Official Title: University of Alabama at Birmingham (UAB) Pediatric CBD Program

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UAB Pediatric CBD Program

INTRODUCTION

On April 1st, 2014 Governor Robert Bentley signed the Senate Bill 174, also known as "Carly's Law." This is a legislation that allows the study of the safety and tolerability of cannabidiol or CBD Epidiolex®) for the treatment of seizures and epilepsy. The law was named in honor of 3-year-old Carly who suffers from a severe neurological disorder that includes debilitating seizures. This legislature opens a way for the Department of Neurology at the University of Alabama at Birmingham (UAB) to design and conduct a study of CBD for the treatment of seizures in pediatic patients. The Pediatric CBD Protocol includes patients 1 to 18 years of age.

Design:

In this study, participants will receive Epidiolex (cannabidiol or CBD) in addition to their current anti-epileptic drugs. Preliminary studies suggest that Epidiolex may be both safe and effective in treating epilepsy; however, to date, there are no well controlled studies that have established the safety or efficacy of this experimental treatment in the treatment of epilepsy.

Like THC (tetrahydrocannabinol), Epidiolex comes from the plant *Cannabis sativa* or *Cannabis indica.* In contrast to THC, studies suggest that Cannabidiol is not psychoactive and does not have the negative effects on cognition. However, this has not been definitively established. It has been shown that CBD may have therapeutic properties, including pain and nausea relief, and anti-inflammatory effects. In one case report, Epidiolex has been shown to be safe and tolerated in adults at doses up to 1,500 mg per day, but there is no data available on the safety and tolerability of Epidiolex available yet in children from well controlled clinical trials.

The purpose of this study is to evaluate the safety and tolerability of Epidiolex at various doses between 5mg/kg/day and 50 mg/kg/day as an additional (add-on) drug for treating debilitating, drug-resistant epilepsy**.**

The specific goals of this phase I dose-finding study conducted in consecutively enrolled patients 1-18 years of age are to prospectively and longitudinally assess the safety and tolerability, including cognitive effects, of CBD at various doses between 5mg/kg/day and 25mg/kg/day with additional titration in some subjects up to 50mg/kg/day. In order to participate in the study, participants will need to fulfill the inclusion and exclusion criteria.

The goal of the study is to fulfill the mandate of "Carly's Law" and to provide patients with debilitating epileptic conditions with access to CBD as an add-on treatment. Other care including routine neurological care that is not related to participation in the CBD study will need to be provided by patients' primary/current treating neurologist.

Specific Aims:

The goals of this phase 1 dose-finding study are to assess the safety and tolerability, including cognitive effects, of CBD in patients with epilepsy who have failed several standard treatments as indicated in the inclusion criteria:

1. The safety outcome measures will include:
    a. Severe adverse events (increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization),
    b. Change in resting blood pressure or heart rate by 25% if considered significant by managing neurologist,
    c. Any change in laboratory tests considered by managing neurologists as clinically significant.
2. The seizure frequency and severity outcome measures will include:
    a. Change in seizure frequency as measured in total number of seizures per month at various doses of CBD between 5 and 50 mg/kg/day,
    b. Change in seizure severity as measured by the Chalfont Seizure Severity Scale (Duncan & Sander, 1991, JNNP).
3. Other data that will be collected on all enrolled participants include:
    a. videoEEG (30 minute to 60 minutes to include wake and sleep if possible,
    b. Cognitive and Developmental Assessment (NIH Toolbox and NIH Common Data elements, ABAS-II, and Bayley Scales),
    c. Quality of Life Childhood Epilepsy,
    d. Adverse Event Profile,
    e. Emotional Measure from the NIH Toolbox and Bayley Scales
    f. Social Determinants of Health (SDH).
    g. Columbia Suicide Severity Rating Scale (C-SSRS)
    h. Child Behavioral Checklist Assessment

Previous Human Experience with CBD use in Epilepsy patients:

GW Pharma, the company supplying the study medication has observed 213 patients with difficult to control epilepsies (including children) who received CBD oral solution (Epidiolex) as reported from uncontrolled non-GW sponsored Investigator INDs/Expanded Access Program studies under FDA regulations; however this has not been within a formal clinical study (there was no placebo* or 'dummy' treatment).

*The placebo is a dummy treatment that looks like the real thing. It does not contain any active medication but does contain colorings and flavorings so that it looks, smells, and tastes like the active medication.

Safety information was made available on the above mentioned 213 patients and the summary of side effects considered to have a plausible causal relationship to Epidiolex are listed in the below section.

The following side effects were experienced in the 213 patients taking CBD oral solution; all were considered to be caused by the study medication. They have been categorized by the likelihood of them occurring, and listed in the order they have most commonly been reported.

Very common side effects which may affect more than one person in every 10 are: Feeling drunk, sleepy or abnormal, feeling tired, diarrhea and eating less than usual.

Common side effects which may affect more than one person in every 100 are (excluding the very common side effects above): Eating more than usual, weight gain, weight loss, convulsions, difficulty walking and amounts of medicines in the body were higher than usual.

Some patients have also developed rashes during treatment with CBD oral solution. The following information is provided based on the current version of the Investigator Brochure (GW Pharmaceuticals) and is updated periodically based on any Development Core Safety Information received from GW Pharmaceuticals:

The table 2 summarizes all undesirable effects considered to have a plausible causal relationship to CBD oral solution (Epidiolex) observed in patients (including children) using Epidiolex as reported from uncontrolled non-GW sponsored Investigator INDs/Expanded Access Program studies under FDA regulations. In these studies, Epidiolex was being administered primarily in a pediatric population but also some adults with severe refractory epilepsies. The optimal dose regimen of Epidiolex was specific to each patient. In this program, Epidiolex (25mg/ml or 100mg/ml CBD concentration), was titrated typically up to a daily maximum dose of 25mg/kg/day and, in some cases higher. Epidiolex contains CBD (in an oral strawberry flavored solution) and contains anhydrous ethanol, sucralose, and sesame oil as excipients.

Table 2	**Undesirable effects with a plausible causal relationship to CBD solution (Epidiolex) - Reported from Non- comparative Investigator-led Studies in Patients (including children) With Severe Refractory Epilepsies**
System Organ Class Preferred Term	**Related causality** CBD (Epidiolex) (n=213)
Gastrointestinal Disorders	
Diarrhea	**29 (14%)**
General Disorders and Administration Site Conditions	
Fatigue	**36 (17%)**
Gait disturbance	**10 (5%)**
Investigations	

Weight increased	**12 (6%)**
Weight decreased	**10 (5%)**
Drug level increased	**9 (4%)**
Metabolism and Nutrition Disorders	
Decreased appetite	**31 (15%)**
Increased appetite	**15 (7%)**
Nervous System Disorders	
Somnolence	**44 (21%)**
Lethargy	**12 (6%)**
Convulsion	**11 (5%)**
Sedation	**7 (3%)**

Events of rash have been reported during treatment with Epidiolex.

For this open access phase 1 dose finding study, GW Pharmaceuticals and the Food and Drug Administration (FDA) have approved, based on the data from the studies mentioned above, to begin CBD with a starting dose of 5mg/kg/day in twice daily dosing. The titration of CBD is to be an initial dose of 5 mg/kg/day given in two divided doses and titrated by 5 mg/kg/2 weeks up to 25 mg/kg/day; additional increases in dosing, by 5mg/kg/day up to a maximum of 50 mg/kg/day may be instituted at the discretion of the treating PIs Patients will be monitored for adverse events and the dose reduced or the titration slowed if there are intolerable side-effects. The dose may be maintained at any point in the titration if seizures are completely controlled or there are dose-limiting side effects. This titration is overall slower than the titration in other Expanded Access Programs approved by GW Pharmaceuticals and the FDA. The titration in those programs (N=151 patients enrolled thus far) is typically initiated at the dose of 2-5 mg/kg/day followed by increases of 5 mg/kg/week up to 25 mg/kg/week; several investigators reported anecdotal use of the CBD oil (Epidiolex) in doses up to 50mg/kg/day. With this titration schedule, CBD is tolerated well with only 2/151 (1.3%) patients discontinuing CBD because of adverse events. It is expected that an even slower titration schedule proposed in our study will result in less adverse events and that this slower titration schedule will be better or equally well tolerated.

CBD Supply and Dispensing:

GW Pharma will provide its investigational cannabidiol (CBD) product, Epidiolex®, free of charge for this study. GW will export Epidiolex® in finished form to:

Catalent CTS (Clinical Trial Supplies), LLC.,
10245 Hickman Mills Drive
Kansas City, Missouri 6417
(816)767-6000

Dr. Martina Bebin will order Epidiolex from Catalent CTS using DEA Form 222 in amounts and at times that are sufficient to provide ongoing treament to patients in accordance with the study protocol.

GW Pharma is contracted to provide CBD for up to 70 patients, at the maximum dose allowed, throughout their participation in this study.

The CBD will be shipped to and stored in the Children's of Alabama (COA) Pharmacy Department and dispensed by the Investigational Pharmacy Staff at COA. All storage and accountability of the CBD will be handled by the COA Investigational Pharmacy Staff. The CBD will be dispensed by the COA Investigational Pharmacy Staff listed on the protocol. The CBD Medication orders will only be filled at the COA Investigational Pharmacy only. The prinicipal investigator will submit a medication order the COA Investigational pharmacy, the pharmacy will fill the medication order and dispense the CBD to the study coordinator. The study coordinator will deliever the patient's CBD medication order, dosing instructions and package leaflet information (provided by GW Pharma) to the study patient.

The Investigator's Brochure provides additional information for the CBD formulations (100mg/mL) used in our protocol. Information Leaflets created by GW for 100mg/mL solution for study participants using the CBD product are included in the attached documents. Also, Physician Prescribing Information documents for 100mg/mL oral solution are attached for review. We are only using the 100mg/mL solution for this expanded access protocol. The manufacturer, GW Pharma, will supply the 100mg/ml solution for this IND. The higher concentration will provide the least amount of alcohol that can be accurately dispensed by the caregiver. We have confirmed that both of the CBD oral solutions (25 mg/mL and 100 mg/mL) contain 79 mg/mL of ethanol.

Risks, Side Effects, Discomforts, and Inconveniences:

The following are risks and discomforts that you may experience during participation in this research study. Some side effects occurred in more than 10% of study participants who have previously taken CBD for seizures/epilepsy. These side effects may or may not be related to CBD and include:

- diarrhea,
- fatigue (feeling tired)
- changes in liver function tests, change in blood counts which can affect the clotting of the blood (platelet), changes in seizure medications levels measured in the blood,
- decreased or increased appetite
- weight loss or weight gain
- difficulty walking
- rash,
- feeling drunk, sleepy or abnormal
- convulsions

As with any drug, not all risks are known. If participants experience any side effects, they will be instructed to inform the study doctor or research staff. All side effects will be treated appropriately.

Although there have been no known deaths in human research participants, there have been deaths in animal studies. The significance of this is unknown.

As with any drug, it is possible that participants could experience an allergic reaction to any of the drugs or combination of the drugs used in this study. Symptoms of any allergic reaction can include a rash, hives, itching, and/or difficulty breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death. If participants think they are having a severe allergic reaction, they will be instructed to dial 9-1-1 and seek medical attention immediately. Patients should inform their study doctor, before signing this document, if they have ever had an allergic reaction to CBD or CBD-like products. The study medicine contains the following: CBD, Sesame oil, Ethanol, Sucralose (artificial sweetener), and strawberry flavoring. If subjects are allergic to any of these they should not take part in this study.

The study drug must be kept out of the reach of children or those with limited ability to understand.

During blood draws, participants may experience some discomfort, bruising, or temporary pain at the site of needle entry into the vein, as they might during any blood draw. There is a remote risk of fainting. Infection could occur at the place where the needle goes into the arm. However, study staff will take all available precautions to prevent an infection by using sterile technique.

The 30-60 minute EEG may cause some inconvenience to the participant because the paste or glue used to apply the electrodes onto the scalp, may get stuck in the participant's hair and require more than one shampooing to remove completely. In rare instances, the paste or glue may cause mild skin irritation. This normally will heal by itself.

In addition, there might be risks or inconveniences to participants, an embryo, a fetus, or a breast-feeding infant that are currently unforeseeable. Becoming pregnant could pose unforeseeable risks to the embryo, fetus, or breast-feeding infant.

There is also the minor risk of loss of confidentiality.

The interactions between CBD and other drugs that are metabolized in a similar manner are not well understood. There may be an increased risk of toxicity and or side effects such as sedation when CBD is administered with other anti-epileptic drugs. If there is a suspicion that a change in the patient's clinical status may be attributed to such concomitant medication, careful monitoring of plasma levels of the medication and/or its metabolites should be followed. Periodic blood levels of anti-epileptic drugs may need to

be measured during the course of this study. If you experienced symptoms of toxicity such as drowsiness and feel that you need a blood test to determine if other anti-epileptic blood levels have been increased by CBD, tell the doctor or nurse involved in this study. Also, you should tell other doctors or nurses who care for you that you are on this investigational drug.

It is important to know that long-term use of CBD has not been studied in any patients with seizures/epilepsy. The risks to younger children, when considering growth and development, from long-term CBD exposure are unknown at this time. Also, there is no specific information available about use of CBD in patients with kidney or liver problems/failure.

The use of CBD may have no impact on, a reduction of, or a worsening of seizures/epilepsy.

Driving and/or use of machinery

The study medication may produce side effects such as dizziness, or feeling drunk, sleepy or abnormal. This may affect the ability to do skilled tasks. Subjects are advised not to drive, use machinery or take part in any dangerous activity until it is known that the study medication is not affecting their ability to do these tasks.

Alcohol

Alcohol may interact with the study medicine and produce a much more powerful effect than usual, which can easily cause accidents in the home or elsewhere. Subjects are strongly advised either to avoid alcohol for the duration of the study or to consume it in moderation. Moderate consumption of alcohol is defined by the Royal College of Physicians as 15 to 21 units per week for men (7-10 pints of beer or standard 175 ml glasses of wine in a week) and 11 to 14 units per week for women (5-7 standard 175 ml glasses of wine in a week).

Travel

Subjects may not take the study medication outside the country they live in as it is illegal to transport it across many international borders. Subjects cannot take part in this study if they plan to take a trip abroad during the period of the study. It is also possible that subjects may not be able to take their study medication into another state.

Food

Eating food with the medication does not affect how the study medication works for subjects.

Blood Donation

Subjects should abstain from donation of blood during the study.

Recruitment and Enrollment:

Participant Recruitment:

Epilepsy patients interested in the CBD program have been contacting our department since the Senate Bill 174 passed in April 2014. When the Alabama Senate Bill 174 was passed, a CBD phone line was established to field all calls inquiring about this research program (both adult and pediatric).

We have collected patients' names and phone numbers, per IRB personnel instruction, and created a list of interested participants. The patients were informed once additional information was available, they would be contacted by our Program Manager or study coordinator(s). Patients who have previously contacted us about participation, whether part of the PI's or Sub-I's direct clinic population or not, will be contacted using the information provided during their last contact with the Program Manager.

Program manager and/or study coordinator(s) will reach out to all patients on our list and request a mailing address. Information packets will be sent to all patients on our list at the initiation of the study. The information packet will include instructions for submitting required screening information for consideration into the study (copy of example packet is attached). The study personnel will also provide a website address in the packet information, where the packet details can be found electronically. The website address is www.uab.edu/cbd. Once all patients who are on the list of interested participants have provided their mailing address, a mass mailing of packets will go out at one time. Any patients contacting us after the start of the study will be provided with the same information. We will gather their mailing address to send an information packet and let them know the information can be found electronically at www.uab.edu/cbd. The information packets will provide instructions for patient to have certain medical record information submitted for review by the CBD Treatment Approval Committee. We have attached a phone script for the Program Manager or study coordinator(s) to use when contacting the participant. The phone script also includes screening questions for basic entry criteria. Whether the participant is a part of the PI's/Co-PI's or Sub-I's direct clinic populations or is treated by an outside neurologist, the patient's primary treating neurologist will need to provide the CBD Treatment Approval Committee with the required information. The CBD Treatment Approval Committee will review the records of the interested participants and "approve/recommend" or "disapprove/not recommend" the interested participants for treatment in the CBD open access program. The decision of the Committee will be communicated to the patient and the referring provider via a letter. A partial waiver of authorization for recruitment/screening purposes will be submitted to the IRB.

The enrollment goal for this study is set at up to 100 patients (includes patients enrolled as part of this adult protocol and patients enrolled as part of the pediatric protocol). There is no minimum required duration the participant will need to remain in the study. This is a naturalistic, longitudinal, observational, phase 1 dose-finding study with participants and providers able to discontinue participation at any time.

Prior to Enrollment:

Potential study subjects will be referred to the CBD study by their primary/current treating neurologists. A Partial Waiver of Authorization will be obtained from the IRB to review patient medical records for screening purposes, prior to participants providing consent. Potential study participants will be referred to the CBD study by their primary/current treating neurologist. Once the written referral from the provider and the required medical information are available, the potential participants' data will be referred to the CBD Treatment Approval Committee for review. The required medical information includes:

- Cover letter checklist
- Documentation/Proof of Alabama Residency, (The Alabama residency criteria used for this study was pulled from two sources: the criteria used to determine in-state residency status for incoming UAB students and the criteria Oregon uses to determine residency in their state, as it relates to the Death with Dignity Act),
- Referral letter from primary/current treating neurologist
- Report of most recent Brain MRI
- Video/EEG monitoring report confirming the diagnosis of epilepsy,
- Digital copy of a routine EEG along with the formal written report performed within 3 months prior to submitting these records for CBD Treatment Approval Committee review,
- Report of most recent Electrocardiogram (ECG)
- Documentation of failed AEDs, including one trial of a combination of two concomitant AEDs, without successful seizure control.
- Documentation of between 1-4 baseline anti-epileptic drugs at stable doses for a minimum of 4 weeks prior to submitting these records for CBD Treatment Approval Committee review.
- If applicable, documentation of VNS or RNS implantation and evidence that settings have not been adjusted within 3 months prior to submitting these records for CBD Treatment Approval Committee review,
- If on ketogenic diet, documentation that patient has been on stable ratio for a minimum of 3 months.
- Documentation indicating seizure type(s), and number of seizures of each type per month
- Documentation of seizure calendar for at least 3 months prior to submitting these records for CBD Treatment Approval Committee review. The patient will need to provide an updated calendar at the time of enrollment.

- Results of routine laboratory studies, including but not limited to CBC, CMP, LFTs, renal panel, UA and levels of all AEDs within 3 months prior to submitting these records for CBD Treatment Approval Committee review. If AED dose was adjusted in the preceding 3 months, level on the new dose will need to be provided.
- Results of any metabolic or genetic testing that have been completed.

Once records are received by the study program manager, they will be forwarded to the CBD Treatment Approval Committee, via secure email, for review. Thereafter the members of the CBD Treatment Approval Committee review the patients' medical information and approve/disapprove enrollment in the study. To qualify for the study, subjects must meet all inclusion and none of the exclusion criteria based on the committee's review of their medical records. The following physicians have agreed to serve on the committee:

- Dr. Leon Dure
- Dr. Tony McGrath
- Dr. Krisztina Harsanyi-Jilling

If one of the above physicians refers their patient to the study, she or he will need to excuse herself/himself from the discussion of the Committee and Dr. Szaflarski or Dr. Bebin will serve on the Committee instead. In order for the patient to be deemed "approved" for treatment through the CBD study, all three committee members must agree the participant should be included. Once records are reviewed and the patient is deemed "approved" as a suitable study candidate, all records, along with the written decision of the CBD Treatment Approval Committee, will be referred to the study nurse coordinator. Copy of the letter will be forwarded to the treating/referring provider and to the patient. The records will be maintained by the study physician and his staff during the time the patient is enrolled in the study.

After receiving the CBD Treatment Approval Committee's decision, the study nurse coordinator will contact the patient or parent/LAR regarding participation and send the IRB approved informed assent and/or consent forms for review. Once the participant or participant's parent/LAR expresses interest in participating, the study nurse coordinator will schedule the screening and enrollment visits.

If the patient is deemed ineligible for study participation a letter from the CBD Treatment Approval Committee will be forwarded to the patient and the referring provider with an explanation as to why the patient does not qualify. Records of the disqualified patients will be kept for later IRB reporting.

Not all patients who submit information for consideration by the CBD Treatment Approval Committee will have an opportunity to enroll in the study. The UAB CBD program-Pediatric phase 1 dose-finding study can enroll at least 70 subjects. GW Pharma has contracted with us to provide CBD for up to 140 subjects, including the pediatric and adult protocols. We estimated the enrollment will be split evenly, 70 subjects enrolled into the pediatric protocol and 70 enrolled into the adult protocol. However, if enrollment

for the adult protocol is not moving as quickly as the pediatric protocol, the dividing of patients may not be split 50 / 50, and vice versa. The two protocols (adult and pediatric) may not enroll over ~140 total subjects without prior approval from GW Pharmaceuticals.

After enrollment has been met, entry into the program will be placed on hold until which time additional Cannabidiol can be provided for additional subjects. It is possible that GW Pharmaceuticals may approve increased enrollment if eligible patients are still available and interested in participation after the planned enrollment has been met. We will inform potential subjects of the hold and if a patient has submitted their documentation for consideration during such time, the subject' packets will be held for 3 months while the UAB CBD program works through access to additional CBD for additional enrollment. If we are not successful during that time, the subject's information will be destroyed and a new information packet requested once enrollment is open again. The patient will be contacted and informed the study enrollment is on hold and notified when enrollment opens again.

If we are unable to secure additional CBD, to continue enrollment over the original 100 subjects, we will notify all interested subjects and officially close enrollment to the program.

Participant Compensation and Costs:

Patients will receive monetary compensation for completing the Study Visit 1/Day 0 and Study Visit 10/Month 12 (or early termination visit) study visits. This amount will be set at $100.00/visit. Other visits will not be reimbursed. Subjects will receive the study medication at no charge during their participation in this CBD study.

In addition to the above compensation, patients 15 years and older who agree to participate in an optional fMRI substudy will receive $100.00 for each visit where an fMRI procedure is performed (in addition to the compensation provided for participation in the main study).

Participants may incur costs related to travel to and from the study site for visits and parking at study site for visits. Participants will also incur costs for the required blood and urine tests that assess for side effects and toxicity levels. The participants' insurance will be billed for all blood tests and urine tests. If the insurance will not pay or the participant does not have insurance, the participant will be responsible for payment of these blood and urine tests.

Inclusion/Exclusion Criteria:

- **Inclusion criteria**

- Patients between 1 years (12 months)-18 years with drug resistant epilepsy confirmed by video EEG recording report, and
- Patient should have history of a trial of at least four drugs, including one trial of a combination of two concomitant drugs, without successful seizure control. Vagal nerve stimulation, RNS deep brain stimulation, or the ketogenic diet can be considered equivalent to a drug trial. Patient suffering from an epileptic syndrome that is known to be refractory to treatment, such as Dravet or Lennox Gastaut Syndrome, may be included after a trial of only two drugs, and
- Between 1-4 baseline anti-epileptic drugs at stable doses for a minimum of 4 weeks prior to submitting records for review by the CBD Treatment Approval Committee.
- VNS or RNS must be on stable settings for a minimum of 3 months.
- If on ketogenic diet, must be on stable ratio for a minimum of 3 months.
- Review of the following patient medical information:
    - Most recent Brain MRI report,
    - Most recent ECG report,
    - Video/EEG monitoring report confirming the diagnosis of epilepsy,
    - Evidence that the patient has failed 4 AEDs as indicated above,
    - Patient must have at least 4 clinically countable seizures per month,
    - Seizure history to include a documented history of generalized (drop, atonic, tonic clonic, and/or myoclonic) seizures, focal seizures without loss of consciousness with a motor component, focal seizures with loss of consciousness, or focal seizures with secondary generalization, complex partial seizures with a motor or tonic component, and / or altered awareness seizures,
    - Results of routine testing including blood work (CBC, CMP, LFTs renal panel, Urinary Analysis, and levels of all AEDs) and digital copy of a routine EEG along with the formal written report performed within 3 months prior to submitting records for CBD Treatment Approval review. If applicable, results of any metabolic or genetic testing performed should be included in submitted records for review. If any AED dose was adjusted in the preceding 3 months, level on the new dose will need to be provided.
    - If applicable, documentation (including date of surgery) of prior VNS, RNS, Corpus Callostomy, or other epilepsy surgery the patient has received.
- Acceptable method of contraception (or abstinence) for women of childbearing potential and for male patients with partners of childbearing potential, and female patients must have a negative urine pregnancy test on the day of initating CBD.

- For patients who agree to participate in the optional neuroimaging substudy, an MRI screen will be obtained to show that the patient does not have contraindication to receiving MRI/fMRI at 3 Tesla (e.g., metallic artifact).
- Patients are able to supply investigator with seizure calendars for the past 3 months prior to submitting records for CBD Treatment Approval Committee review. The patient will need to provide an updated calendar at the time of enrollment.
- Approval for inclusion by the CBD Treatment Approval Committee.
- Current State of Alabama Resident
  - Acceptable documentation of Alabama residency includes the following:
    - a state issued ID, such as a driver's license, from patient or patient's parent/ legally authorized representative (LAR).
    - documents showing the patient or patient's parent/LAR rents/owns property in the state,
    - state voter registration from patient or patient's parent/LAR, or
    - a recent state tax return from patient or patient's parent/LAR.

- **Exclusion criteria**
  - Active Psychogenic non-epileptic seizures (PNES); Patients with more than 1 year freedom from PNES will not be excluded,
  - Patients who are pregnant, breastfeeding, or not using acceptable methods of contraception during the course of the study and for three months thereafter,
  - Male patient's partner is of child bearing potential; unless willing to ensure that they (male patients) or their partner(s) are using acceptable methods of contraception during the course of the study and for three months thereafter
  - History of substance abuse/addiction,
  - Use of medical marijuana or CBD based product in the past 30 days,
  - Initiation of felbamate within last 12 months,
  - Allergy to CBD or any marijuana-type products,
  - ALT >5 × ULN or AST >5 × ULN, as seen in participant's laboratory results submitted to the CBD Treatment Approval Committee for review.
  - Hemoglobin <10 or Hematocrit <30 or WBC < 2000, as seen in participant's laboratory results submitted to the CBD Treatment Approval Committee for review.
  - In Investigator's judgement, active medical condition/treatment that impacts study activities.
  - Unable to provide consent (and no LAR),

- Unable/Failure to comply with study visits/requirements and/or instructions.
- Confirmed diagnosis for Dravet Syndrome or Lennox Gastaut Syndrome that qualifies the patient for a GW Dravet Syndrome or Lennox Gastaut Syndrome randomized controlled clinical trial for which the patient is eligible pursuant to the GW clinical trial enrollment criteria unless
- (a) there is no study that is either actively open for enrollment of patients at UAB or that is expected to actively begin enrolling patients at The University of Alabama at Birmingham within two (2) months of the date on which the patient is screened for the UAB Pediatric CBD Program or UAB Adult CBD Program.Primary residence in a State different than Alabama.
- Subjects with contraindications to MRI/fMRI at 3 Tesla (e.g., metallic artifact) will not be offered participation in the optional substudy.

Other care including routine neurological care that is not related to participation in the CBD study will be provided by the patients' primary treating neurologist.

Informed Consent:

Assent and/or consent will be obtained in a quiet setting prior to the initiation of any study procedures. The patient and/or legally authorized representative (LAR) will be given opportunity to delay assent/consent until he/she has taken adequate time to read and understand the written assent/consent and discuss the study with others outside the clinic setting. Patients and/or LAR will not be consented in writing until they are able to demonstrate adequate understanding of all aspects of the study and assent/consent process. A copy of the assent and/or consent form will be given to the patient. The signed assent and/or consent form remains in the participant's study files at the clinical center.

The University of Alabama at Birmingham Institutional Review Board observes the definition of LAR as a person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subject's research, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.The CBD study requires review of medical records by the UAB CBD Treatment Approval Committee prior to participant's signing an informed consent document. A Partial Waiver of Authorization will be submitted to the IRB for recruitment and screening purposes used to determine a paticipant's eligibility.

Randomization:

This study is not randomized.

Visit Schedule and Study Procedures:

UAB CBD Program: Children's Protocol Schedule of Events (Patients 1 years to 18 years of age) -Page 1 of 5

Activities/Procedures:	Prequalification Period	Enrollment Visit	SV1/Day 0	Phone Visit 1/Day 7 (+/-1 day), Phone Visit 2/Day 21 (+/- 1 day), Phone Visit 3/Day35 (+/- 1 day), Phone Visit 4/Day 49 (+/- 1 day), Phone Visit 5/Day 63 (+/- 1 day)	SV2/Day 14/Week 2 (+/-3 days), SV3/Day 28/Week 4 (+/- 3 days), SV4/Day 42/Week 6 (+/-3 days) :	SV5/Day 56/Week 8 (+/- 3 days), SV6/Day70/Week 10 (+/- 3 days):
Referral Letter from Primary Treating Neurologist	X					
Medical Record Info Submitted for Review	X					
Enrollment: Informed Consent/Assent		X				
Verification of Medical Record Information		X				
Inclusion/Exclusion		X				
Seizure Frequency (Historical Data) Calendar		X*	X*			
Chalfont Seizure Severity Scale		X*	X*	X	X	X
Neurological Exam		X*	X*		X	X
General Physical Exam		X*	X*		X	X
Laboratory Assessments[e]		X[e]	X[e]		X[e]	X[e]
Functional MRI (fMRI) *Optional			X[f]			X[f]
ECG, UA, other laboratory assessment data collected from historical data in medical record information.			X			
Urine Pregnancy Test (only for women of child bearing potential)		X*	X*		X	X
Menstrual History Data		X*	X		X	X
EEG[a] (30-60 minute) duration					X[a]	X[a]
Vital Signs (age, weight, height, HR, BP, temperature)		X*	X*		X	X
Pediatric Cognitive Testing (NIH Toolbox), ABAS-II or Bayley Functional Scales[b]			X			
Quality of Life in Childhood Epilepsy (QOLCE)			X			
Adverse Events Profile			X		X	X

Columbia Suicide Severity Rating Scale (C-SSRS)		X*	X		X	X
Child Behavioral Checklist Assessment		X*	X			
Seizure Diary Training		X*				
Seizure Frequency through Diary Data Collection			X	X	X	X
NIH Emotional Measures or Bayley Emotional Scales[d]			X			
Social Determinants of Health data collection			X			
Titrate CBD (if needed)					X	X
Dispense Medication			X		X	X
AE/SAE Monitoring/Reporting				X	X	X

UAB CBD Program: Children's Protocol Schedule of Events (Patients 1 years to 18 years of age) -Page 3 of 5

Activities/Procedures:	SV7/Day 84 (+/- 3 days) or Follow up study visit 28 days after after Target dose is reached:	SV10/Day168/Wk 24/Month 6 (+/- 7 days), SV 14/Day 504/Wk 96/Month 24 (+/- 7 days), SV18/Day 840/Wk 192/Month 48 (+/- 7 days):	SV8/Day 112/Wk 16/Month 4 (+/- 7 days), SV9/Day140/Wk 20/Month 5 (+/- 7 days), SV11/Day 252/Wk 36/ Month 9 (+/- 7 days), SV12/Day 336/Wk 48/ Month 12, SV13/Day420/Wk72/ Month 18, SV15/Day 588/Wk 120/ Month30, SV16/Day 672/Wk 144/Month 36, SV17/Day 756/Wk 168/ Month 42:	Unscheduled Visit or Early Termination Visit (prior to year 1 visit):	Post-Termination Study Visit (approximately 28 days after CBD wean):
Seizure Frequency through Diary Data Collection	X	X	X	X	X
Chalfont Seizure Severity Scale	X	X	X	X	X
Neurological Exam	X	X	X	X	X
General Physical Exam	X	X	X		
Laboratory Assessments[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Electrocardiogram (ECG)				X (at early term visit prior to year 1 only)	X
Urine Pregnancy Test (only for women of child bearing potential)	X	X	X	X	X
Menstrual History Data	X	X	X	X	X
EEG[a] (30-60 minute) duration	X	X[a]	X[a,g]	X[c]	
Vital Signs (age, weight, height, HR, BP,	X	X	X	X	X
Pediatric Cognitive Testing (NIH Toolbox), ABAS-II or Bayley Functional Scales[b]		X		X[c]	
Quality of Life in Childhood Epilepsy (QOLCE)		X		X[c]	
Adverse Events Profile	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X[a]	X	X	X	X
Child Behavioral Checklist Assessment	X	X			
NIH Emotional Measures or Bayley Emotional		X (SV10 only)	X (SV12 only)		
Social Determinants of Health data collection		X		X[c]	
Titrate CBD (if needed)	X	X	X	X	
Dispense Medication	X	X	X	X (if needed)	
AE/SAE Monitoring/Reporting	X	X	X	X	X

X* =Participants' who have an Enrollment Visit and Study Visit1/Day 0 conducted on the same day will have the following activities performed only once during the visit: Urine Pregnancy test, Seizure Frequency Calendar, Chalfont Seizure Severity Scale, Neurological Exam, General Physical Exam, and Vital signs.

a An EEG will be performed at the first of the follow up study visit where the Principal Investigator determines the patient has reached their target dose of CBD. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.

b NIH Toolbox Measures include: For ages 3-6 years: Dimensional Change Card Sort Test (DCCS), Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, Picture Vocabulary, Oral Reading Recognition test (for children who have developed letter and/or word recognition skills). For ages 7-14 years: Dimensional Change Card Sort Test (DCCS), Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, Picture Vocabulary Test, Oral Reading Recognition Test, List Sorting Working Memory Test, Pattern Comparison Processing Speed Test. For ages 15-18 years: Dimensional Change Card Sort Test (DCCS), Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, List Sorting Working Memory Test, Pattern Comparison Processing Speed Test, Reading Recognition Test. For participants between the ages of 1 year (12 months) and less than 3 years of age, and/or who are unable, due to cognitive impairment, to complete the Cognitive subtests from the NIH Toolbox, their legal guardian will be asked to complete the Adaptive Behavior Assessment Scale – II (ABAS-II). The ABAS-II measures adaptive behavior, using parent-report to evaluate function across a variety of environments. Test results include four domain composite scores (Conceptual, Social, Practical, and General Adaptive Composite) and 10 skill area scores (Communication, Community Use, Functional Academics, Health and Safety, Home or School Living, Leisure, Self-Care, Self-Direction, Social, and Work/Motor). For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Functional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Cognitive assessments.

c During any early termination or unscheduled visit, individual decision will be made by the managing study doctor regarding further participation, medication titration (up or down), medication wean, etc. If the patient and provider agree on terminating participation prior to 1 year visit, the following data points will be collected at that visit (or at year 1 visit).

d NIH Toolbox for Emotional Assessment: Emotion Measures from the NIH Toolbox will be administered to each participant and/or their legal guardian. The Emotion Measures from the NIH Toolbox assess four major domains: Negative Affect (NA), Psychological Well-Being (PWB), Social Relationships (SR), and Stress/Self-Efficacy (SSE). For participants ages 3 – 7, the following age-appropriate subtests from the NIH Toolbox Emotion Parent Proxy Battery will be administered: Negative Affect (NIH TB NA Anger – Parent Report, NIH TB NA Fear-Over Anxious Parent Report for Children, NIH TB NA Fear-Separation Anxiety Parent Report FFSF, NIH TB NA Sadness Parent Report FFSF for Children), Psychological Well-Being (NIH TB PWB General Life Satisfaction Parent Report SF-FF, NIH TB PWB Positive Affect Parent Report CAT), Social Relationships (NIH TB SR Empathic Behaviors Parent Report CAT, NIH TB SR Peer Rejection Parent Report FFSF, NIH TB SR Positive Peer Interaction Parent Report FFSF,NIH TB SR Social Withdrawal Parent Report FF-SF). For participants ages 8 – 12, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered: Negative Affect (NIH TB NA Anger-SF,NIH TB NA Fear SF, NIH TB NA Sadness SF), Psychological Well-Being (NIH TB PWB General Life Satisfaction SF, NIH TB PWB Positive Affect Parent Report CAT), Social Relationships (NIH TB SR Emotional Support SF,NIH TB SR Friendship SF, NIH TB SR Loneliness SF, NIH TB SR Perceived Hostility SF, NIH TB SR Perceived Rejection SF), Stress & Self Efficacy (NIH TB SSE Self-Efficacy CAT). Additionally, legal guardians of participants ages 8-12 will complete the following Emotion Parent Proxy Battery subtests: Negative Affect (NIH TB NA Anger-Parent report CAT, NIH TB NA Fear Parent Report CAT, NIH TB NA Sadness Parent Report CAT), Psychological Well-Being (NIH TB PWB Positive Affect Parent Report CAT), Social Relationships (NIH TB SR Empathic Behaviors Parent Report CAT, NIH TB SR Peer Rejection Parent Report FFSF, NIH TB SR Positive Peer Interactions Parent Report FFSF, NIH TB SR Social Withdrawal Parent Report FF-SF), Stress & Self Efficacy (NIH TB SSE Perceived stress-Parent report, NIH TB SSE Self-Efficacy Parent report CAT). For participants ages 13 – 17, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered: Negative Affect (NIH TB NA Anger-SF, NIH TB NA Fear SF, NIH TB NA Sadness SF), Psychological Well-Being (NIH TB PWB General Life Satisfaction CAT, NIH TB PWB Positive Affect CAT), Social Relationships (NIH TB SR Emotional Support SF, NIH TB SR Friendship SF, NIH TB SR Loneliness SF, NIH TB SR Perceived Hostility SF, NIH TB SR Perceived Rejection SF), Stress & Self Efficacy (NIH TB SSE Perceived Stress CAT, NIH TB SSE Self-Efficacy CAT). For participants age 18, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered: Negative Affect (NIH TB NA Anger Hostility SF, NIH TB NA Anger Physical Aggression SF, NIH TB NA Anger-CAT , NIH TB NA Fear-Affect CAT, NIH TB NA FEAR-Somatic Arousal SF, NIH TB NA Sadness CAT), Psychological Well-Being (NIH TB PWB Meaning and Purpose CAT, NIH TB PWB Positive Affect CAT), Social Relationships (NIH TB SR Emotional Support SF, NIH TB SR Friendship SF, NIH TB SR Instrumental Support SF, NIH TB SR Loneliness SF, NIH TB SR Perceived Hostility SF, NIH TB SR Perceived Rejection SF), Stress & Self Efficacy (NIH TB SSE Perceived Stress CAT, NIH TB SSE Self-Efficacy CAT). For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition

(Bayley-III®)-Emotional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Emotional Measures assessments.

[e] Laboratory Assessments collected at Study Visit 1 will include a CMP and CBC. The study doctor may order additional laboratory testing (blood and/or urine tests) at follow up study visits to assess for side effects and toxicity. The laboratory assessments would include: CMP, CBC, Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels). Subjects approved for the UAB CBD Open Access Program must have laboratory studies within 3 months of the committee review which include: CBC, Complete Metabolic Panel, Urine Analysis and anti-epileptic drug levels. If the subject enrolls in the program and completes the screening visit within 3 months of the required baseline laboratory studies, they are not repeated at Study Visit #1. If the subjects enrolls outside the three month window, the laboratory studies are repeated (CBC, CMP, anti-epileptic medication levels) at Visit #1. During the initial 3 months of the titration of CBD up to 25 mg/kg/day (study visit every 2 weeks), repeat laboratory studies will be done at 4-week intervals until the 6-month visit and then every 3 months (9-month and 12-month visit) and then at 6-month intervals for the duration of the study. At each visit, complete vital signs are taken and review of potential adverse events and menstrual history will be done. If there is any concern of the anti-epileptic medication interaction with CBD, additional AED levels are drawn at the study visit. Particular attention is given if the subject is currently taking valproic acid and clobazam because of potential drug interactions. A urine analysis is completed at Study Visit #1 and will be completed as needed throughout the protocol to monitor for toxicity or potential side effects. A urine analysis schedule will be added at 3-month intervals during the first year of the study and every 6 months for years 2 and 3. An ECG is obtained as part of the screening process, but will be repeated at 6 months, 12 months and then yearly while participants are enrolled in the study. The early discontinuation visit will include a CBC, CMP, UA and an ECG.

[f] Patients have the option of participating in an fMRI Substudy.

[g] An EEG will be performed at the first annual (12 month) study visit. If participant has already pasted this visit, the EEG will be performed at their next study visit.

CRFs for this program were created using the NINDS common data elements CRFs and other common Epilepsy data collection resources.

Withdrawal of Participant Consent and Early Termination/Discontinuation of Study Drug:

Study participation may be discontinued for any of the following reasons:

- Administrative decision by the investigator or GW Research Ltd or Regulatory Authority.
- Subject decision to withdraw consent/assent for study.
- Withdrawal of parent/legal authorized representative consent.
- Pregnancy.
- Evidence of allergy to administered products.
- Lost to follow up
- Patient non-compliance
- Protocol deviation that is considered to potentially compromise the safety of the patient.
- In Investigator's judgement, development of active medical condition/treatment that impacts study activities.
- Intolerable adverse event as judged by study investigator and participant.
- Serious Adverse Event, which in the investigator's opinion compromises the safety of the patient.
- 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%)
- For any clinically significant (> 3 x ULN) elevation of ALT or AST in children under 21 years of age being treated with Epidiolex in an Expanded Access IND, the following laboratory measures, at minimum, should be assessed within 72 hours: repeat ALT/AST, total bilirubin, alkaline phosphatase, and GGT.
- All trial subjects with elevated LFTs should be followed until all abnormalities return to the baseline state as assessed by the investigator with AST/ALT < 3X ULN.
- If a subject has elevated LFTs (>3x ULN) and is on valproic acid the subject must stop the CBD and the LFTs must be monitored until the return to baseline state. If the subject has shown an improvement in their seizure frequency with the addition of CBD the option to "rechallenge" CBD will be at the discretion of the study PI. It would require that the subject taper off valproic acid and be on a stable dose of antiepileptic medication for 30 days prior to restarting the CBD. They would have repeat baseline labs (CBC, CMP and AED levels) prior to restarting the CBD.
- Development of anemia with Hemoglobin <10 or Hematocrit <30 or WBC < 2000

If the subject wishes to discontinue the study drug for any reason, the subject will be seen for an early termination visit/end of study visit. The early discontinuation visit will include a CBC, CMP, UA and an ECG.

Study Design

Dosing Adjustment/Schedule:

The titration of CBD will start with a dose of 5 mg/kg/day given in two divided doses and titrated by 5 mg/kg/2 weeks up to 25 mg/kg/day; in some patients additional titration by 5mg/kg/day every 2 weeks upto 50mg/kg/day may be instituted at the discretion of the PI upon discussion with the Co-PI (Dr. Szaflarski) Patients will be monitored for adverse events and the dose will be reduced or the titration slowed if there are dose-limiting side-effects.

For any clinically significant (> 3 x ULN) elevation of ALT or AST, the following laboratory measures, at minimum, should be assessed within 72 hours: repeat ALT/AST, total bilirubin, alkaline phosphatase, and GGT.

- Epidiolex® will be discontinued in patients who have:
  - 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%)

All trial subjects with elevated LFTs will be followed until all abnormalities return to the baseline state as assessed by the investigator with AST/ALT < 3X ULN.

If a subject has elevated LFTs (>3x ULN) and is on valproic acid the subject must stop the CBD and the LFTs must be monitored until the return to baseline state. If the subject has shown an improvement in their seizure frequency with the addition of CBD the option to "rechallenge" CBD will be at the discretion of the study PI. It would require that the subject taper off valproic acid and be on a stable dose of antiepileptic medication for 30 days prior to restarting the CBD. They would have repeat baseline labs (CBC, CMP and AED levels) prior to restarting the CBD.

The dose may be maintained at any point in the titration if seizures are controlled (no seizures since last medication adjustment) or there are limiting side effects, or the maximum dose is reached.

After the participant completes Study Visit 1, CBD will be dispensed with the following proposed dose schedule (dose increases will be dependent on presence/absence of seizures and presence/absence of dose-limiting side effects – see below):

- Weeks 1-2 (Day 0-Day 14) CBD dosage: 5 mg/kg/day in twice daily dosing (participant will be followed with a phone visit at Day 7 and study visit in-person at Day 14).
- Weeks 3-4 (Day 15-Day 28) CBD dosage: 10 mg/kg/day in twice daily dosing, if determined appropriate (participant will be followed with a phone visit at Day 21 and study visit in-person at Day 28).
- Weeks 5-6 (Day 29-Day 42) CBD Dose: 15 mg/kg/day in twice daily dosing, if determined appropriate (participant will be followed with a phone visit at Day 35 and study visit in-person at Day 42).
- Weeks 7-8 (Day 43-Day 56) CBD Dose: 20mg/kg/day in twice daily dosing, if determined appropriate (participant will be followed with a phone visit at Day 49 and study visit in-person at Day 56).
- Week 9 and thereafter CBD Dose: 25/mg/kg/day, if determined appropriate (participant will be followed with a phone visit at Day 63 and study visit in-person at Day 70).

As indicated above the initial dose of CBD may be adjusted upward every 2 weeks in increments of 5mg/kg/day (up to the dose of 25mg/kg/day) in twice daily dosing until:

a) a dose that adequately controls seizures (no seizures since last medication adjustment) has been reached and there are no dose-limiting side effects that prevent, in the opinion of the treating study physician and/or the patient, further CBD dose increases, or,

b) the subject experiences a protocol defined "clinically significant" or "dose limiting" adverse event if she/he has:
    1) any Grade 3 or higher adverse event (AE) per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.0) for which there is reasonable possibility that CBD caused the event, or
    2) meets the criteria for a Severe Adverse Event (SAE).

While the dose of 25 mg/kg/day divided into two daily doses will be the standard maximum dose, patients who did not achieve complete seizure control but have exhibited clear improvements in seizure control (e.g., minimum decrease ion seizure frequency by 50%) and who have no or minimal side effects of the CBD oil additional increases by 5 mg/kg/day every 2 weeks up to the maximum dose of 50 mg/kg/day may be instituted if both PIs (Szaflarski & Bebin) agree that this is in the best interest of the patient. <u>This approach mimics clinical practice as antiepileptic drugs are typically adjusted based on clinical response and presence or absence of side effects</u>.

If a subject experiences a "clinically significant" or "dose limiting" AE or SAE attributable to CBD, the investigator will determine if a dose reduction or taper is necessary. Dose decreases will occur if the patient needs to be tapered off CBD (dose-limiting side effects or lack of tolerability); these decreases will occur in 5 mg/kg/day increments every two week (or at a rate that is felt appropriate by the treating provider).

The CBD cannot be stopped all at once as this could cause the patients seizures/epilepsy to become worse.

The participant may be maintained on a dose lower than maximum amount (50mg/kg/day)if that dose, in the opinion of the patient, LAR, and the study physician, has adequately improved their seizure frequency or severity. The investigator, in consultation with the subject and/or caregiver, will determine when an adequate level of seizure frequency and/or severity of control has been achieved.

Once the subjects reach the dose of 10 mg/kg/day further dose adjustments (upward or downward) can be made biweekly at study visits in order to evaluate safety and establish a target dose up to a maximum dose of 50mg/kg/day in twice daily dosing. Dose adjustments (upward, downward, or taper) may continue until seizure control reached (target dose), maximum dose reached, or dose-limiting side effects are experienced.

Patients referred to the CBD study and approved by the CBD Treatment Approval Committee may have an enrollment visit combined with Study Visit 1 (Day 0), at the discretion of the investigator.

Enrollment Visit Procedures:

The study staff will discuss study responsibilities with the participant and/or participant's LAR. Participation in this study will not change subjects' primary treating neurologist's treatment of their epilepsy. The study medication, CBD, is to be taken in addition to subjects' current epilepsy therapies, including anti-epileptic medications, ketogenic diet restrictions, or any other therapies prescribed by their primary treating neurologist.

- Informed Assent and/or Consent Document Process with study team member

- Verification of information from medical record including:
  - Complete medical history
  - Physical examinations
  - Complete baseline and ongoing vital sign assessments
  - Neurological evaluations
  - Laboratory results and diagnostic imaging results (results are those of previously performed procedures as part of the subject's standard care)

- Inclusion/Exclusion Verification (**Subjects who do not meet the inclusions/exclusion criteria will be terminated from the study and no further data will be collected on these terminated subjects; the collected data will be maintained in secure storage for further reporting

- **Subjects approved for the program must have laboratory studies (CBC, CMP, UA, AED levels) within 3 months of review. If the subject enrolls in the program and completes the screening visit within 3 months of the required baseline studies, they are not repeated at Study Visit #1. If the subject enrolls

outside the three month window, the laboratory studies (CBC, CMP, AED levels) are repeated at Study Visit #1.

- Average monthly seizure frequency (historical data) by type, and severity
  - Average monthly seizure frequency will be calculated by dividing the number of seizures reported by the patient by number of months (seizure calendar for at least 3 full months needs to be available)
- Chalfont Seizure Severity Scale: Questionnaire/scale used to determine seizure severity based on patient responses.

- General physical and neurological Examination
  - To be performed by the study physician at each visit

- Vital Signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- Columbia Suicide Severity Rating Scale (C-SSRS)Questionnaire
- Child Behavioral Checklist for participants between ages 1-18 years old
- Seizure Diary Training for patient with the study staff
- Menstrual History collected by study staff

Study Visit 1/Day 0 :

This visit may be combined with the Enrollment Visit. It must occur within 30 days of the enrollment visit.

Procedures for Study Visit 1 include:

- Seizure Calendar or Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Adverse event and serious adverse event monitoring (e.g.,increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Chalfont Seizure Severity Scale
- General physical and neurological Examination
  - To be performed by the study physician at each visit
- Vital Signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Complete Blood Count (CBC), and Comprehensive Metabolic Panel (CMP)
- Electrocardiogram (ECG) and Urinary Analysis (UA) collected by the study staff (completed as needed throughout the protocol)
- AED levels
- Urine Pregnancy Test (only for women of child bearing potential)
- Columbia-Suicide Severity Rating Scale (C-SSRS) Questionnaire
- Child Behavioral Checklist for participants between ages 1-18 years old

- Pediatric Cognitive performance testing (NIH Toolbox; performed at study visit 1 and annually) – NIH Toolbox is a multidimensional set of royalty-free measures that researchers can use to assess cognitive, sensory, motor and emotional function in people ages 3-85. This suite of measures can be administered to study participants in two hours or less, across diverse study designs and settings. The measures have been normed and validated in a broad sample of the U.S. population. For this study, the Cognitive subtests from the NIH Toolbox will be administered. These tests are designed to have a wide range of utility with people with varying levels of cognitive capacity, but for those participants who are unable to complete the cognitive tests from the NIH Toolbox, parent-report measures pertaining to functional adaptive status will be administered.

For participants ages 3-6, these measures from the NIH Toolbox include:

- NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility
- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary
- NIH Toolbox Oral Reading Recognition Test (for children who have developed letter and/or word recognition skills)

For participants ages 7-18, these measures from the NIH Toolbox include:

- NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility
- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary Test – vocabulary knowledge
- NIH Toolbox Oral Reading Recognition Test - reading
- NIH Toolbox List Sorting Working Memory Test – working memory
- NIH Toolbox Pattern Comparison Processing Speed Test – speed of processing

For participants who are unable, due to cognitive impairment, to complete the Cognitive subtests from the NIH Toolbox, their legal guardian will be asked to complete the Adaptive Behavior Assessment Scale – II (ABAS-II). The ABAS-II measures adaptive behavior, using parent-report to evaluate function across a variety of environments. Test results include four domain composite scores (Conceptual, Social, Practical, and General Adaptive Composite) and 10 skill area scores (Communication, Community Use, Functional Academics, Health and Safety, Home or School Living, Leisure, Self-Care, Self-Direction, Social, and Work/Motor).

For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Functional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Toolbox Cognitive assessments.

- Quality of Life in Childhood Epilepsy Questionnaire– QOLCE is composed of 16 subscales assessing seven domains of HRQL (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life)
- Adverse events profile (AEP) – Pediatric equivalent is a systematic screening instrument with a brief 19-item self-report format. The AEP is used to assess adverse effects of AEDs and improve subjective health status.
- NIH Toolbox for Emotional Assessment: Emotion Measures from the NIH Toolbox will be administered to each participant and/or their legal guardian. The Emotion Measures from the NIH Toolbox assess four major domains: Negative Affect (NA), Psychological Well-Being (PWB), Social Relationships (SR), and Stress/Self-Efficacy (SSE).

For participants ages 3 – 7, the following age-appropriate subtests from the NIH Toolbox Emotion Parent Proxy Battery will be administered:

- Negative Affect
  - NIH TB NA Anger – Parent Report
  - NIH TB NA Fear-Over Anxious Parent Report for Children
  - NIH TB NA Fear-Separation Anxiety Parent Report FFSF
  - NIH TB NA Sadness Parent Report FFSF for Children
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction Parent Report SF-FF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Empathic Behaviors Parent Report CAT
  - NIH TB SR Peer Rejection Parent Report FFSF
  - NIH TB SR Positive Peer Interaction Parent Report FFSF
  - NIH TB SR Social Withdrawal Parent Report FF-SF

For participants ages 8 – 12, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger-SF
  - NIH TB NA Fear SF
  - NIH TB NA Sadness SF
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction SF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships

    - NIH TB SR Emotional Support SF
    - NIH TB SR Friendship SF
    - NIH TB SR Loneliness SF
    - NIH TB SR Perceived Hostility SF
    - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
    - NIH TB SSE Self-Efficacy CAT

Additionally, legal guardians of participants ages 8-12 will complete the following Emotion Parent Proxy Battery subtests:

- Negative Affect
    - NIH TB NA Anger-Parent report CAT
    - NIH TB NA Fear Parent Report CAT
    - NIH TB NA Sadness Parent Report CAT
- Psychological Well-Being
    - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
    - NIH TB SR Empathic Behaviors Parent Report CAT
    - NIH TB SR Peer Rejection Parent Report FFSF
    - NIH TB SR Positive Peer Interactions Parent Report FFSF
    - NIH TB SR Social Withdrawal Parent Report FF-SF
- Stress & Self Efficacy
    - NIH TB SSE Perceived stress-Parent report
    - NIH TB SSE Self-Efficacy Parent report CAT

For participants ages 13 – 17, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
    - NIH TB NA Anger-SF
    - NIH TB NA Fear SF
    - NIH TB NA Sadness SF
- Psychological Well-Being
    - NIH TB PWB General Life Satisfaction CAT
    - NIH TB PWB Positive Affect CAT
- Social Relationships
    - NIH TB SR Emotional Support SF
    - NIH TB SR Friendship SF
    - NIH TB SR Loneliness SF
    - NIH TB SR Perceived Hostility SF
    - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
    - NIH TB SSE Perceived Stress CAT
    - NIH TB SSE Self-Efficacy CAT

For participants age 18, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger Hostility SF
  - NIH TB NA Anger Physical Aggression SF
  - NIH TB NA Anger-CAT
  - NIH TB NA Fear-Affect CAT
  - NIH TB NA FEAR-Somatic Arousal SF
  - NIH TB NA Sadness CAT
- Psychological Well-Being
  - NIH TB PWB Meaning and Purpose CAT
  - NIH TB PWB Positive Affect CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Instrumental Support SF
  - NIH TB SR Loneliness SF
  - NIH TB SR Perceived Hostility SF
  - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
  - NIH TB SSE Perceived Stress CAT
  - NIH TB SSE Self-Efficacy CAT

For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Emotional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Emotional Measures assessments.

- Social Determinants of Health (SDH) – standard social and psychosocial data will be collected per Institute of Medicine recommendations (IOM 2014 "Capturing social and behavioral domains in electronic health records: Phase I"):
  - Biosocial variables (age, date of birth, sex/gender)
  - Socio-demographic variables (race, ethnicity, education, family structure, family income, financial strain, US/non-US born, health insurance status, overall health, health care access/utilization)
  - Psychosocial variables (health literacy, health information sources, social stress, social support, optimism, self-efficacy)
  - Behavioral variables (physical/social activity)
  - Individual-level social relationship domains (exposure to discrimination/violence, self esteem rating, religious participation)
  - Geocodable information (address to identify US census tract/block) to link to neighborhood/community-level published national/state socioeconomic and racial/ethnic composition indicators

– Prior Cannabis Use for Seizure control questions will be asked during the SDH assessment.

Comprehensive SDH data collection will be performed at the onset. Selected socio-demographic, psychosocial, behavioral, social relationship, and geocodable information will be re-assessed at year 1, and annually thereafter.

- Adverse Event and Serious Adverse Event Monitoring
- Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)
- Functional MRI (fMRI; Optional Substudy Procedure only for participants 15 and older)

OPTIONAL Functional MRI (fMRI) Sub-study

Subjects who are enrolled in the CBD study will be offered participation in an optional substudy that includes assessing the effects of CBD on cognition using the neuroimaging procedure, functional MRI (fMRI).

Magnetic resonance imaging (MRI) is a test that uses a magnetic field and pulses of radio wave energy to provide pictures of organs and structures inside the body. The MRI does not include any type of contrast or radioactive contrast agent administered during the procedure. In many cases, MRI provides information that cannot be obtained from an X-ray, ultrasound, or CT scan. Functional MRI (fMRI) is a procedure that has been approved by the FDA. However, the use of the fMRI in this study to assess the effect of CBD on congition is considered investigational. It is similar to the standard MRI with the exception that during this study the subject will be asked to perform certain tasks for example, respond to images of faces or answer math questions. Subjects will wear headphones during the scan and will perform fMRI task to assess working memory function and related activation patterns and another fMRI task to assess attention performance and related activation patterns.

The MRI technologist and/or study coordinator will perform a standard safety screening. He/she will go through a checklist of medical history and safety questions used by the Civitan Functional Neuroimaging Laboratory in routine medical scanning. If subjects are women able to have children, they will have a urine pregnancy test. All study subjects will follow the same treatment/scanning routine.

To be eligible for a participation in the fMRI substudy, subjects will need to be able to cooperate with the neuroimaging procedures and have no contraindications to having fMRI procedure. Specifically, in addition to the main study exclusion criteria listed above, subjects will not be able to participate in the fMRI substudy if they are:

- Pregnant or a positive pregnancy test result on the day of the research session;
- Any contraindication to an MRI scan (i.e., claustrophobia, metal implants, etc);

- Orthodontic braces or permanent orthodontic retainers in both upper and lower teeth; MR images of the brain are generally distorted in patients with braces/retainers particularly at higher magnetic field strengths as proposed in this study;
- Over 300 lbs (weight limit for subjects for the 3T MRI scanner is 300 lbs);
- Mental handicap (FSIQ < 80, if tested) or history of special education and/or not being able to finish high school.

Once a subject qualifies for participation in the fMRI substudy, they will be approached for participation during the consent process at Study Visit 1. The fMRI procedure will take approximately one hour (up to 2 hours with transportation to the imaging center-Civitan International Research Center; CIRC) in addition to the time it takes to complete the main study procedurs and activities. Subjects will be scanned in the research-dedicated MRI magnet in the Civitan Functional Neuroimaging Lab (CFNL) located in the first floor of the CIRC. A high-resolution anatomical scan, resting-state fMRI, and DTI will be acquired. The fMRI procedure will be conducted prior to the start of CBD treatment at Study Visit 1 and again within 1 week after the maximal dose of CBD has been achieved (estimated to be at Study Visit 6 or 7), for a total of two fMRI scans. Subjects will be offered $100.00 for each visit where an fMRI procedure is performed (in addition to the compensation provided for participation in the main study).

Phone Visit 1/Day 7 (+/-1 day) :

After subject has completed Day 0 through Day 6 (+/-2 days) of CBD medication, the following will be accessed via phone visit 1 with study staff.

- Adverse event and Severe adverse event monitoring/reporting (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure frequency and severity data collected using participant monthly seizure diary, and the Chalfont Seizure Severity Scale.

Study Visit 2/Day 14/Wk 2 (+/-3 days) and Study Visit 3/Day 28/Wk 4 (+/- 3 days), Study Visit 4/Day 42/Wk 6 (+/- 3 days):

Procedures for this visit include:

- Adverse Event and Serious Adverse Event Monitoring(e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Physical and Neurological Examination
- CBC and CMP (collected at Study Visit 3/Day 28/Wk 4 only); Study doctor mayorder additional laboratory testing (blood and/or urine tests) and/or more

frequent testing to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels,
- Urine Pregnancy Test (only for women of child bearing potential)
- AEP Questionnaire
- Columbia-Suicide Severity Rating Scale (C-SSRS) Questionnaire
- Conditional Procedure: EEG– an video EEG (30-60 minutes recording) will only be performed at the first follow up study visit where the participant reaches their target dose of CBD, as judged by the clinician. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.
- Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)

Phone Visit 2/Day 21 (+/-1 day) :

After subject has completed Day 15 through Day 20 (+/-2 days) of CBD medication, the following will be accessed via phone visit 2 with study staff.
- Adverse event and Severe adverse event monitoring/reporting (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure frequency and severity data collected using participant monthly seizure diary, and the Chalfont Seizure Severity Scale.

Phone Visit 3/Day 35 (+/-1 day):
After subject has completed Day 29 through Day 35 (+/-2 days) of CBD medication, the following will be accessed via phone visit 3 with study staff.
- Adverse event and Severe adverse event monitoring/reporting (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure frequency and severity data collected using participant monthly seizure diary, and the Chalfont Seizure Severity Scale.

Phone Visit 4/Day 49 (+/-1 day) :

After subject has completed Day 42 through Day 49 (+/-2 days) of CBD medication, the following will be accessed via phone visit with study staff.
- Adverse event and Severe adverse event monitoring/reporting (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure frequency and severity data collected using participant monthly seizure diary, and the Chalfont Seizure Severity Scale.

Phone Visit 5/Day63 (+/-1 day) :

After subject has completed Day 56 through Day 63 (+/-2 days) of CBD medication, the following will be accessed via phone visit 5 with study staff.

- Adverse event and Severe adverse event monitoring/reporting (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure frequency and severity data collected using participant monthly seizure diary, and the Chalfont Seizure Severity Scale.

Study Visit 5/Day 56/Wk 8 (+/- 3 days) and Study Visit 6/Day70/Wk 10 (+/- 3 days):

Procedures for this visit will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- CBC and CMP (performed at V5/Day 56/Wk 8 only); Study doctor mayorder additional laboratory testing (blood and/or urine tests) and/or more frequent testing to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels,
- Physical and Neurological Examination
- AEP Questionnaire
- Columbia-Suicide Severity Rating Scale (C-SSRS) Questionnaire
- Conditional Procedure: EEG– a video EEG (30-60 minutes recording) will only be performed at the first follow up study visit where the participant reaches their target dose of CBD, as judged by the clinician. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.
- Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)

****If patient reaches target dose prior to or after Study Visit 6, patient will have additional in-person study visit 28 days (+/- 3days) after target dose is reached. The procedures performed and information collected at the additional study visit will be the same procedures collected at Study Visit 7. However, it could be that some patients reach target dose before or after Study Visit 7. Regardless, the second fMRI will be performed at the first follow-up study visit where target dose has been reached.**

In some cases, where both PIs agree to increase the dose above 25 mg/kg/day but not higer than 50 mg/kg/day increases by 5 mg/kg/day will be made with f/u visits every

2 weeks until a maintainance dose of CBD is determined. The protocol visits will be adjusted in accordance to the titration of the CBD dosing. Once the m,aintance dose is determined the subject will be seen for a follow up vist in 28 days (4 weeks) and continue on the outlined study protocol visit schedule.

Standard assessments will be conducted on those days including

- Information on any adverse event or severe adverse events since your last visit will be collected.
- Seizure Diary information reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale Assessment: Questionnaire/scale used to determine how severe your seizures are based on your responses to questions.
- Vital signs (including age, weight, height, heart rate, blood pressure, and temperature)
- Physical and Neurological Examination performed by study physician
- The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels,
- Urine Preganancy Test (only for females who are able to become pregnant)
- AEP Questionnaire
- Columbia-Suicide Severity Rating Scale: Questionnaire about suicide risk
- POMS Questionnaire
- CBD Medication Order dispensed with dosing schedule
- Functional MRI (fMRI; Optional Substudy Procedure only)

STUDY VISIT 7/Day 84(+/- 3 days) or Follow up study visit after target dose is reached:

Procedures for this visit will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- CBC and CMP; (Study doctor mayorder additional laboratory testing (blood and/or urine tests) to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels),
- Physical and Neurological Examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Child Behavioral Checklist for participants between ages 6-18 years old

- AEP Questionnaire
- Conditional Procedure: EEG– a video EEG (30-60 minutes recording) will only be performed at the first follow up study visit where the participant reaches their target dose of CBD, as judged by the clinician. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.
- Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)

Study Visit 10/Day168/Wk24/Month 6(+/- 7 days), Visit 14/Day504/Wk 96/ Month 24 (+/- 7 days), V18/Day 840/Wk 192/ Month 48 (+/- 7 days):

Procedures for these visits will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- Physical and Neurological Examination
- CBC andCMP; Study doctor mayorder additional laboratory testing (blood and/or urine tests) to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels,
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Child Behavioral Checklist for participants between ages 6-18 years old
- AEP Questionnaire
- NIH Toolbox for Emotional Assessment**: Emotion Measures from the NIH Toolbox will be administered to each participant and/or their legal guardian. The Emotion Measures from the NIH Toolbox assess four major domains: Negative Affect (NA), Psychological Well-Being (PWB), Social Relationships (SR), and Stress/Self-Efficacy (SSE). ****Performed at Study Visit 10/Day168/Wk24/Month 6 only****

For participants ages 3 – 7, the following age-appropriate subtests from the NIH Toolbox Emotion Parent Proxy Battery will be administered:

- Negative Affect
  - NIH TB NA Anger – Parent Report
  - NIH TB NA Fear-Over Anxious Parent Report for Children
  - NIH TB NA Fear-Separation Anxiety Parent Report FFSF
  - NIH TB NA Sadness Parent Report FFSF for Children

- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction Parent Report SF-FF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Empathic Behaviors Parent Report CAT
  - NIH TB SR Peer Rejection Parent Report FFSF
  - NIH TB SR Positive Peer Interaction Parent Report FFSF
  - NIH TB SR Social Withdrawal Parent Report FF-SF

For participants ages 8 – 12, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger-SF
  - NIH TB NA Fear SF
  - NIH TB NA Sadness SF
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction SF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Loneliness SF
  - NIH TB SR Perceived Hostility SF
  - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
  - NIH TB SSE Self-Efficacy CAT

Additionally, legal guardians of participants ages 8-12 will complete the following Emotion Parent Proxy Battery subtests:

- Negative Affect
  - NIH TB NA Anger-Parent report CAT
  - NIH TB NA Fear Parent Report CAT
  - NIH TB NA Sadness Parent Report CAT
- Psychological Well-Being
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Empathic Behaviors Parent Report CAT
  - NIH TB SR Peer Rejection Parent Report FFSF
  - NIH TB SR Positive Peer Interactions Parent Report FFSF
  - NIH TB SR Social Withdrawal Parent Report FF-SF
- Stress & Self Efficacy
  - NIH TB SSE Perceived stress-Parent report
  - NIH TB SSE Self-Efficacy Parent report CAT

For participants ages 13 – 17, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger-SF
  - NIH TB NA Fear SF
  - NIH TB NA Sadness SF
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction CAT
  - NIH TB PWB Positive Affect CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Loneliness SF
  - NIH TB SR Perceived Hostility SF
  - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
  - NIH TB SSE Perceived Stress CAT
  - NIH TB SSE Self-Efficacy CAT

For participants age 18, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger Hostility SF
  - NIH TB NA Anger Physical Aggression SF
  - NIH TB NA Anger-CAT
  - NIH TB NA Fear-Affect CAT
  - NIH TB NA FEAR-Somatic Arousal SF
  - NIH TB NA Sadness CAT
- Psychological Well-Being
  - NIH TB PWB Meaning and Purpose CAT
  - NIH TB PWB Positive Affect CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Instrumental Support SF
  - NIH TB SR Loneliness SF
  - NIH TB SR Perceived Hostility SF
  - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
  - NIH TB SSE Perceived Stress CAT
  - NIH TB SSE Self-Efficacy CAT

For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Emotional Assessments will be

completed by the parent or LAR of the participant, instead of the NIH Emotional Measures assessments.

- Quality of Life in Childhood Epilepsy Questionnaire – QOLCE is composed of 16 subscales assessing seven domains of HRQL (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life)
- Conditional Procedure: EEG– a video EEG (30-60 minutes recording) will only be performed at the first follow up study visit where the participant reaches their target dose of CBD, as judged by the clinician. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.
- Pediatric Cognitive performance testing (NIH Toolbox; performed at study visit 1 and annually) – NIH Toolbox is a multidimensional set of royalty-free measures that researchers can use to assess cognitive, sensory, motor and emotional function in people ages 3-85. This suite of measures can be administered to study participants in two hours or less, across diverse study designs and settings. The measures have been normed and validated in a broad sample of the U.S. population. Only the Cognition Domain measures from the NIH Toolbox will be utilized in this study limiting the duration of the testing to less than 1 hour.

For participants ages 3-6, these measures include:

- NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility
- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary
- NIH Toolbox Oral Reading Recognition Test (for children who have developed letter and/or word recognition skills)

For participants ages 7-18, these measures include:

- NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility
- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary Test – vocabulary knowledge
- NIH Toolbox Oral Reading Recognition Test - reading
- NIH Toolbox List Sorting Working Memory Test – working memory
- NIH Toolbox Pattern Comparison Processing Speed Test – speed of processing

For participants who are unable, due to cognitive impairment, to complete the Cognitive subtests from the NIH Toolbox, their legal guardian will be asked to complete the Adaptive Behavior Assessment Scale – II (ABAS-II). The ABAS-II measures adaptive behavior, using parent-report to evaluate function across a variety of environments. Test results include four domain composite scores (Conceptual, Social, Practical, and General Adaptive Composite) and 10 skill area scores (Communication, Community Use, Functional Academics, Health and Safety, Home or School Living, Leisure, Self-Care, Self-Direction, Social, and Work/Motor).

- For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Functional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Toolbox Cognitive assessments.

- Social Determinants of Health (SDH) – selected SDH variables will be re-assesed at year 1and annually thereafter:
  - Biosocial variables (age, date of birth)
  - Socio-demographic variables (education, family structure, family income, financial strain, health insurance status, overall health, health care access/utilization)
  - Psychosocial variables (health literacy, health information sources, social stress, social support, optimism, self-efficacy)
  - Behavioral variables (physical/social activity)
  - Individual-level social relationship domains (exposure to discrimination/violence, self esteem rating, religious participation)
  - Geocodable information (address to identify US census tract/block) to link to neighborhood/community-level published national/state socioeconomic and racial/ethnic composition indicators
  - Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)

Subsequent Visits: Study Visit 8/Day 112/Wk 16/Month 4 (+/- 7 days), Study Visit 9/Day140/Wk 20/Month 5 (+/- 7 days), Study Visit 11/Day 252/Wk 36/ Month 9 (+/- 7 days), Study Visit 12/Day 336/Wk 48/ Month 12, Study Visit 13/Day420/Wk72/ Month 18, Study Visit 15/Day 588/Wk 120/ Month30, Study Visit 16/Day 672/Wk 144/Month 36, Study Visit 17/Day 756/Wk 168/ Month 42:

Procedures for these visits will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)

- CBC and CMP (collected at SV8, SV9, SV12, SV16 only); Study doctor mayorder additional laboratory testing (blood and/or urine tests) and/or more frequent testing to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels,
- Physical and Neurological Examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- AEP Questionnaire
- NIH Toolbox for Emotional Assessment**: Emotion Measures from the NIH Toolbox will be administered to each participant and/or their legal guardian. The Emotion Measures from the NIH Toolbox assess four major domains: Negative Affect (NA), Psychological Well-Being (PWB), Social Relationships (SR), and Stress/Self-Efficacy (SSE). ****Performed at Study Visit 12/Day336/Wk48/Month 12 only****

For participants ages 3 – 7, the following age-appropriate subtests from the NIH Toolbox Emotion Parent Proxy Battery will be administered:

- Negative Affect
  - NIH TB NA Anger – Parent Report
  - NIH TB NA Fear-Over Anxious Parent Report for Children
  - NIH TB NA Fear-Separation Anxiety Parent Report FFSF
  - NIH TB NA Sadness Parent Report FFSF for Children
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction Parent Report SF-FF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Empathic Behaviors Parent Report CAT
  - NIH TB SR Peer Rejection Parent Report FFSF
  - NIH TB SR Positive Peer Interaction Parent Report FFSF
  - NIH TB SR Social Withdrawal Parent Report FF-SF

For participants ages 8 – 12, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger-SF
  - NIH TB NA Fear SF
  - NIH TB NA Sadness SF
- Psychological Well-Being
  - NIH TB PWB General Life Satisfaction SF
  - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Loneliness SF

    - NIH TB SR Perceived Hostility SF
    - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
    - NIH TB SSE Self-Efficacy CAT

Additionally, legal guardians of participants ages 8-12 will complete the following Emotion Parent Proxy Battery subtests:

- Negative Affect
    - NIH TB NA Anger-Parent report CAT
    - NIH TB NA Fear Parent Report CAT
    - NIH TB NA Sadness Parent Report CAT
- Psychological Well-Being
    - NIH TB PWB Positive Affect Parent Report CAT
- Social Relationships
    - NIH TB SR Empathic Behaviors Parent Report CAT
    - NIH TB SR Peer Rejection Parent Report FFSF
    - NIH TB SR Positive Peer Interactions Parent Report FFSF
    - NIH TB SR Social Withdrawal Parent Report FF-SF
- Stress & Self Efficacy
    - NIH TB SSE Perceived stress-Parent report
    - NIH TB SSE Self-Efficacy Parent report CAT

For participants ages 13 – 17, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
    - NIH TB NA Anger-SF
    - NIH TB NA Fear SF
    - NIH TB NA Sadness SF
- Psychological Well-Being
    - NIH TB PWB General Life Satisfaction CAT
    - NIH TB PWB Positive Affect CAT
- Social Relationships
    - NIH TB SR Emotional Support SF
    - NIH TB SR Friendship SF
    - NIH TB SR Loneliness SF
    - NIH TB SR Perceived Hostility SF
    - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
    - NIH TB SSE Perceived Stress CAT
    - NIH TB SSE Self-Efficacy CAT

For participants age 18, the following age-appropriate subtests from the NIH Toolbox self-report Emotion Battery will be administered:

- Negative Affect
  - NIH TB NA Anger Hostility SF
  - NIH TB NA Anger Physical Aggression SF
  - NIH TB NA Anger-CAT
  - NIH TB NA Fear-Affect CAT
  - NIH TB NA FEAR-Somatic Arousal SF
  - NIH TB NA Sadness CAT
- Psychological Well-Being
  - NIH TB PWB Meaning and Purpose CAT
  - NIH TB PWB Positive Affect CAT
- Social Relationships
  - NIH TB SR Emotional Support SF
  - NIH TB SR Friendship SF
  - NIH TB SR Instrumental Support SF
  - NIH TB SR Loneliness SF
  - NIH TB SR Perceived Hostility SF
  - NIH TB SR Perceived Rejection SF
- Stress & Self Efficacy
  - NIH TB SSE Perceived Stress CAT
  - NIH TB SSE Self-Efficacy CAT

For participants < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Emotional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Emotional Measures assessments.

- Conditional Procedure: EEG– a video EEG (30-60 minutes recording) will only be performed at the first follow up study visit where the participant reaches their target dose of CBD, as judged by the clinician. At the discretion of the investigator, an additional EEG may be performed at follow up visits, depending on clinical course.

- Study Drug CBD Medication Order and/or adjustments in CBD dosing (as described under Dosing Adjustment/Schedule section above)

Unscheduled Study Visit:

Unscheduled study visit(s) will be performed when deemed necessary by the study physician. Indication for such visit will include e.g., side effects, increase in seizures, request to discontinue CBD treatment, etc.

Procedures for these visits will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)

- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- Neurological Examination
- Columbia-Suicide Severity Rating Scale (C-SSRS) Questionnaire
- CBC and CMP (Study doctor mayorder additional laboratory testing (blood and/or urine tests) to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels),AEP
- Study Drug CBD Medication Order and/or adjustments in CBD dosing (if needed)

- Individualized decision will be made by the managing study physician regarding further participation, AED medication titration (up or down), CBD medication adjustment/wean, etc. If the patient and provider agree on terminating participation prior to 1 year visit, the following data points will be collected at that early termination visit:

  - Video EEG (30-60 minute recording)
  - ECG
  - Study doctor may order laboratory testing (blood and/or urine tests) to assess for side effects and toxicity. The laboratory assessments would include: CMP,CBC, Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels),
  - Child Behavioral Checklist for participants between ages 6-18 years old Quality of Life in Childhood Epilepsy Questionnaire – QOLCE is composed of 16 subscales assessing seven domains of HRQL (physical function, social function, emotional well-being, cognition, behavior, general health and general quality of life)
  - Pediatric Cognitive performance testing (NIH Toolbox; <u>performed at study visit 1 and annually</u>) – NIH Toolbox is a multidimensional set of royalty-free measures that researchers can use to assess cognitive, sensory, motor and emotional function in people ages 3-85. This suite of measures can be administered to study participants in two hours or less, across diverse study designs and settings. The measures have been normed and validated in a broad sample of the U.S. population. Only the Cognition Domain measures from the NIH Toolbox will be utilized in this study limiting the duration of the testing to less than 1 hour.

For participants ages 3-6, these measures include:

  - NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility

- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary
- NIH Toolbox Oral Reading Recognition Test (for children who have developed letter and/or word recognition skills)

For participants ages 7-18, these measures include:

- NIH Toolbox Dimensional Change Card Sort Test (DCCS) – cognitive flexibility
- NIH Toolbox Flanker Inhibitory Control and Attention Test – attention and inhibitory control
- NIH Toolbox Picture Sequence Memory Test – episodic memory
- NIH Toolbox Picture Vocabulary Test – vocabulary knowledge
- NIH Toolbox Oral Reading Recognition Test - reading
- NIH Toolbox List Sorting Working Memory Test – working memory
- NIH Toolbox Pattern Comparison Processing Speed Test – speed of processing

- For participants who are unable, due to cognitive impairment, to complete the Cognitive subtests from the NIH Toolbox, their legal guardian will be asked to complete the Adaptive Behavior Assessment Scale – II (ABAS-II). The ABAS-II measures adaptive behavior, using parent-report to evaluate function across a variety of environments. Test results include four domain composite scores (Conceptual, Social, Practical, and General Adaptive Composite) and 10 skill area scores (Communication, Community Use, Functional Academics, Health and Safety, Home or School Living, Leisure, Self-Care, Self-Direction, Social, and Work/Motor).

- For participants who are < 3 years of age, Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)-Functional Assessments will be completed by the parent or LAR of the participant, instead of the NIH Toolbox Cognitive Assessments.

- Social Determinants of Health (SDH) – Comprehsensive SDH information will be collected at the onset. Selected SDH variables may be re-assesed and includes:
    - Biosocial variables (age, date of birth)
    - Socio-demographic variables (education, family structure, family income, financial strain, health insurance status, overall health, health care access/utilization)
    - Psychosocial variables (health literacy, health information sources, social stress, social support, optimism, self-efficacy)
    - Behavioral variables (physical/social activity)
    - Individual-level social relationship domains (exposure to discrimination/violence, self esteem rating, religious participation)

- Geocodable information (address to identify US census tract/block) to link to neighborhood/community-level published national/state socioeconomic and racial/ethnic composition indicators

Post-Termination Study Visit (approximately 28 days after end of CBD study):

Procedures for this visit will include:

- Adverse Event and Serious Adverse Event Monitoring (e.g., increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization)
- Seizure Diary Data reviewed and collected by study staff
- Menstrual History collected by study staff
- Chalfont Seizure Severity Scale
- Vital signs: Age, Weight, Height, Heart Rate, and Blood Pressure, Temperature
- Urine Pregnancy Test (only for women of child bearing potential)
- Neurological Examination
- C-SSRS (Columbia Suicidality Symptom Rating Scale Questionnaire
- CBCand CMP; (Study doctor mayorder additional laboratory testing (blood and/or urine tests) to assess for side effects and toxicity. The laboratory assessments would include: Liver Functional Tests (LFTs), Urinary Analysis and any anti-epileptic drug (AED) levels),
- ECG
- AEP Questionnaire

Information collected for the NIH Cognitive and Emotional measures are collected via laptop. The assessments are performed electronically by the participant and/or parent/LAR. A brief description of each test and a link to a preview of each test is included in the Appendix A document associated with this protocol.

ABAS-II and Bayley Scales of Infant and Toddler Development assessments are performed manually.

Patient will be in the study for approximately three years.

Any abnormal laboratory results collected during the course of this study will be reported to the patient's referring neurologist for treatment and/or follow-up.

Safety Data:

Adverse Events :

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for

example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All treatment emergent AEs will be recorded on source documents (i.e. original documents, data, and records). AEs include those reported spontaneously by the subject and those noted incidentally or as observed by the investigator or study personnel. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded using standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together and recorded as a single AE (e.g. cough and rhinitis should be reported as an "upper respiratory tract infection").

Baseline conditions at study entry will be documented during screening/baseline medical history.

Adverse Events (AEs) for this study are defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition (s) that may occur after the patient's signed the informed consent for the study. Abnormal laboratory values or test results occurring after the informed consent is signed constitutes adverse events only if they induce clinical signs or symptoms, are clinically significant, require therapy, or changes in study medication(s).

AEs that begin or worsen after the informed consent should be recorded in the Adverse Event CRF and will be entered in the UAB CBD data coordinating center database. Conditions that are already present at the time of informed consent will be documented as part of the patient's medical history. Subjects and their families will be provided with contact information in order to notify study personnel of any adverse events, with availability at all times. Upon notification of an AE, a determination will be made by study personnel with regard to whether the AE is study related. This determination will be made within 24 hours of receipt of documentation of the AE. If the AE has involved participation of any other medical personnel or facilities, documentation of that activity will be obtained by study personnel for review. The AE will be monitored until it has resolved by the study investigator. AEs will be assessed to determine the following parameters: severity, duration, relationship to the CBD administration, action taken or treatment instituted, and whether the AE meets the criteria for a serious AE. Adverse Events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE).

All clinically significant abnormalities noted upon physical examination, or other diagnostic test results should be reported as an AE, except for baseline measurements that may be considered part of the medical history. In addition, all clinically significant AEs that continue at Study Termination should be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolved, or is determined to have resolved with sequelae. All AEs will be evaluated for

intensity and causal relationship with use of the study medication (or study procedures if applicable) by the investigator.

AEs that occur following completion of study termination/early termination procedures should be recorded on the AE page of the source documents only if the investigator considers the event as clinically significant and as related to study medication or study procedures.

All adverse events that are deemed to be serious and meet the definitions provided in section below for serious adverse events will be reported as SAEs.

Serious Adverse Events :

Serious adverse event is defined as "ANY TREATMENT EMERGENT SAE THAT OCCURS AFTER THE SIGNING OF THE INFORMED CONSENT FORM through 30 DAYS after administration of the last dose of study medication. Any AE that results in any of the following outcomes will be considered an SAE. The following outcomes are defined according to Code of Federal Regulations (CFR) Title 21 part 312.32.

- Death
- Life-threatening situation (subject was at risk of death at the time of the event. This does not refer to an event that might have caused death if it was of greater intensity.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment), e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe pain); the event itself, however, may be of relatively minor medical significance (such as severe headache). By contrast, the term "serious" is used to describe an event based on an event outcome or actions usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If the adverse event meets the criteria of an SAE, it should be reported as soon as possible, within 24 hours of the event. The study personnel should enter this information into the UAB study database. Each study investigator should also report these related SAEs to one of the co-directors of the UAB CBD program, UAB IRB, and GW Pharmaceuticals.

Any severe and unexpected SAE's will be reported to the Food and Drug Administration agency.

Data Safety Monitoring Board (DSMB):

Study **Data Safety Monitoring Board (DSMB)** will be established:

A Data Safety Monitoring Board has been established for monitoring to detect risks and monitor safety. The DSMB will meet after enrolling the first 12 subjects but not later than 6 months after the initiation of the study (whichever comes first). DSMB will then meet every 6 months until the last visit has been completed. Last DSMB meeting will be after the last subject exits the study and final statistical analyses are available. Meetings will be either in person or via e-mail as determined by the DSMB Chair. While DSMB will periodically review all study data, incidence of severe adverse events will be monitored for the purpose of study participation continuation/discontinuation. If more than 25% of participating subjects have severe adverse events (SAEs), deemed to be drug related, indicating an unfavorable benefit-to-risk profile, the study will be terminated.

Once the study staff receives documentation of an SAE, including death and regardless of causality, the information will be forwarded to the Principle Investigator, DSMB Chairperson, and the Program Manager. These persons will assure that the documented SAE information is sent, within 24 hours of receipt, electronically and securely to the other DSMB members for review.

At each DSMB meeting, the board will evaluate whether there are significant issues pertaining to study design, conduct, or safety results that warrant a recommendation to the principal investigator. The DSMB may make a recommendation regarding any aspect of the conduct or design of the study, including early termination. After each planned meeting, the DSMB Chairperson will communicate recommendations to the principal investigator in a timely fashion following the close of the DSMB meeting.

DSMB recommendations will be communicated to the principal investigator in writing. The DSMB is expected to make its recommendations based on its best judgment, drawing on its clinical and biostatistical expertise and experience, and taking into account all available sources of information, including other studies if available and the totality of the data reviewed.

In the case of recommendations for early trial termination or modification of trial protocol from the DSMB, the principal investigator and study team will thoughtfully review and consider the DSMB recommendations and will communicate its decisions to the DSMB in writing.

In the event that the Principal Investigator, Martina Bebin, decides to prematurely terminate the study, it is the Principal Investigator's responsibility to promptly inform sub-investigators and other study staff, relevant regulatory authorities, GW Pharma, and the DSMB.

The principal investigator will be responsible for reporting SAE, AEs and unanticipated problems involving risks to subjects to their local IRBs/ethics committees (ECs) in accordance with local regulations, and any other regulatory agencies that require SAE/AE reporting. All deaths, regardless of presumed causality, unexpected fatal, or life threatening unexpected/suspected adverse reactions will be reported, as required, to the IND and the Division of Neurology Products at the FDA, as IND safety reports.

No special procedures, precautions or follow-up, except for an early termination visit, will occur with currently enrolled participants if the study is stopped. Subjects will be advised to continue treatment with their primary treating neurologist. Subjects will receive standard of care from their primary treatment team regardless.

The study team excludes pregnant women and does testing to minimize the risk of enrolling these women. Further, patients who are women of childbearing potential and male patients with partners of childbearing potential are informed that they should use an effective form of birth control during study participation to avoid any study drug effects on the fetus.

It is important to know that long-term use of CBD has not been studied in any patients with seizures/epilepsy. The risks to younger children, when considering growth and development, from long-term CBD exposure are unknown at this time. Also, there is no specific information available about use of CBD in patients with kidney or liver problems/failure. The study includes frequent visits and safety lab assessments to monitor renal and liver function while participants are taking CBD.

GW Pharma will not participate in the analysis of our study data. GW will collect certain data from our study to perform their own analysis.

Members of the DSMB will include:

David G. Standaert, MD, PhD (Chair of the DSMB)
Erica Liebelt, MD
Nita Limdi, Pharm.D.
Brenda Denson, Pharm.D.
Charity Morgan, PhD, Statistician

The DSMB members will not perform any protocol driven activities or procedures.

Data Analysis

The Adult and Pediatric protocols will enroll acombined total of 100 subjects. The data analysis will be split into groups based on age ranges. The groups will be divided as follows: Toddler/Early Childhood (1-5 years of age), Middle Childhood (6-11 years of age), and Early Adolescence (12-18 years of age), and Adults (19+ years of age).

After the 100 subjects have been enrolled and followed for 1 year the following data analysis will be performed:

1. The safety outcome measures will be the Primary Measure and will include:

    a. Severe adverse events (increase in seizure frequency by more than 100% leading to emergency room visit or hospitalization),
    b. Change in resting blood pressure or heart rate by 25% if considered significant by managing neurologist,
    c. Any change in, CBC, CMP, Liver function tests (LFTSs), Urinary Analysis or Antiepileptic drug (AED) levels considered by managing neurologists as clinically significant. Clinically significant will be determined by using the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03. Adverse events categorized as a grade 3 or above will be considered clinically significant. Adverse Events graded 4 or above will be considered severe adverse events (SAE).

The analysis plan is focused on safety. The information on safety will be tabulated as the percent of participants with each safety outcome AE and SAE, or others reported as meaningful as well as the number of occurrences of each AE and SAE. This enables an event rate calculation per exposure time as well as the average number of occurrences per participant with an AE or SAE. In addition, common AEs and SES (>=10%) will be assessed estimating the time to the occurrence of such endpoints to provide clinically meaningful data on what can be expected when in the course of therapy. This will be summarized using Kaplan-Meier survival curve approaches.

When the sample size is 100 (50 patients from the adult protocol and 50 patients from the pediatric protocol), a two-sided 90% confidence interval for a single proportion using the large sample normal approximation will extend 0.049 from the observed proportion for an expected proportion of 0.10; 0.066 when the event rate is 0.20; 0.075 when the event rate is 0.30; 0.081 when the event rate is 0.40 and 0.082 when the event rate is 0.50.

2. The secondary analysis will assess the frequency and severity of seizures outcome measures will include:
    a. Decrease in seizure frequency as measured in total number of seizures per month,
    b. Decrease in seizure severity as measured by the Chalfont Seizure Severity Scale (Duncan & Sander, 1991, JNNP).

The analysis plan for frequency and severity of seizures (secondary outcome) will assess the pattern of change over time. Since the baseline measure is reported at the time of screening there may be some tendency to overestimate the severity in the historically reported interval. This can be examined by comparing the initial study visits improvement versus the pattern of control over time. This will be assessed using

graphic techniques and summary statistics. Repeated measures linear regression models will be used to examine the changes over time using random effects for participant. Various measure of control will be defined (i.e. 10% reduction in seizure frequency, 25%, 50%, etc.) will be used to assess the duration, pattern and durability of control. Measuring the percent of time over the duration of follow up that control is obtained will summarize effectiveness. The variability of control will be assessed once control is achieved to assess the reliability and stability of the control. Subgroups will be examined (i.e. are males different than females in response, younger versus older, etc.)

As an observational study, power is not a relevant parameter. However, when the sample size is 100, a two-sided 90.0% confidence interval for the estimated mean will extend 0.164 standard deviation units from the observed mean, and the confidence interval is based on the large sample z statistic.

Other data that will be collected on all enrolled patients include:

c. EEG (30-60 minute),
d. Pediatric Cognitive performance (NIH Toolbox),
e. Quality of Life in Childhood Epilepsy Questionnaire,
f. Adverse Events Profile,
g. NIH Emotional Assessment,
h. Social Determinants of Health (SDH),
i. Columbia-Suicide Severity Rating Scale (C-SSRS) Questionnaire,
j. Child Behavioral Checklist Assessment.

The analyses of the exploratory data will include descriptive statistics, graphic techniques, and repeated measures random coefficient models using techniques as described above for the frequency and severity of seizures endpoints.

IRB:

The University of Alabama at Birmingham IRB will be utilized for this study.

Publication Strategy:

Standard scientific outlets will be utilized for this purpose. Study results will be presented in part or in its entirety at the Annual Meetings of the American Academy of Neurology, Annual Meetings of the American Epilepsy Society, and Child Neurology Society. Manuscripts resulting from this work will be submitted to high-impact scientific journals e.g., Neurology or Epilepsia.