI or co-Investigator that is an MD, based on their clinical expertise.

Assessment of tolerability of each dose level

Tolerability will be assessed at each dose via collection of adverse events during administration of the standardized phone script by appropriate study staff. 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 a follows:

- For subjects with a grade 1 adverse event the dose will be increased by up to 5 mg/kg/day, or if they are on the maximal targeted dose (20 mg/kg/day) it will be continued.
- For subjects with a grade 2 adverse event the dose will be reduced by 5 mg/kg/day or less.
- For subjects 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., subject is stable after a hip fracture repair, the dose will be increased unless they are already on the maximum targeted dose.
- For subjects with a grade 3 or 4 adverse event that the Investigator determines is related the study drug will be stopped and not restarted.

The Investigaor will determine relatedness as described in Section IV. C.8, and will consider the adverse event related if she determines there is at least a reasonable possibility.

The major dose limiting effect, per GW, is somnolence. To monitor for this closely, the daytime sleepiness part to the SCOPA-sleep will be administered during each phone call, 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 subject being instructed to drop to the prior dose for three more days before increasing the dose.

Additional assessments of safety and tolerability is done at the study visit when the subject is on the maximum tolerated or targeted dose. The same protocol for dosing is applied for both adverse events found during phone assessments and during study visits.

The results of safety and tolerability assessments in Stage 1 will be studied to determine if additional evaluations during Stage 2 are warranted. For example, if grade 1 or 2 advere events occur in ≥ 2 subjects then additional surveillence will be conducted during Stage 2. Further, safety and tolerability Stage 1 results determine participant and study stopping parameters, described in Section IV C.7.

The CTCAE criteria are used to determine dose level adjustments and for participant and study stopping rules (Section IV C.7). Adverse events for both Stage 1 and 2 will be collected and reported as discussed in Section IV C.8.

To mitigate potential risk during the study, the subjects will be told not to drive cars or operate dangerous machinery while taking study drug in the Open Label Dose Escalation Tolerability study (Stage 1). Instructions to subjects in the Randomized Controlled Trial (Stage 2) will be developed after Stage 1 is completed, with COMIRB guidance.

Procedures at each visit

Visit 1-Screening visit: Consent, demographics, family medical history, concomitant medications, formal drug interaction assessment, vital signs, orthostatic blood pressures, history & physical examination (complete physical exam and detailed neurological exam), tremor evaluation (question 3.17 of the MDS-UPDRS), MOCA, MDS-UPDRS III, H&Y rating, Drug, alcohol and tobacco abuse screening test, safety assessments (as listed in section IV A, except for RBDSQ, IRLS), EKG and safety labs (complete blood count, hemoglobin A1C, complete metabolic profile and urinalysis), blood cannabis analysis testing, serum pregnancy test (for women childbearing potential), and inclusion/exclusion criteria are done. Study subjects are instructed not to take cannabis from outside source throughout the study.

Visit 2-Baseline visit: Eligibility confirmation, medical history, and concomitant medications, formal drug interaction assessment, vital signs, orthostatic blood pressures, brief physical exam (heart and lung auscultation), MDS-UPDRS, UDysRS, and inclusion/exclusion criteria, RBDSQ, IRLS, C-SSRS, urine drug (THC) test (urine dipstick testing), urine pregnancy test (women childbearing potential), safety assessments, and drug and home diary dispensing are done. Subjects will take the first dose in clinic and will be monitored and vital signs (including orthostatic blood pressure and pulse) will be taken to check for study drug tolerability at 1 hour after taking the study drug. Subjects are instructed on how to take the medication and how to fill out the diary at home. To make sure the diary is recorded correctly, subjects will be asked to mail, email or fax a copy or image of the diary they filled out within 3 days of increasing from 5 to 7.5 mg/kg/day. This is so that diary errors can be corrected early. Subjects 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. Subjects are also instructed to bring in empty, partially used and unused bottles of study drug at next clinical visit. Subjects will be given two urine cups, 100 mL each, and will be instructed to collect their urine the morning of the final assessment visit. They are asked to fill each cup at least 3/4 full, if possible, and to bring them to the visit (no refrigeration needed).

Visit 3-Final Assessment visit: Medical history and concomitant medications collection, formal drug interaction assessment, vital signs, orthostatic blood pressures, complete physical exam and detailed neurological exam, and all efficacy and safety assessments are repeated that were done in the screening, baseline and 20 mg/kg/day assessment visit, except for the cannabis, drug, alcohol and tobacco abuse questionnaire. Adverse event check is done. Subjects will take the study drug upon their arrival to the clinic and record the time. On the morning of the visit, subjects 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. Blood draw is performed 3 hours after the dose is taken, for cannabis testing and safety labs. Subjects will be monitored and vital signs and orthostatic blood pressures will be checked at 1 and 3 hours after taking the study drug. Returned study drug is counted. Compliance will be checked by study drug count and cannabis analysis testing. Home diary is collected and reviewed.

Visit 4-Safety follow up: Concomitant medications, formal drug interaction assessment, vital signs, orthostatic blood pressures, history & complete physical examination, MDS UPDRS, H&Y rating, UDysRS, MoCA, QUIP-RS, C-SSRS, NPI, SCOPA-sleep, RBDSQ, Anxiety short form, Depression short form, Emotional and behavioral dyscontrol short form, Fatigue Severity Scale, Pain Intensity and Interference short form, IRLS, adverse event check, blood cannabis lab testing and urine pregnancy test (women childbearing potential). Safety labs and EKG will be done if there was a clinically significant change at the assessment visit compared to baseline visit. The PI will evaluate the subject for signs of withdrawal.

C.3 Stage 2: RCT

The main study is a randomized, placebo controlled, double-blind crossover design with two treatment phases, each of approximately 7 weeks duration separated by a 3-week washout phase. In each 7 week treatment phase subjects will start study drug and titrate up to the maximum tolerated or targeted dose (20 mg/kg/day). Each subject will have a screening visit, baseline visit within 3 weeks, a low dose visit (when on 5 mg/kg/day for 10-15 days), an assessment visit while on 20 mg/kg/day, a first end of 7 weeks treatment phase visit (subject reaches maximum tolerated or targeted dose), a start of second 7-week treatment phase visit, a low dose visit (when on 5 mg/kg/day for 10-15 days), an assessment visit when on 20 mg/kg/day, a second end of 7 weeks treatment phase visit, and a safety visit (10 visits total). At the start of second 7-week treatment phase, subjects are dispensed and instructed to take study drug for the next treatment phase. To maximize compliance the coordinator calls the subject to remind them the next day's clinical visit. Subjects will be called every 3rd day during dose escalation and every 10th day during the dose maintenance period (up to

25 mg/kg/day). During phone calls subjects are monitored for adverse events, as well as changes in medical history and concomitant medications. Subjects are also called 3 days after stopping the study drug to check for signs of withdrawal. Further, in case CBD alters the reliability of self - report, repeated measures will be taken of a set of tests three times: at baseline, low dose and high dose. During the 10 days that subjects are on a low dose the measurements will be taken on the 3rd and 9th day by phone and at the visit on the 10th to 15th day. During the 28 days on high dose the measurements will be taken on the 12th and 22nd day by phone and at the visit on the 28th +/- 4 days. The phone assessments include the primary outcome (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. At low dose visit (end of 10 days on 5 mg/kg/day), each 20 mg/kg/day visit and each end of treatment phase assessment visits, urinary CBD and metabolites will be tested. To increase compliance with taking study drug, subjects will be asked to fill out a diary at home. The diary will be a record of the date and time subjects take study drug, adverse and beneficial events, and whether they talked to study staff on phone that day, and if so what they were told to do with the dose. Study drug is dispensed at the baseline visit and at the start of the second 7-week treatment phase visit so that subject has enough to take until they return for the low dose visit. At that visit they are given enough to last through 20 mg/kg/day. At the 20 mg/kg/day visit they are given enough for the time on 25/mg/kg/day. As in Stage 1, the purpose of the visit at 20 mg/kg/day is to limit the amount of study drug that is dispensed at any one time and facilitate compliance, safety and drug control. In the instance that a subject does not reach the 20 mg/kg/day dose, due to intolerance, then they will come in when and if they need more study drug to complete 10-15 days on their maximal tolerated dose. If they have enough to last through the 10-15 days then they return for the Final Asssessment visit, and therefore have fewer total visits.

Inclusion & Exclusion criteria:

These are the same as in stage 1, except an additional exclusion criteria is: Participated in Stage 1. Criteria for driving will be decided based on results from Stage 1, with COMIRB guidance.

Dose escalation strategy:

In each of the two 7-week periods, study product (CBD or placebo) will be started at 5 mg/kg/day and increased as tolerated to a maximum weight-adjusted target dose that is determined as a result of the Stage 1 study. The dose escalation strategy is the same as in Stage 1 for each treatment phase, except that subjects will take 5 mg/kg/day for 10 -15 days, and have a study visit before increasing further. The reason for a range of 10-15 days instead of exactly 10 days is to allow for some flexibility in getting subjects in for the study visit. Then the dose is escalated at 3-day intervals (with 5 mg/kg/day increased each interval) until the subject reaches the maximum target dose or experiences intolerable adverse effects, in which case the dose will be dropped to the last tolerated dose. Tolerability will be assessed on the third day of each dose and the subject is instructed whether or not to change the dose on the next day. The maximal tolerated dose is the dose at which 5 mg/kg/day higher was not tolerated on two trials. When subject achieves the maximal tolerated dose or the maximum targeted dose, they will maintain that dose for 28 +/-4 days.

Urine collection, storage and transfer for cannabis and metabolites test protocol is as described in Stage 1.

Procedures at each visit

Visit 1- Screening visit: Consent, demographics, concomitant medications, formal drug interaction assessment, family medical history, medical history & 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, except for RBDSQ, IRLS, PDQ-39 and EQ-5D), EKG and safety labs (as in dose escalation study), blood cannabis analysis testing, serum pregnancy test (for women childbearing potential) and inclusion/exclusion criteria are done. Study subjects are instructed not to take cannabis from outside source throughout the study.

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, RPW, 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), RBDSQ, C-SSRS, IRLS, PDQ-39, EQ-5D, urine drug (THC) test (urine dipstick test), urine pregnancy test (women childbearing potential) and study drug dispensing is done and, if appropriate, randomization. Home diary is also dispensed. Subjects take the first dose and are instructed on how to take the medication and how to fill out the diary at home. Subjects will be monitored and vital signs and orthostatic blood pressures will be checked at 1 hour after taking the study drug. Subjects are also told to bring in empty, partially used and unused bottles of study drug at next clinical visit. Subjects 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. Subjects will be given two urine cups, 100 mL each, and will be instructed to collect their urine the morning of the low dose visit. They are asked to fill each cup at least 3/4 full, if possible and to bring them to the visit (no refrigeration needed).

Visit 3 and Visit 7-Low dose visit (end of 10 days on 5 mg/kg/day): On the morning of the visit, subjects 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. Concomitant medications, formal drug interaction assessment, change in medical history, vital signs, orthostatic blood pressures, brief physical exam, MDS-UPDRS, UDysRS, H&Y rating, RPW, 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, IRLS, EQ-5D, PDQ-39, CGI, PGI, and urine pregnancy test are done. Study drug compliance check, adverse event check and blinding assessment are done. Subjects 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 3 hours after the dose. Subjects will be monitored and vital signs and orthostatic blood pressures will be checked at 1 and 3 hours after taking the study drug. Home diary is collected and reviewed. The next study drug supply and home diary are dispensed. Subjects are instructed on how to fill out the diary at home and are told to bring in empty, partially used and unused bottles of study drug at next clinical visit. Subjects will again be given urine cups and instructions.

Visit 4 and Visit 8-20 mg/kg/day Assessment visit: Subjects will be on 20 mg/kg/day for 5 days. They will come back to clinic on either day from 2nd through 5th day while on 20 mg/kg/day. On the morning of the visit, subjects 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. Medical history and concomitant medications collection, formal drug interaction assessment, vital signs, orthostatic blood pressures, brief physical exam, CGI, PGI, and adverse event (including SCOPA-Sleep and C-SSRS) check are done. Blood is drawn for complete metabolic profile. Study drug is collected and counted. Study drug is dispensed: and subject is instructed in how to take it. Home diary is collected and reviewed. The next home diary is dispensed. Subjects 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. Subjects will again be given urine cups and instructions.

Visit 5-End of first 7-week (47 days) and Visit 9-second 7-week (115 days) treatment phase assessment visits: Same procedures are conducted as at the previous low dose visit, except for study drug and home diary dispensation. In addition, complete physical exam, detailed neurological exam, blood draw, urinalysis, ECG, and full cognitive assessment battery are done. Subjects 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 3 hours after the dose. Subjects will be monitored and vital signs and orthostatic blood pressures will be checked at 1 and 3 hours after taking the study drug.

Visit 6-Start of second 7-week treatment phase: Study drug and home diary dispensation and instruction will be performed. Formal drug interaction assessment will be done. Subjects take the first dose of study drug. Subjects will be monitored and vital signs and orthostatic blood pressure will be taken at 1 hour after taking the study drug. Subjects are also told to take study drug and record the taking time upon their arrival to clinic on the next clinical visit day.

Visit 10-Safety follow up: Vital signs, orthostatic blood pressures, history & complete physical examination, concomitant medications collection, formal drug interaction assessment, MDS-UPDRS, H&Y rating, UDysRS, RPW, MoCA, 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, 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 subject for signs of withdrawal.

C.4 Study Drug: Epidiolex:

Purified CBD from GW is a strawberry flavored liquid, in sesame oil, provided as 100 mg/ml, extractd from high CBD plant material. The placebo is the same, but without CBD. 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 subjects experience nausea. It is to be taken twice daily at a standard time, minimum of 6 hours apart. Subjects are instructed to take it before breakfast (30 to 60 minutes) and the same before dinner. Further detail is proprietary. Subjects are instructed not to drink grapefruit for 7 days prior to the first dose of study medication and during the rest of the study (both Stages).

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.

Subjects take their routine anti-PD medication on the day of clinical visit, and when ON (PD medications are working) the testing is done.

CBD and metabolite levels will be measurements:

- In Stage 1, blood CBD and metabolite levels will be measured at the screening visit, final assessment visit and safety follow up visit. Urinary CBD and metabolites levels will be tested at the final assessment visit.
- In Stage 2, blood CBD and metabolite levels will be measured at screening visit, baseline, low dose visit (end of 10 days on 5 mg/kg/day) and end of each treatment phase assessment visits. Urinary CBD and metabolites levels will be tested at the low dose visit, 20 mg/kg/day visit and the end of each treatment phase assessment visit.

Potential drug-drug interactions

The PI has worked with Jacci Bainbridge, Pharm D, and GW to study possible drug interactions. See GW Pharmaceutical's Investigator Brochure on CBD, especially pages 4-5, 47-51 and 105-106 and their CBD;CBD BDS Development Core Safety Information dated August 2015 pages 2-4 for detailed information. Also, Appendix 2 is a list of drugs with potentially interactions with CBD, thus the PI will monitor for clinical effects. 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. Subjects 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 same study drug as in our trial at similar doses there was ~twice as much somnolence AEs reported in subjects on both CBD and clozabam than in subjects 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 subjects 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 Subjects at the End of Each Stage:

We wil 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 casues 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 symtoms. The precise effects of all the substances in cannabis is unkown. In this study we are using Epidiolex. It is >99% pure CBD with only a trace amount of THC (<0.15%) and it has more data regarding safety, tolerability, dosing and efficacy than most other forms. 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.5 Randomization and drug dispensation:

Patients who consent will be stratified by age (45 – 60 and 61-78) 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 each of two sequence groups. One group will receive the control first and the treatment second, and the other group will receive the treatment first and the control second. Since all subjects receive both treatments randomization and stratification are less critical then in studies with fixed treatment groups, unless order effects are important or an expectedly large number of patients drop out.

The study drug, Epidiolex, and matching placebo will be provided by GW Pharmaceuticals. GW will ship the drug according to British and US regulations. Initially enough study drug will be provided for the Stage 1 open label study, and replenishment shipments will follow. Dr. Leehey, the PI, will obtain a Schedule 1 license and all procedures of drug handling will be according to DEA specifications. Briefly, designated study personnel will receive the study drug, store it, measure and label it (Jacci Bainbridge, PharmD and her fellow) and dispense to the subject (study coordinator).

C.6 Blinding assessment and Un-blinding procedures:

Blinding assessment:

Active drug and placebo will look and taste the same. Subjects and all study personnel except for Drs. Sillau, Bainbridge and her fellow, are blinded.

During each visit when on study drug and at the safety follow up visit, 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 subjects can be revealed in an emergency only. The PI is responsible for ensuring that the instructions on how to request unblinding 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 subject 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 subject’s treatment assignment should only be un-blinded when knowledge of the treatment is essential for the safety of the subject. Un-blinding for any other reason will be considered a protocol deviation.

C.7 Stopping rules:

Note there are no interim analyses planned.

Participant stopping rules (Both Stages):

- If subject cannot tolerate the study drug at any dose level
- if subject 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 subject to terminate treatment
- Failure by the subject to attend consecutive study visits;
- Subject 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 subject 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 subjects who complete the study will be summarized by treatment group. The number and percentage of subjects 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.

Subjects will be advised that they are free to withdraw from the study at any time. Reasons that subjects may be withdrawn from the study include the following:

Subject discontinued study medication and wishes to withdraw.

Subject consent is withdrawn.

Study stopping rules (Both Stages)

- Subjects are unable to be recruited
- Study drug becomes unavailable
- Subjects 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 subjects, i.e., development of the same adverse event, CTCAE criteria grade ≥3, related to study drug in ≥2 subjects
- At the discretion of the IRB, Food and Drug Administration (FDA).

Any of the above occurring during Stage 1 will lead to a hold and reassessment of starting Stage 2.

C.8 Adverse events assessments:

Adverse events will be classified according to ICH Good Clinical Practice (GCP) definitions. 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 three defined categories as follows:

- Mild: the AE is easily tolerated by the subject, causes minimal discomfort, and does not interfere in a significant manner with the subject's normal functioning level or activities;
- Moderate: the AE is sufficiently uncomfortable to interfere with normal everyday activities, but is not hazardous to health;
- Severe: the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's reports, the physician's observations, and the physician's prior experience. 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 subject might have a severe headache that does not require hospitalization and is consequently not serious; or a subject 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" refersto an event in which the subject, in the view of the Investigator, is at risk of death at thetime of the event; it does not refer to an event that hypothetically might cause death if itwas 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: Out-patient 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 subject 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, subjects 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 subject 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.

Relationship to Study Drug

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 not 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.

Reporting Serious Adverse Events to Regulatory Agencies

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 7 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.9 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) (21%). Other side effects, in order of prevalence, include: fatigue (17%), diarrhea (17%), increased appetite (17%), decreased appetite (16%), and weight loss (9%). [Devinsky O, et al. 2014] Other side effects include extrapyramidal symptoms, increased prolactin levels, weight gain increased serum concentrations of antiepileptic drugs and elevated liver function tests .

Table 2 and 3 show the adverse reactions of CBD from the IB (CBD) provided by GW Research Ltd.

Table 2. The adverse reactions with a plausible causal relationship to purified CBD solution—reported at a daily maximum of 25 mg/kg/day

Adverse Reactions	**Related causality CBD (n=213)**
Most frequently (5 to 10%)	

Somnolence	44 (21%)
Fatigue	36 (17%)
Decreased appetite	31 (15%)
Diarrhoea	29 (14%)
Lethargy	12 (6%)
Increased appetite	15 (7%)
Weight increased	12 (6%)
Convulsion	11 (5%)
Weight decreased	10 (5%)
Gait disturbance	10 (5%)
Less frequently (1 to 5%)	
Drug level increased	9 (4%)
Sedation	7 (3%)

Table 3. Most frequently adverse reactions of purified CBD reported at 200, 400, and 800 mg/day

Adverse reactions	**CBD 200 mg/day (n=7)**	**CBD 400 mg/day (n=6)**	**CBD 800 mg/day (n=7)**
Diarrhoea	4 (57%)	3 (50%)	5 (71%)
Dyspepsia	0	1 (17%)	1 (14%)
Defaecation urgency	0	0	1 (14%)
Eructation	0	0	1 (14%)
Frequent bowel movements	0	0	1 (14%)
Gastritis	1 (14%)	0	0
Gastrointestinal hypermotility	0	1 (17%)	0
Vomiting	1 (14%)	0	1 (14%)
Fatigue	1 (14%)	1 (17%)	0
Product size issue	1 (14%)	0	0

Aspartate aminotransferase increased	1 (14%)	0	0
Gamma-glutamyltransferase increased	1 (14%)	0	0
Platelet count decreased	1 (14%)	0	0
Decreased appetite	1 (14%)	0	1 (14%)
Dysgeusia	0	0	1 (14%)
Headache	1 (14%)	2 (33%)	0
Pollakiuria	0	0	1 (14%)
Rash generalised	0	0	1 (14%)
Rash maculo-papular	0	0	1 (14%)

Based on data of Epidiolex and previous studies, some side effects, such as diarrhea, weight loss, and decreased appetite, required reduction of the dose resulting in improvement of symptoms. The large majority of adverse events were mild to moderate and transient. No significant laboratory abnormalities were observed.

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. If this is found then subject could be harmed by participating and thus would be excluded. Also 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 subject 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 subjects. To minimize discomfort subjects 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 contacted by phone every 3rd or 10th day and the 3rd day following discontinuation of study drug as described in Section C during in both the dose escalation safety study and the RCT to monitor for adverse effects or withdrawal, as well as changes of medical history and concomitant medications. These phone calls will be done by a RN, APP or MD.
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 subject dies or is lost to follow-up.
6. Safety assessments are comprehensive and include vital signs, history & physical examination, concomitant medications collection, EKGs, safety labs, 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. Subjects 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 subjects are on study drug. In addition, if these labs are abnormal at the end of study visit they will be repeated at the safety follow up visit two weeks later and repeated until back to baseline values. During each phone call that assesses effects of 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 subject 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 3x 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 subjects with normal baseline measures or 2-fold increases above baseline values for subjects 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 subject 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 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 2 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 subject's information in the database. All of this information in the computer is password protected. The code will be linked to the subject'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 intergrity this study was peer reviewed by the Colorado Department of Health & Safety (CDPHE) before receiving funding. In addition it has been reviewed in detail by scientific members of the company providing study drug, GW Research, Ltd. 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 1500 PD patients in our UCH Movement Disorders clinic annually, and our 8 Movement Disorders providers also cover the VAMC and Denver Health. We do not expect problems with unblinding because the placebo will be identical and does not taste or smell different from active drug and because CBD is generally well tolerated. Also, to reduce risk of

unblinding if the dose escalation study shows that the maximal dose tolerated is less than 25 mg/kg/day, then the maximal dose for the RCT study will be reduced accordingly.

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 subject agrees, the de-identified data would be shared within CDPHE Marijuana grantee consortium for future research.

Stage 1: Open Label Dose Escalation Tolerability Study

Primay Specific Aim: To confirm that the dosage regimen of CBD, in the form of Epidiolex, is safe and tolerated in 10 subjects with PD.

The primary outcome is safety and tolerability of the proposed dose of CBD and will be assessed in 4 ways:

1. Frequency of study-related adverse events at each dose level collected at standardized phone script administration and at study visits. Analysis of frequency will be mostly descriptive, and proportions and confidence intervals will be calculated. Comparisons on repeated measures can be analyzed with McNemar's test, for binary outcomes at 2 time points, or GEE models/GLMMs. Logistic or relative risk models can be used for binary outcomes, and Poisson models for counts.

2. Vital signs, orthostatic blood pressures, physical exam, EKG and labs (hematology, complete metabolic profile, urinalysis) during study visits. For vital signs and labs, means and their confidence intervals will be calculated at the two time points (baseline and the end of the open label dose escalation tolerability study), and a paired T-test will compare them. Physical exam and EKG will be descriptive.

3. Standardized assessment tools (MoCA, Anxiety short form, NPI, SCOPA-Sleep, RBDSQ, QUIP-RS, C-SSRS, Depression short form, Emotional Behaviroral dyscontrol short form, Fatigue severity scale, MDS UPDRS, UDysRS, Pain Intensity 3a short form and Pain Interference 4a short form, IRLS) during study visits. Means and their confidence intervals will be calculated for each outcome at the two time points (baseline and the end of the open label dose escalation tolerability study), and paired T-tests will compare them.

4. Proportion of subjects drop out of the study due to study drug intolerance. It will be descriptive and proportions and confidence intervals will be calculated. No tests are applicable since there is nothing to compare to.

The Secondary Specific Aim is to examine the effect of CBD on severity & duration of intractable tremor and other symptoms of PD.

The secondary outcomes are tremor and the changes from baseline to the end of the open label study on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder. In this open label study the aim is to obtain preliminary data on the effect of CBD on severity & duration of intractable tremor in PD. This study is not intended to be powered to obtain a clinically significant result. A paired T-test is applied to compare the data at the two time points. Analysis of binary outcomes can be performed with McNemar's test, generalized estimating equations models, and generalized mixed models.

Stage 2: Randomized Controlled Trial

For the RCT 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 for both the low dose (5 mg/kg/day) and highest tolerated dose.

Primary Specific Aim: To evaluate the safety and tolerability of CBD, in the form of Epidiolex, in PD.

The primary outcome is safety and tolerability and will be assessed in 4 ways:

1. Frequency of study-related adverse events at each dose level collected at standardized phone script administration and 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 subjects 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) during study visits. For vital signs and labs, data will be analyzed as a simple two-period crossover trial. Means and confidence intervals will be presented for each group * treatment, and for the change scores in each group. A two sample T-test will compare the means of the two groups, those in the CBD-placebo group vs. those in the placebo-CBD group, on the change scores between period 1 to period 2. The difference between the means of the two group will be equal to twice the treatment effect. Physical exam and EKG will be descriptive between the two groups (treatment vs. placebo). More complex situations, including testing for treatment * order interaction, can be analyzed with longitudinal regression models.

3. Standardized assessment tools (MoCA, Cognition assessment battery, Anxiety short form, NPI, SCOPA-Sleep, RBDSQ, QUIP-RS, C-SSRS, Depression short form, Emotional Behaviroral 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 crossover trial. Means and confidence intervals will be presented for each group * treatment, and for the change scores in each group. A two sample T-test will compare the means of the two groups, those in the CBD-placebo group vs. those in the placebo-CBD group, on the change scores between period 1 to period 2. The difference between the means of the two group will be equal to twice the treatment effect. More complex situations, including testing for treatment * order interaction, can be analyzed with longitudinal regression models.

4. Proportion of subjects drop out of the study due to study drug intolerance. Analysis (proportions of subjects drop out of the study due to study drug intolerance in the two groups, treatment vs. placebo) will be mostly descriptive, and proportions and confidence intervals will be calculated. Proportion differences between groups can be compared with the standard test.

The difference between the mean change scores of the two group will be equal to twice the treatment effect. We will test the null hypothesis of no treatment effect. To test and control for a possible time/order effect, longitudinal regression models will be fit with a time/order variable included.

Secondary Specific Aim is to examine the effect of CBD on severity & duration of intractable tremor in PD.

For the secondary outcome, tremor, the data will be analyzed as a simple two-period crossover trial. Means and confidence intervals will be presented for each group * treatment, and for the change scores in each group. A two sample T-test will compare the means of the two groups, those in the CBD–placebo group vs. those in the placebo–CBD group, on the change scores between period 1 to period 2. The difference between the means of the two groups will be equal to twice the treatment effect. We will test the null hypothesis of no treatment effect. To test and control for a possible time/order effect, longitudinal regression models will be fit with a time/order variable included. Covariates, such as age or baseline disease severity (H&Y) may be adjusted for as covariates, especially if unbalanced between the sequence groups.

Exploratory Outcome Measures: The effects of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, and motor and non-motor PD signs, restless legs syndrome, REM sleep behavior disorder and quality of life are evaluated using the aforementioned assessment tools. The change from baseline to 10th day of 5 mg/kg/day (low dose analysis) and from baseline to the maximum tolerated or targeted dose is compared.

Exploratory analyses: (1) To study the effect of CBD on cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder, (2) To evaluate the effects of CBD on these conditions at a low dose.

Exploratory outcomes includes assessments of cognition, anxiety, psychosis, sleep, daytime sleepiness, mood, fatigue, pain, impulsivity, other motor and non-motor PD signs, restless legs syndrome and REM sleep behavior disorder. The effect of CBD at both a low dose (5 mg/kg/day) and the maximum tolerated or targeted dose is studied. 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, and generalized mixed models, and with McNemar's test for binary outcomes.

Sample Size Justification

Stage 1. Open Label Dose Escalation Tolerability Study

Ten patients are recruited to the safety study. A 95% confidence interval derived from the T distribution, for a continuous outcome, would have a total width of 1.43 times the standard deviation of the change score. For the test for a difference, with an alpha level of 0.05, an effect size of 1.00 relative to the standard deviation would be required for 80% power, and an effect size of 1.16 would be required for 90% power. For a binary event, the probability of no "success" in 10 independent runs is less than 5% if the true probability is 26% or greater, and less than 2.5% if the true probability is 31% or greater.

Stage 2: Randomized Controlled Trial

The primary outcome, safety and tolerability, will mostly be analyzed descriptively. For the main secondary outcome, testing for a treatment effect on tremor, a sample size of 38 patients would achieve 90% power with an alpha level of 0.05, a standard deviation of the differences of 3 units on the outcome scale, and an absolute value mean effect on the outcome scale of 1.625, approximately 25% (this would be a clinically significant effect). We anticipate a dropout rate of 10%, necessitating 43 patients, and we then increase to 48 for safety, rounding and because of the 2x2 stratification plan. Note that each patient serves as his/her own matched control.

Since other outcomes are either descriptive and/or exploratory, and sample size is limited, there will be no adjustment for multiple testing adjustments are not planned.

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.

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APPENDIX 1: Schedule of Events—Stage 1

Appendix A Schedule of events Stage 1 Open label dose escalation tolerability study												
	Screening	Baseline	Treatment Period							Safety Followup		
Week		1	1-4							4	5-6	6
day	< negative 21	1	1-3	4-6	7-11	12-16	17-19	20-25	26-31 (k)	27-29	30-39	40 (+/- 4)
Clinic visit	1	2							3			4
Telephone call*			1	2	3	4	5	6 (h)		7(i)	8(h)	
Dosage of CBD or placebo mg/kg	0	5(take the first dose in clinic)	5	7.5	10	15	20	20	20 (take the study drug prior to clinic visit)	0	0	0
Informed consent	√											
Eligibility Criteria	√	√										
Demographics	√											
Medical History (a)	√											
Family medical history	√											
Medical History - interval	√	√	√	√	√	√	√		√	√		√
Concomitant Medications	√	√	√	√	√	√	√		√	√		√
Study drug compliance check									√			
Dispense study drug and instruction		√										
Adverse Events (b)			√	√	√	√	√		√	√		√
Formal drug interaction assessment	✓	✓							✓			✓
Vital Signs(c)	√	√ (l)							√ (n)			√
Orthostatic Blood Pressures check	√	√ (l)							√ (n)			√
Height and Weight	√	√							√			√
Complete Physical Exam (d)	√								√			√
Neurological exam	✓								√			
Brief physcial exam (heart and lung ausculation)		✓										
Hematology (e)	√								√			√ (j)
Hemoglobin A1C	✓											
Complete metabolic profie (f)	√								√			√ (j)
Blood cannabis analysis	√								√ (m)			√
Urinalysis (g)	√								√			√ (j)
Urine Drug (THC) test		✓										
Urine CBD and metabolites levels test (o)									✓			
Urine cups dispense and urine collection instruction		✓										
ECG (12-LEAD)	√								√			√ (j)
Serum Pregnancy Test (for women childbearing potential)	√											
Urine Preganancy Test (for women childbearing potential)		√							√			√
Assessment of past marijuana use	√											
Drug, alcohol and tobacco abuse screening test	√											
MOCA	√								√			√
MDS-UPDRS part III	√											
MDS-UPDRS		√							√			√
Unified Dyskinesia Rating Scale (UDysRS)		√							√			√
H & Y rating	√								√			√
QUIP-RS	√								√			√
C-SSRS	√	√							√			√
NPI	√								√			√
SCOPA-sleep	√		√	√	√	√	√		√	√		√
RBDSQ		√							√			√
IRLS		√							√			√
Anxiety short form	√								√			√
Depression short form	√								√			√
Emotional behavioral dyscontrol short form	√								√			√
Fatigue severity scale	√								√			√
Pain intensity and interference short form	√								√			√
CGI									√			
PGI									√			
Home diary dispense & instruction		√										
Home diary collection & review									√			
Fax, mail or email a copy or image of the diary filled out				√								
* phone call is made on the third day of each dose (between 5-10 mg/kg/day) and fifth day of each dose (between 10-20 mg/kg/day)												

Schedule of Event- Stage 1 note

Note: regarding the rows of days and weeks, it is variable, because of note k and also because some patients will take shorter or longer to get to their maximum tolerated dose than those that titrated to 20 mg/kg/day.
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 of the first dose of study drug. 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. Body temperature will be obtained at screening, Day 1, and at the final follow up visit. Blood pressure, respiratory rate and heart rate will be measured once each day assessed. During screening only, after the seated blood pressure has been obtained, the blood pressure will be repeated within 3 minutes of the subject standing up. This procedure may be repeated, if appropriate, following hydration. If repeated, a total of two additional pairs of BP assessments (sitting/standing) should be obtained, and the results of the last attempt should be reported.
d. Complete PE to include: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.
e. 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.
f. 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), γ-glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
g. Urinalysis will be performed locally using sponsor-supplied 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.
h. Call patient to remind them the clinical visit next day
i. Call patient to collect adverse events and information of signs of withdrawal
j. Hematology, chemistry, urinalysis and EKG will be done if there was a clincally significant change at the end of study visit compared to baseline visit.
k. For some patients, the visit can occur during 10-15 days on max dose, not just on the 10th day.
l. Subject will be monitored and vital signs will be checked at before and 1 hour after taking the study drug.
m. Blood draw will be performed 3 hours after taking the study drug of the clinical visit day.
n. Subject will be monitored and vital signs will be checked at before and 1 and 3 hours after taking the study drug.
o. Clean catch urine collection after taking the study drug. Urine is collected in a 500 mL container and stored in 3-4 samll cups (120 mL, fill up to 3/4).

Schedule of Event—Stage 2

Appendix B schedule of event Stage 2 RCT																																				
schedule of events																																				
	screening	baseline	Treatment Period												Washout			Treatment Period															Safety Followup			
week (number of days)		1	1-7 (47 days)												7 to 10 (21 days)			10 to 17 (47 days)															17	17 to 19(10 days)		19
Days	< negative 21	1	1-3	4-9	10 (+5) (k)	11-13	14-16	17-21	22-24	25-34	35-44	45-48	49 (+/-4) (l)	50-52	53-69	70	71	71-73	75-79	80 (+5) (k)	81-83	84-86	87-91	92-94	95-104	105-114	115-118	119 (+/- 4) (l)	120-122	123-132	133 (+/- 4)					
Dosage of CBD or placebo mg/kg	0	5 (take the first dose in clinic)	5	5	5 (take the study drug prior to clinic vist)	10	15	20	25	25	25	25	25 (take the study drug prior to clinic vist)	0	0	0	5	5	5	5 (take the study drug prior to clinic vist)	10	15	20	25	25	25	25	25 (take the study drug prior to clinic vist)	0	0	0					
Clinical visit*	1	2			3			4					5				6			7			8					9			10					
Telephone call**			1	2 (i)		3	4(q)		5	6	7	8 (i)		9 (j)		10 (i)		11	12 (i)		13	14(q)		15	16	17	18 (i)		19 (j)	20 (i)						
Informed consent	√																																			
Eligibility Criteria	√	√																																		
Demographics	√																																			
Medical History (a)	√																																			
Medical History	√	√	√	√	√	√	√	√	√	√	√		√	√				√	√	√	√	√	√	√	√	√	√	√	√		√				√	
Family medical history	√																																			
Concomitant Medications	√	√	√	√	√	√	√	√	√	√	√		√	√				√	√	√	√	√	√	√	√	√	√	√	√		√				√	
Randomization		√																																		
Blinding assessment					√								√							√							√									
Study drug compliance check					√								√							√							√									
Dispense study drug and instruction		√			√			√									√			√			√													
Adverse Events (b)			√	√	√	√	√	√	√	√	√		√	√				√	√	√	√	√	√	√	√	√	√	√	√		√				√	
Formal drug interaction assessment	√	√			√			√					√				√			√			√					√			√				√	
Vital Signs (c)	√	√ (n)			√(p)			√					√(p)				√ (n)			√(p)			√				√(p)			√				√	
Orthostatic Blood Pressures check	√	√ (n)			√(p)			√					√(p)				√ (n)			√(p)			√				√(p)			√				√	
Height and Weight	√	√			√			√					√							√			√				√			√				√	
Complete Physical Exam (d)	√												√														√			√				√	
Neurological exam (e)	√												√														√									
Brief physcial exam (heart and lung ausculation)		√			√			√												√			√												
Hematology (f)	√												√														√			√ (m)					
Hemoglobin A1C	√																																			
Complete metabolic profile (g)	√				√			√					√							√			√				√			√ (m)					
Blood cannabis analysis	√				√ (o)								√ (o)							√ (o)							√ (o)			√					
Urinalysis (h)	√												√														√			√ (m)					
Urine drug (THC) test		√																																		
Urinary CBD and metabolites levels test *					√			√					√							√			√				√									
Urine cups dispense and urine collection instruction		√			√			√									√			√			√													
ECG (12-LEAD)	√												√														√			√ (m)					
Serum Pregnancy Test (for women childbearing potential)	√																																			
Urine Preganancy Test (for women childbearing potential)		√			√								√							√							√			√					
Assessment of past marijuana use	√																																			
Drug, alcohol and tobacco abuse screening test	√																																			
MOCA	√	√			√								√							√							√			√					
Cognitive assessment battery		√											√														√									
MDS-UPDRS part III	√																																			
MDS-UPDRS (all 4 parts)		√			√								√							√							√			√					
H & Y rating	√	√			√								√							√							√			√					
RPW		√			√								√							√							√			√					
QUIP-RS	√				√								√							√							√			√					
C-SSRS	√	√			√								√							√							√			√					
RBDSQ		√			√								√							√							√			√					
NPI	√				√								√							√							√			√					
Anxiety short form	√		√	√	√				√	√			√					√	√	√				√	√		√	√		√					
Depression short form	√		√	√	√				√	√			√					√	√	√				√	√		√	√		√					
Emotional and behavioral dyscontrol short form	√		√	√	√				√	√			√					√	√	√				√	√		√	√		√					
SCOPA-sleep	√		√	√	√	√	√	√	√	√	√		√					√	√	√	√	√	√	√	√	√	√	√		√					
RLS		√			√								√							√							√			√					
Fatigue severity scale	√				√								√							√							√			√					
Pain intensity and interference short form	√				√								√							√							√			√					
PDQ-39		√			√								√							√							√			√					
EQ-5D		√	√	√	√				√	√			√					√	√	√				√	√		√	√		√					
CGI					√			√					√							√			√				√									
PGI					√			√					√							√			√				√									
Unified Dyskinesia Rating Scale (UDysRS)		√			√								√							√							√			√					
Home diary dispense & instruction		√			√			√									√			√			√													
Home diary collection & review					√			√					√							√			√				√									
*Clinical visit: visit 3 and 5 are low dose vists, 10th day of 5 mg/kg/day; visit 4 and 6: end of first and second treatment phase.																																				
**phone call is made on the third day of each dose; x means the phone call is only to remind subject to come in for visit the next day.																																				
Note: regarding the rows of days and weeks, it is variable, because of note (k) and note (l), and because some patients will take shorter or longer to get to their maximum tolerated dose than those that titrate to the target dose (determined in stage 1).																																				

Schedule of Event—Stage 2 note

Note: regarding the rows of days and weeks, it is variable, because of note (k) and note (l), and because some patients will take shorter or longer to get to their maximum tolerated dose than those that titrate to the target dose (determined in stage 1).
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 of the first dose of study drug. 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. Body temperature will be obtained at screening, Day 1, and at the final follow up visit. Blood pressure, respiratory rate and heart rate will be measured once each day assessed. During screening only, after the seated blood pressure has been obtained, the blood pressure will be repeated within 3 minutes of the subject standing up. This procedure may be repeated, if appropriate, following hydration. If repeated, a total of two additional pairs of BP assessments (sitting/standing) should be obtained, and the results of the last attempt should be reported.
d. Complete PE to include: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.
e. Targeted PE to include: skin, lungs-chest, heart, abdomen, neurological, extremities.
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), γ-glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
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. Visits 3 and 5 can occur on 5 mg/kg/day for 10-15 days (not just on the 10th day).
l. Visits 4 and 6 can occur on the max tolerated or the target dose, whichever patient get to, on the 28 +/- 4 days. (not just on the 28th day)
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. Regular phone call, also remind patient the clinical visit on either day from 2nd to 5th day while they are on 20 mg/kg/day
r. Clean catch urine collection after taking the study drug. Urine is collected in a 500 mL container and stored in 3-4 sam l cups (120 mL, fill up to 3/4).

APPENDIX 2

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 metabolized 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	Rotigitine
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)	Pantoprazxole(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)									
	Fluvoxamine			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)									

APPENDIX 2

	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)										