**DETAILED PROTOCOL: CANNABIDIOL AS A NEW TREATMENT FOR DRUG RESISTANT EPILEPSY**

**Version: April 23, 2015**

**Version 9**

1. **BACKGROUND AND SIGNIFICANCE**

Drug resistant epilepsy is a serious and potentially life-threatening condition that impacts the day to day functioning of those affected. Patients with drug resistant epilepsy are at a higher risk for Sudden Unexpected Death in Epilepsy (SUDEP), as frequency of generalized tonic clonic seizures, poly therapy, number of anti-epileptic drugs used, and propensity for nocturnal seizures are the leading risk factors for SUDEP.[[1]](#endnote-1) Annual SUDEP risk for patients with epilepsy is 1/1000; whereas SUDEP risk for patients with drug resistant epilepsy is 1/150.[[2]](#endnote-2)

Patients with drug resistant epilepsy do not respond or respond incompletely to FDA approved AEDs. Children living with drug resistant epilepsy are particularly vulnerable, and urgently need more effective medications because those suffering from early-onset and high seizure burden epilepsies suffer the greatest neurodevelopmental problems, including intellectual disability and autism. In some syndromes such as Dravet Syndrome, recent evidence suggests that more effective early control of epilepsy is associated with better developmental outcomes than in children who were treated 20-30 years ago.[[3]](#endnote-3)

Parents of children with drug resistant epilepsy often turn to alternative treatment options out of desperation to gain some control over their children's health. Some parents in states that allow the use of medical marijuana are using a variety of artisanal CBD preparations to treat their children’s seizures. Porter and Jacobson of Stanford University surveyed 19 parents to determine their observations about the effect or lack of effect of CBD on their children’s seizure frequency.[[4]](#endnote-4) The children ranged in age from 2 to 16 years. Thirteen children had Dravet syndrome (one of whom had epilepsy in female with mental retardation, EMFR), three children had Doose syndrome, and one each had myoclonic astatic epilepsy, Lennox-Gastaut syndrome and idiopathic early-onset epilepsy. The children experienced a variety of seizure types including focal, tonic-clonic, myoclonic, atonic and infantile spasms. The children had unsuccessfully tried an average of 12 other AEDs before their parents began cannabidiol-enriched cannabis treatment. The doses of cannabidiol the parents reported providing ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day. The doses of THC contained within those samples were reported to range from 0 to 0.8mg/kg/day. Seizure frequency before administering cannabidiol-enriched cannabis ranged from 2 per week to 250 per day. Sixteen (84%) of the 19 parents reported a reduction in their child’s seizure frequency. Two parents reported that their child became seizure-free after more than 4 months of cannabidiol-enriched cannabis use. Of the remaining 14 parents reporting a change in seizure frequency, 8 reported a greater than 80% reduction in seizure frequency, three reported a greater than 50% seizure frequency reduction and three reported a greater than 25% seizure frequency reduction. Three parents reported no change. Twelve parents weaned their child from another AED after starting cannabidiol-enriched cannabis treatment. Beneficial effects of cannabidiol-enriched cannabis other than reduced seizures included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%) and decreased self-stimulation (6/19, 32%). Negative side effects included drowsiness (7/19, 37%) and fatigue (3/19, 16%). Limitations of this data include lack of control data, lack of randomization and blinding associated with open-label use, as well as uncertainty of the dosage in artisanal preparations. However, this survey lends hope that CBD may be a useful pharmaceutical alternative to existing therapies in drug resistant epilepsy, and sheds light as to what doses are being used experimentally that seem to be tolerated.

It is hoped that CBD may provide a viable alternative epilepsy treatment with a new mechanism of action that may improve seizure control and quality of life in this small group of patients. Such results may provide a better understanding for how CBD can be used in the future as a potential treatment for drug-resistant epilepsy.

*Preclinical Data:*

Early pre-clinical work demonstrated that Cannabidiol (CBD) possesses anti-convulsant properties. Izquierdo et al. demonstrated that CBD provides a significant protective effect against the maximal electroshock (MES) model of generalized seizure with an ED50 of 3 mg/kg CBD.[[5]](#endnote-5) Chesher et al. examined the effects of CBD upon pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizures in mice and found that orally administered CBD (50-200 mg/kg) exhibited no anti-convulsant effects in either model of generalized seizures.[[6]](#endnote-6) However, no pharmacokinetic, metabolic or bioavailability data for oral administration of CBD were captured in this study, making interpretation of results difficult.[[7]](#endnote-7) In rats, CBD was an effective and relatively potent anti-convulsant in the MES and audiogenic seizure models with ED50 values of 12 and 17 mg/kg respectively; findings that compared favorably with the clinically used AEDs including phenytoin, phenobarbital, carbamazepine, and ethosuximide. 5,6,[[8]](#endnote-8),[[9]](#endnote-9) Further, CBD enhanced the anti-convulsant potencies of phenytoin or phenobarbital in the MES and audiogenic models of seizures. 5,[[10]](#endnote-10),[[11]](#endnote-11),[[12]](#endnote-12) CBD diminished the effects of clonazepam and ethosuximide in the MES model, as well as chlordiazepoxide and trimethadione in the audiogenic model of seizure.7,9

Karler et al. examined whether tolerance to the anti-convulsant effects of CBD (120 mg/kg) developed in electrically-induced models of seizure.[[13]](#endnote-13) Repeatedly dosed mice (daily for 3-4 days) revealed CBD, phenytoin and phenobarbital produced no change in their anti-convulsant sensitivity in the MES model compared to those dosed acutely. Moreover, repeated dosing increased the sensitivity of CBD in the 6 Hz electroshock-threshold test, whereas, phenytoin exhibited no change in potency, but tolerance developed to phenobarbital.

Turkanis et al. reported in electrically kindled limbic seizures, CBD (0.3-3 mg/kg) raised the epileptic after-discharge threshold recorded by chronically implanted electrodes, consistent with the known effects of phenytoin in this model.[[14]](#endnote-14) However, in common with the effects of ethosuximide, CBD also decreased the after-discharge amplitude, duration and propagation in this model of seizure and concluded that “CBD was the most efficacious of the drugs tested against limbic after-discharges and convulsions”. 14

Consroe et al. revealed CBD pre-treatment (>100 mg/kg) prevented tonic convulsions in mice caused by either MES seizures, GABA antagonists or inhibitors of GABA synthesis, in addition to reliably protecting against 3-mercaptoproprionic acid-induced lethality.[[15]](#endnote-15)

More recently, Jones et al. reported significant anti-epileptiform and anticonvulsant activity using a variety of in vitro and in vivo models.[[16]](#endnote-16) Using in vitro models, spontaneous epileptiform local field potentials (LFPs) were induced, by omission of Mg2+ ions from, or addition of the K+ channel blocker, 4-aminopyridine (4-AP) to the bathing solution, in acute, transverse hippocampal brain slices. In the Mg2+-free model, CBD (100 μM) decreased epileptiform LFP burst amplitude and duration, whilst in the 4-AP model, CBD (100 μM) decreased LFP burst amplitude in one hippocampal region only but decreased burst duration in CA3 and dentate gyrus, and burst frequency in all regions; CBD exerted no effect upon propagation of epileptiform activity.

Subsequently, the team examined the anti-convulsant actions of 1, 10 and 100 mg/kg CBD in three different in vivo seizure models using Wistar Kyoto rats.[[17]](#endnote-17) In the PTZ-induced acute, generalized seizures model, 100 mg/kg CBD significantly decreased mortality and the incidence of tonic-clonic seizures, while in the acute pilocarpine model of temporal lobe seizures all doses of CBD significantly reduced the percentage of animals experiencing the most severe seizures.17 Finally, in the penicillin model of partial seizures, 10 and 100 mg/kg CBD significantly decreased the percentage of animals dying as a result of seizures and all doses of CBD also decreased the percentage of animals experiencing the most severe tonic–clonic seizures. 17

*Clinical Data: CBD in Epilepsy*

A Cochrane report from 2012 reviewed cannabinoids for epilepsy.[[18]](#endnote-18) This report describes four clinical studies where CBD was used to treat epilepsy. In 1978, Mechoulam et al. randomized nine adult patients to either 200mg of CBD (4 patients) or placebo (5 patients). The patients all had uncontrolled temporal lobe epilepsy who had failed treatment with multiple medications. During the three-month trial, two of four patients treated with CBD became seizure free for the entire duration and one patient showed partial improvement, whereas none of the five patients receiving placebo experienced a reduction in seizure frequency. No toxic effects were observed.

In second clinical trial by Cunha et al., 15 adult patients with treatment-resistant secondary generalized epilepsy (all having at least one generalized convulsion each week for a period of at least a year) were randomly divided into two groups and treated with either placebo (8 patients) or 200-300mg of CBD (7 patients) daily for up to 18 weeks. One patient was transferred to the treatment group after one month. Four of eight patients in the CBD treated group became almost seizure free, and three of the eight experienced a partial reduction in seizures. Only one of the seven patients on placebo experienced a reduction in seizures. The most often reported side effect of CBD was somnolence. No patients reported psychotropic effects. Patients remained on their previously prescribed AEDs throughout the trial.

Ames et al. describes a placebo-controlled trial of 12 institutionalized, intellectually disabled patients with frequent seizures uncontrolled on conventional AEDs. The patients were divided into two groups but it is unclear if they were randomized or if they were evenly split. The treatment group was given 300 mg cannabidiol daily for the first week followed by 200 mg daily for the next three weeks. At the end of the study, there were no statistically significant differences between the two groups. There were no immediate side effects reported except for mild drowsiness. The only report was a letter to the editor of the South African Medical Journal which lacked detail about specific seizure frequencies or other parameters. There was no indication that the patients continued on their AED medication during the study.

Trembly et al. described a cross-over design in which 12 patients with incompletely controlled epilepsy were initially given only their standard AEDs for three months followed by six months of placebo. Patients AEDs were allowed to change in this period but not afterwards. This was followed by a randomization to placebo or 100 mg cannabidiol given three times a day for six months. At the end of this period the patients on active treatment received placebo and those on placebo received cannabidiol for a further six months. Both groups subsequently had a three month period with no placebo or treatment. The published abstract did not report any statistical analysis. There were only safety (lab tests) and verbal statements regarding no discernible effect on MMPI (Minnesota Multiphasic Personality Inventory), Beck depression inventory, trail making test, and finger tapping test. The same study was later summarized in a book chapter by Consroe in 1992. Interestingly, the summary stated that there were only 10 patients in the study and that Trembly reported that there were no effects on seizure pattern, character or frequency. The authors of the Cochrane report attempted to contact Trembly’s group for clarification but were unsuccessful.

*Clinical Data: Chronic dosing of CBD in Other Disease States*

CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free pateints with Huntington's Disease. Effects after oral CBD (10 mg/kg /day for 6 weeks) or placebo (sesame oil for 6 weeks) intake were evaluated weekly under a double - blind, randomized crossover design. CBD showed no significant or clinical differences compared to placebo in the Cannabis side effect inventory, clinical lab tests or other safety outcome measures. [[19]](#endnote-19)

A published case report showed that a 19 year old diagnosed with schizophrenia who experienced severe side effects after treatment with conventional antipsychotics demonstrated significant improvement of symptoms with no adverse effects after hospitalization and 4 weeks of treatment with increasing doses of CBD up to 1500 mg/day.[[20]](#endnote-20)

CBD monotherapy was administered to three patients with treatment resistant schizophrenia. The initial oral dose was 40 mg/day and was increased to 1280 mg/day for up to 4 weeks with no side effects reported, even at the highest dose. [[21]](#endnote-21)

Two patients with bipolar affective disorder received 600 - 1200 mg/day CBD for up to 24 days with no side effects reported at any dose. [[22]](#endnote-22)

1. **SPECIFIC AIMS**

The objective of this study is to determine the safety, tolerability, and optimal dose of CBD as an adjunct treatment in children and young adults with drug resistant epilepsy.

1. **SUBJECT SELECTION**

The study population will include pediatric and adult patients seen by Elizabeth A. Thiele, MD, PhD and Ronald L. Thibert, DO, MPH at MGH's Pediatric Epilepsy Clinic and The Herscot Center for Tuberous Sclerosis who were identified as candidates through routine visits. The investigators will follow 50 patients with drug-resistant epilepsy who are actively taking the study drug. Listed below are the inclusion criteria:

* Documentation of a diagnosis of drug resistant epilepsy as evidenced by failure to control seizures despite appropriate trial of two or more AEDs at therapeutic doses and / or having the diagnosis of Dravet syndrome or Lennox Gastaut syndrome which are, by definition, drug resistant epilepsy syndromes.
* Between 1- 7 baseline anti-epileptic drugs at stable doses for a minimum of 2 weeks prior to enrollment. Vagus nerve stimulator (VNS), ketogenic diet and modified Atkins diet do not count toward this limit.
* VNS must be on stable settings for a minimum of 4 weeks.
* If on ketogenic diet, must be on stable ratio for a minimum of 4 weeks.
* Written informed consent obtained from the patient or the patient’s legal representative must be obtained prior to beginning treatment.
* Between the ages of 1 and 40 years.

Patients will also be excluded if they meet any of the following criteria:

* Subject has a history of an allergic reaction or significant sensitivity to cannabidiol or any other ingredients in the investigational drug.
* Subject has a clinically significant unstable hepatic, hematological, renal, cardiovascular, gastrointestinal, or pulmonary disease or malignancy.
* Subject has taken or used any investigational drug or device in the 30 days prior to the study entry
* Subject has a clinically significant abnormal laboratory value.
* Subject has a history of drug or alcohol abuse.
* Subject is pregnant
* If female and of childbearing potential:
  + Is not willing to comply with a method of birth control acceptable to the investigator during the study and for 4 weeks following completion of the study
  + Subject is breastfeeding.
* Subject has a history of poor compliance on past antiepileptic therapy.
* Subject has inadequate supervision by parent or guardian.
* Subject has a progressive lesion confirmed by MRI or CT scan.
* Subject is currently taking long-term systemic steroids (excluding inhaled medication for asthma treatment) or any other daily medication known to exacerbate epilepsy.
  + An exception will be made of prophylactic medication, for example, for idiopathic nephritic syndrome or asthma.

1. **SUBJECT ENROLLMENT**

This is one of five sites independently studying the safety and tolerability of pure cannabidiol provided by GW pharma. The other sites include The New York University Medical Center (IRB approved September 10, 2013 for patients age 1 year and older), The University California San Francisco Medical Center, Children’s Hospital of Chicago, and Children’s Hospital of Philadelphia.

Informed consent will be obtained for each subject who participates in the study. The research nurse will initially explain the study, provide the informed consent form, and answer any questions from the subjects and their family members. Subjects will be given adequate time to make their decision. Subjects will have the opportunity to take the consent form home, and call back if they wish to participate. Subjects will also be encouraged to discuss any concerns they have with other health care providers. Informed consent for all subjects will be obtained by Dr. Elizabeth Thiele. The potential for coercion will be avoided through ensuring the subject that participation in the study is completely voluntary, and that deciding not to take part in the study will not affect the care or benefits to which the subject is otherwise entitled. Subjects will be enrolled in the study once informed consent has been obtained.

For subjects under 18 years of age, legal consent to participate in research will be provided by a parent or an individual authorized under applicable state or local law to provide consent on the child’s behalf to general medical care. It is sufficient for consent to be obtained from just one parent. Before the PI allows an individual other than a parent to consent on behalf of a child, she will document the basis for the individual’s authority to consent on behalf of the child to general medical care and place any relevant documentation in the research file.

In addition to permission of the parent(s) or guardian, assent to participate in the study must be obtained from each child age 7 years or older who, in the opinion of the PI, is able to provide assent based on their age, maturity or psychological state. When obtained, assent will be documented in writing using the PHRC-approved consent/assent form. When assent is not obtained, the PI will document her rationale in the research records.

The following categories of surrogates (listed in general order of preference) may provide consent in writing on behalf of potential subjects incapable of providing informed consent:

* 1. court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research;
  2. health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research; or
  3. spouse, adult child, or other close family member who knows the subject well and has been involved in their care.

Assent of subjects will be a requirement for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. If the individual objects to participation, s/he will not be enrolled. When surrogate consent is relied upon, the Investigator will ensure that the surrogate understands that his or her decisions should be based on “substituted judgment.” This means that the decision reflects a potential subject's own views when s/he had the capacity to express them. The PHRC preferred order of surrogates will be followed, and the Investigator will document the relationship of the surrogate to the subject in the research record.

1. **STUDY PROCEDURES**

The investigational drug to be used in this study is pure cannabidiol manufactured by GW Pharma. Cannabidiol oral solution 25 mg/ml or 100mg/ ml or cannabidiol 50mg capsule will be administered. The patients will be treated on an outpatient basis and will not require hospital admission.

After starting on the investigational drug, Subjects will be required to make clinic visits every 2 weeks (+/- 3 days) for the first 2 months, and then monthly (+/- 14 days) visits thereafter for the following 11 months. Additionally, for the first four months on the study drug, subjects will be monitored weekly by telephone or email, when they are not examined in person. After month 12, subjects will have visits every 4 months.

The starting dose will be 5 mg/kg/day, given in two divided doses. The dose will be increased by 5 mg/kg/day every seven days up to a maximum dose of 25 mg/kg/day given in two divided doses over a minimum of five weeks to determine optimal dose with regards to safety and tolerability. Subjects will be titrated until they reach steady state, which is defined as staying on the same dosage of the investigational drug for 1 month.

At each study visit, subjects will be giving an information sheet detailing the potential risk for adverse events seen up to that point, along with any other relevant study updates, how they will be monitored and what measures will be taken in the event that a subject does experience an adverse event.

For subjects who continue to have seizures and are tolerating the study drug at 25mg/kg/day, the dose will increased to a maximum dose of 50mg/kg/day. The dose will be increased by 5mg/kg/day every seven or more days until a maximum dose is reached (not exceeding 50mg/kg/day). The study drug will be administered in at least two divided doses each day.

Subjects taking greater than 25mg/kg/day will be monitored by telephone or email twice weekly throughout the titration period. Subjects will have an office visit every month.

For each blood draw, about 7-10 mL of blood will be drawn from the subject.

Please refer to table 1 for a summary of the visit procedures.

**Visit 1:** Elizabeth A. Thiele, MD, PhD or Ronald L. Thibert, DO, MPH will obtain a complete medical and neurological history and confirm candidate eligibility. Subjects will also be asked to return their signed consent form if they have not already done so. They will then be given a full physical and neurological examination and an electroencephalogram (EEG), unless they have had one within the past 6 months. Baseline values for height, weight, and vital signs will be taken. Subjects will then be given their seizure diary, where they will be asked to monitor their seizure frequency for the duration of the trial. Subjects will also be given a neuropsychological evaluation by Dr. Amy Morgan, PhD, one of the neuropsychologists affiliated with the department, unless they have been given a comparable neuropsychological evaluation in the past 3 months. If possible, they will be asked to complete a few questionnaires assessing their intelligence, executive function, language, visual-spatial abilities and fine motor abilities, and their memory. In addition, their parents or legal guardians will be asked to fill out questionnaires assessing their executive function, attention, mood/anxiety, daily living, socioeconomic status, and quality of life (Refer to table 2 for details on the neuropsychological testing to be done).

If patients and/or their caregivers have recorded detailed seizure counts for each seizure type for the past 28 days, Visits 1 and 2 may be combined, removing the 28-day baseline period.

**Visit 2** (1 month after Visit 1)**:** Subjects will be given full physical and neurological examination, where values for height, weight, and vital signs will be taken. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured. Concomitant AED plasma concentrations will also be measured. For female subjects of child-bearing age, a pregnancy test will be administered. Then, the subject will be given the investigational drug.

**Visit 3** (1.5 months after Visit 1)**:** Subjects will be given a physical and neurological exam, and values for height, weight, and vital signs will be taken. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug.

**Visit 4** (2 months after Visit 1)**:** Subjects will be given a physical and neurological exam, and values for height, weight, and vital signs will be taken. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured. Concomitant AED plasma concentrations and serum CBD concentrations will also be measured. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug.

**Visit 5** (3 months after Visit 1)**:** Subjects will be given a physical and neurological exam and values for height, weight, and vital signs will be taken. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured. Concomitant AED plasma concentrations and serum CBD concentrations will also be measured.

The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. Subjects will also be given a neuropsychological evaluation. If possible, they will be asked to complete a few questionnaires assessing their intelligence, executive function, language, visual-spatial abilities and fine motor abilities, and their memory. In addition, their parents or legal guardians will be asked to fill out questionnaires assessing their executive function, attention, mood/anxiety, daily living, and quality of life.

*When they are at a steady state of dose greater than 25 mg/kg/day for 4 months, they will be given an EEG and a neuropsychology evaluation.*

*In the following visits, if the subject has reached a dose greater than 25 mg/kg/day since the last visit, they will also receive a physical and neurological exam, and values for height, weight, and vital signs will be taken. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured.*

**Visit 6** (4 months after Visit 1)**:** Subjects will be given a physical and neurological exam andvalues for height, weight, and vital signs will be taken. They will also get an EEG. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug.

*If at this point, the subject is on 600mg/day of the investigational drug and has still not achieved steady state, subjects will undergo the following procedures in addition to the standard ones until they achieve steady state. They will receive a physical and neurological exam, and values for height, weight, and vital signs will be taken. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month.*

**Visits 7 and 8** (5 and 6 months Visit 1)**:** Subjects will return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. Any adverse events since the last visit will be reviewed.

**Visit 9** (7 months after Visit 1): Subjects will be given a physical and neurological exam andvalues for height, weight, and vital signs will be taken. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. Subjects will also be given a neuropsychological evaluation and EEG if they are at a dose of 25 mg/kg/day or lower. If possible, they will be asked to complete a few questionnaires assessing their intelligence, executive function, language, visual-spatial abilities and fine motor abilities, and their memory. In addition, their parents/guardians will be asked to fill out questionnaires assessing their executive function, attention, mood/anxiety, daily living, and quality of life.

**Visits 10 and 11** (8 and 9 months after Visit 1)**:** Subjects will return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. Any adverse events since the last visit will be reviewed.

**Visit 12** (10 months after Visit 1): Subjects will be given a physical and neurological exam andvalues for height, weight, and vital signs will be taken. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug.

**Visits 13 and 14** (11 and 12 months after Visit 1)**:** Subjects will return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. Any adverse events since the last visit will be reviewed.

**Visit 15** (13 months after Visit 1)**:** Subjects will be given a physical and neurological exam, EEG, and values for height, weight, and vital signs will be taken. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured. The investigator or co-investigator will review the subjects’ seizure diaries. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit.

**Visit 16+** Subjects will be given a physical and neurological exam andvalues for height, weight, and vital signs will be taken. The investigator or co-investigator will review the subjects’ seizure diaries, and give them a new one for the upcoming month. They will also review any adverse events since the last visit. The subjects will then return any unused investigational drug since the last visit, and be given a new supply of the investigational drug. CBC, LFT, BUN, electrolytes, and creatinine levels will be measured.If the EEG after 4 months at steady state takes place within a month of Visit 15 (inclusive), the subject will receive their next EEG five months later (and no EEG at Visit 15).

1. **BIOSTATISTICAL ANALYSIS**

The data variables to be collected from each subject will include:

* The number and type of seizures occurring per day
* The duration of the seizures
* CBC, LFT, BUN, electrolytes, and creatinine levels
* The serum CBD concentration after one month of treatment and on visit 5
* The concomitant AED plasma concentration at baseline, after 4 and 8 weeks of treatment.

The study will be complete for each subject after a minimum of one year unless subjects choose to withdraw early of drug therapy. The study will continue until CBD is FDA-approved (GW Pharmaceuticals will continue to provide drug). The sample size of 50 subjects was determined by the maximum number of subjects allowed for an intermediate size population IND under the expanded access program. Statistical tests will include t-tests and Analysis of Variance (ANOVA). Seizure frequency and severity will be compared between baseline and one year of treatment.

1. **RISKS AND DISCOMFORTS**

According to The GW Pharma Investigator's Brochure for pure CBD, in a study involving pure CBD in 13 subjects with type II diabetes, there was one instance of each of the following side effects: trouble sleeping, diarrhea, flatulence, gastric reflux, joint pain, muscle pain, difficulty concentrating, conjunctival hemorrhage, abnormal mood, and change in vision. These may or may not be related to the pure CBD.

Among 4 clinical studies of the treatment of epilepsy with CBD-containing products that were not manufactured by GW Pharma, the most common side effect reported was somnolence.

Additionally, there are possible drug-drug interactions between CBD and any AED that metabolizes through the cytochrome P450 pathway, including valproic acid (VPA) phenytoin, and clobazam. These interactions may lead to elevated AED plasma levels. Side effects may include dizziness, drowsiness, ataxia, irritability/mood change, urinary retention, bone marrow suppression, elevated liver function tests (LFTs), or nystagmus.

For each blood draw, there is a risk of a bruise or pain at the site, and also a small risk of infection, lightheadedness, and/or fainting.

Because there is no tetrahydrocannabinol (THC) in this investigational drug, there are no anticipated psychosocial risks.

Participation in this study does not preclude subjects from seeking alternative means to control their epilepsy. After the completion of the study, they will still be eligible for other treatment modalities, such as FDA approved anti-epileptic drugs, dietary therapy, Vagus nerve stimulator, and surgical epilepsy intervention.

1. **POTENTIAL BENEFITS**

Potential benefits to participating subjects include the possibility for a reduction in seizure frequency and/or severity.

This study will elucidate the effects of pure cannabidiol on the improvement of seizures in children and young adults with intractable epilepsy. Additionally, should the investigation drug be effective, this study will provide new information about the tolerability and appropriate dosing for pure cannabidiol in the treatment of epilepsy.

1. **MONITORING AND QUALITY ASSURANCE**

The Principal Investigator, Dr. Elizabeth Thiele, and co-investigators, Patricia Bruno, RN and Dr. Ronald Thibert, DO, will review all data relating to safety and tolerability throughout the study, after every third patient has been treated, to monitor study conduct and assess patient safety.

All problems having to do with subject safety will be documented, specifically the following:

* all adverse events associated with the study procedures
* all deaths and/or hospitalizations whether or not they are related to study procedures
* any incidents or problems involving the conduct of the study or subject participation, including problems with the recruitment and/or consent processes.

Serious adverse events would be grounds for stopping the study. Serious adverse events would be those which could result in death, are life threatening, require inpatient hospitalization, result in a persistent or significant disability/incapacity, or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention.

If a subject is withdrawn from the study due to an adverse event, the subject will be followed as frequently as necessary until resolution of the event.

The principal investigator will be responsible for monitoring and reporting all adverse events. Review of adverse events will be done at each study visit. Reports of unanticipated problems involving risk to subjects or others will be submitted to the IRB within 5 working days/7 calendar days of the date the investigator first became aware of the problem. Included in the report, will be:

* a detailed description of the adverse event
* the basis for determining that the event is unexpected in nature, severity, or frequency
* the basis for determining that the event is related or possibly related to the research procedures
* the basis for determining that the research places subjects at an increased risk of harm (i.e., a serious adverse event)
* whether any changes to the research or other corrective actions are warranted

In addition to reporting adverse events to the Partner’s IRB, the PI will also report them to the FDA in the form of a written IND safety report. The IND safety report will be submitted on form 3500A and accompanied by form 1571. Unexpected serious suspected adverse reactions will be reported to FDA as soon as possible, but no later than within 15 calendar days following the initial receipt of information, as per FDA regulations. Unexpected fatal or life-threatening suspected adverse reactions will be reported to FDA as soon as possible, but no later than 7 calendar days following the initial receipt of the information, as per FDA regulations.

Monitoring and quality assurance will be done by the PI reviewing all data, including adverse events, by monthly study visits and weekly phone calls and emails for the first 4 months, and then by study visits every 3-months thereafter, in order to assure the adherence to the IRB-approved protocol.

The quality and completeness of questionnaires will also be reviewed by the PI. The PI will also monitor the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and make sure that study drug is being stored, dispensed, and accounted for according to specifications.

Parents/subjects are instructed how to administer the study drug at each study visit.

The PI and study staff monitor compliance and accountability by weighing drug bottles before dispensing and when they are returned each month. The amount of study drug used is compared to the expected amount and any discrepancies will be discussed if applicable.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 1.Tabi**  **Table 1:** | Visit 1 | Visit 2 (4 wks after visit 1) | Visit 3 (2 wks after visit 2) | Visit 4  (2 wks after visit 3) | Visit 5  (1 mt after visit 4) | Visit 6  (1 mt after visit 5) | Visit 7  (1 mt after visit 6) | Visit 8  (1 mt after visit 7) | Visit 9  (1 mt after visit 8) | Visit 10  (1 mt after visit 9) | Visit 11  (1 mt after visit 10) | Visit 12  (1 mt after visit 11) | Visit 13  (1 mt after visit 12) | Visit 14  (1 mt after visit 13) | Visit 15  (1 mt after visit 14) | Visits 16+ (Every 4 months after visit 15) |
| Date of Visit: |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Return informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Neurologic history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Neuropsychological evaluation | X |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |
| EEG | X |  |  |  |  | X |  |  | X |  |  |  |  |  | X |  |
| Physical exam | X | X | X | X | X | X | \* | \* | X | \* | \* | X | \* | \* | X | X |
| Neurological exam | X | X | X | X | X | X | \* | \* | X | \* | \* | X | \* | \* | X | X |
| Height | X | X | X | X | X | X | \* | \* | X | \* | \* | X | \* | \* | X | X |
| Weight | X | X | X | X | X | X | \* | \* | X | \* | \* | X | \* | \* | X | X |
| Vital signs | X | X | X | X | X | X | \* | \* | X | \* | \* | X | \* | \* | X | X |
| Laboratory assessments\*\* |  | X |  | X | X | \* | \* | \* | \* | \* | \* | \* | \* | \* | X | X |
| Concomitant AED plasma concentrations |  | X |  | X | X |  |  |  |  |  |  |  |  |  | X | X |
| Serum CBD concentration |  |  |  | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy test |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dispense seizure diary | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Return seizure diary |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse event assessment |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense investigational drug (ID) |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Return unused ID |  |  | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

\*\*Laboratory assessments include: CBC, LFT, BUN, electrolytes, and creatinine levels.

\*Performed when subject is taking >600mg/day, and has not reached steady state

Table 2. Neuropsychological Protocol for Epilepsy Patients Treated with Cannabidiol

|  |  |  |  |
| --- | --- | --- | --- |
| **Function** | **Patient Measures** | **Age Range** | **Administration**  **Time** |
| *Intelligence*  **IQ** | WPPSI-4 Vocabulary, Matrix Reasoning  WASI-2 Vocabulary, Matrix Reasoning  Including Wechsler: Working Memory/Processing Speed | 2;6-5;11 yrs  6 - adult | 10 minutes  10 minutes |
| *Attention/Exec Funct*  **Trail Making**  **Color-Word** | Trail Making Test D-KEFS  Color-Word Interference D-KEFS | 9 - adult  9 - adult | 3 minutes  10 minutes |
| *Language*  **Naming**  **Fluency** | Expressive One-Word Picture Vocabulary Test-4th Ed  Word Generation NEPSY-2 | 2 - adult  3 - 16 | 5 minutes  5 minutes |
| *Visual-Spatial*  **VMI**  **Geometric Design** | Developmental Test of Visual Motor Integration-6  NEPSY-2 Geometric Puzzles | 2;0 - adult  5-16 | 5 minutes  5 minutes |
| *Fine Motor*  **Pegs**  **Tapping** | Purdue Pegboard  Fingertip Tapping | 4 – adult  5 - adult | 5 minutes  5 minutes |
| *Learning/Memory*  **List Learning** | Children’s Memory Scale subtests: Word List  Wechsler Memory Scale-3rd Edition Word List | 5- 15  16 - adult | 10 minutes  10 minutes |

|  |  |  |  |
| --- | --- | --- | --- |
| **Function** | **Parent Measures** | **Age Range** | **Administration Time** |
| *Executive*  *Attention*  *Mood/Anxiety*  *Daily Living*  *Quality of Life*  *SES* | Behavior Rating Inventory of Executive Function  ADHD Checklist  BASC-2  \*Vineland Adaptive Behavior Scales  PedsQLin Epilepsy  Hollingshead | 3 –21 years  all ages  3-21  all ages  2-18 years  all ages | 5 minutes  1 minute  15 minutes  20 minutes  20 minutes  1 minute |

\* For participants unable to undergo standard testing, the Vineland Scales will be used to assess for changes in cognitive and adaptive living skills.

1. **REFERENCES**

1. Pack A. SUDEP: What are the risk factors? Do seizures or anti epileptic drugs contribute to an increased risk? *Epi Curr* 2012;12(4): 131-132. [↑](#endnote-ref-1)
2. Hirsch L, Donner E, So E et al. Abbreviated report of the NIH/NINDS workshop on SUDEP. *Neurol* 2011;76(22): 1932-38. [↑](#endnote-ref-2)
3. Chieffo D, Battaglia D et al Neuropsychological development in children with Dravet Syndrome. Epilepsy Res 2011;95(1-2):86-93. doi: 10.1016/j.eplepsyres.2011.03.005. Epub 2011 Apr 6. [↑](#endnote-ref-3)
4. Porter, B.E., Jacobson, C. (2013) Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Unpublished paper presented at The NIH Annual Curing the Epilepsies Conference, Washington D.C. [↑](#endnote-ref-4)
5. Izquierdo, I., & Tannhauser, M. The effect of Cannabidiol on maximal electroshock seizures in rats. *J Pharm* 1973; 25(11):916-7. [↑](#endnote-ref-5)
6. Chesher, G., & Jackson, D. Anticonvulsant effects of cannabinoids in mice: Drug interactions within cannabinoids and cannabinoid interactions with phenytoin. *Psychpharmacologica* 1974;37:255-264. [↑](#endnote-ref-6)
7. Consroe, A., & Wolkin, P. Cannabidiol-antiepileptic drug comparisons and interactions in experimentally induced seizuresin rats. *Journal of Pharmacy and Exp Ther* 1977; 201:26-32. [↑](#endnote-ref-7)
8. Chesher, G., Jackson, D., & Mallor, R. Interaction of Δ9-tetrahydrocannabinol and cannabidiol with phenobarbitone in protecting mice from electrically induced convulsions. *Journ Pharm and Pharmacol* 1975; 27:608-609. [↑](#endnote-ref-8)
9. Consroe, P., & Wolkin, A. Anticonvulsant interaction of cannabidiol and ethosuximide in rats. *Journal Pharmacy and Pharmacol* 1977; 29:500-501. [↑](#endnote-ref-9)
10. Jiang R, Yamaori S, Okamoto Y et al. Cannabidiol as a potent inhibitor of the catalytic action of cytochrome P450 2C19. Drug Metab Pharmacokinet 2013: doi;10.2133/dmpk.DMPL-12-RG-129. [↑](#endnote-ref-10)
11. Bornheim L, Everhart T, Li J et al. Characterization of cannabidiol mediated cytochrome P450 inactivation. Biochem Pharmaco 1993;45(6):1323-1331. [↑](#endnote-ref-11)
12. Izquierdo, I., & Tannhauser, M. The effect of Cannabidiol on maximal electroshock seizures in rats. *J Pharm* 1973; 25(11):916-7. [↑](#endnote-ref-12)
13. Karler, R., & Turkanis, S. Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. *Br J Pharmacol* 1980; 68(3):479-84. [↑](#endnote-ref-13)
14. Turkanis, S., Smiley, K., Borys, H., Olsen, D., & Karler, R. An electrophysiological analysis of the anticonvulsant action of Cannabidiol on limbic seizures in conscious rats. *Epliepsia* 1979; 20(4):351-63. [↑](#endnote-ref-14)
15. Consroe, P., Benedito, M., Leite, J., Carlini, E., & Mechoulam, R.. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *Eur J Pharmacol* 1982; 83(3-4):293-8. [↑](#endnote-ref-15)
16. Jones, N., Hill, A., Smith, I., Bevan, S., & Williams, C. Cannabidiol displays antiepileptiform and antiseizure properties In vitro and in vivo. *JournPharmacol Exper Therap* 2010; 332(2): 569-577. [↑](#endnote-ref-16)
17. Jones, N., Glyn, S., Akiyama, S., Hill, T., & Hill, A. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe. *Seizure* 2012;21: 344-52. [↑](#endnote-ref-17)
18. Gloss, D., & Vickrey, B. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 2012; Issue 6. Art.No.: CD009270. [↑](#endnote-ref-18)
19. Consroe P, Laguna J, Allender J et al. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav 1991*;40(3):701-8. [↑](#endnote-ref-19)
20. Zuardi AW, Morais Sl, Guimaraes FS, Mechoulam R. Antipsychotic effect of cannabidiol. J Clin Psychi 1995;56(10:485-6. [↑](#endnote-ref-20)
21. Zuardi AW, Hallak JE, Dursun SM et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol 2006;20(4):683-6. [↑](#endnote-ref-21)
22. Zuardi AW, Crippa J, Dursun S et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol 2010;24(1):135-7. [↑](#endnote-ref-22)