Official Title of the Study: Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome

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1. Abstract (*provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.)*

We hope to gain an understanding of the utility of pure cannabidiol (CBD) used for the treatment of medically refractory epilepsy in Sturge-Weber syndrome (SWS) in this open-label, safety dose-finding, study. Children living with medically refractory epilepsy urgently need more effective medications. Among children with medically refractory epilepsy, those suffering from early-onset and high seizure burden epilepsies suffer the greatest neurodevelopmental problems, including intellectual disability and autism. SWS typically presents in the first year of life with seizures in children with otherwise fairly normal development. About 50% of cases involving medically refractory seizures either at seizure onset, or loss of seizure control, will occur in childhood. Prolonged and repeated seizures in patients with SWS are frequently associated with new neurologic deficits, loss of developmental milestones, and either neurologic regression or slowing in cognitive development. In addition, seizure activity in SWS patients often leads to the development of brain atrophy, hemiparesis, cognitive impairment, and vision deficits. Recent evidence suggests that CBD has multiple, beneficial, effects in patients (such as those with SWS that undergo neurological deterioration) suffering from medically refractory seizures. We hypothesize that CBD will reduce seizure frequency in children and young adults with SWS and will therefore help stabilize and improve their neurologic status. This trial is part of an expanded access program, available through a partnership with GW Pharmaceutical, which has been sanctioned by the FDA to study the safety and efficacy of Epidiolex (cannabidiol/CBD) in participants with SWS and medically refractory seizures.

2. Objectives *(include all primary and secondary objectives)*

The primary objective of this study is to determine the tolerability and optimal dose of CBD as an adjunct treatment in children and young adults with Sturge-Weber syndrome and drug resistant epilepsy.

3. Background *(briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research*)

Sturge-Weber Syndrome (SWS) consists of a vascular birthmark on the face (capillary malformation), abnormal blood vessels in the eye (choroid hemangioma) and a vascular malformation in the brain (leptomeningial angioma). Focal seizures, episodes of status epilepticus, and abnormal interictal EEG in the first year are associated with the tendency for poor developmental outcome. Early and effective therapy for SWS is crucial because implementing strategies that significantly improve seizure control may improve developmental outcome. Recent evidence suggests a strong correlation between effective management of epilepsy and improved developmental outcome in children. Unfortunately, SWS frequently leads to the onset of drug resistant epilepsy in adulthood and, in some cases, sudden death associated with epilepsy has been reported in SWS patients. Children and adults with other drug resistant epilepsies face similar disease burden and impairments in quality of life compared to those with SWS. Porter and Jacobson of Stanford University surveyed 19 parents to gain insight into the efficacy

of CBD on childhood seizure frequency (unpublished data). The children in this survey ranged in age from 2 to 16 years. Thirteen children suffered from Dravet syndrome, three children suffered from Doose syndrome, and one each suffered from myoclonic astatic epilepsy, Lennox-Gastaut syndrome and idiopathic early-onset epilepsy. The children experienced a variety of seizure types including focal, tonic-clonic, myoclonic, atonic, and infantile spasms. The children had unsuccessfully tried an average of 12 other AEDs before starting CBD-enriched cannabis treatment. To obtain dosage information, parents had their preparations tested at commercial medical cannabis testing facilities. The reported doses of CBD ranged from less than 0.5 mg/kg/day, to 28.6 mg/kg/day. The doses of THC contained within these samples ranged from 0 to 0.8mg/kg/day. Seizure frequency prior to the administration of CBD-enriched cannabis ranged from 2 per week to 250 per day. Sixteen (84%) of the 19 cases reported a reduction in seizure frequency. Two parents reported that their child became seizure-free after more than four months of CBD-enriched cannabis use. Of the remaining 14 participants experiencing a change in seizure frequency, eight responded with a greater than 80% reduction in seizure frequency, three responded with a greater than 50% seizure frequency reduction, and three responded with a greater than 25% seizure frequency reduction. Three participants displayed no change. Twelve parents weaned their child from another AED after starting CBD-enriched cannabis treatment.

Beneficial effects of CBD-enriched cannabis other than reduced seizures included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%) and decreased self-stimulation (6/19, 32%). Negative side effects included drowsiness (7/19, 37%) and fatigue (3/19, 16%). Limitations of this data include lack of control data, lack of randomization, and no blinding associated with open-label use, as well as uncertainty of the dosage in artisanal preparations. However, this survey does lend hope that CBD may be a useful pharmaceutical alternative to existing therapies in drug resistant epilepsy, and sheds light as to what doses are being used experimentally that seem to be tolerated. Our study will extend these previous studies to those with Sturge-Weber syndrome and medically refractory epilepsy and will directly study in a clinical research setting both the benefits and the side effects of a pharmaceutical grade preparation of CBD.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Overview: Investigator Initiated Expanded Access Study in 10 participants with Sturge-Weber syndrome brain involvement, medically refractory seizures and Dr. Comi's participants at the Hunter Nelson Sturge-Weber Center at the Kennedy Krieger Institute

We hope to gain an understanding of the utility of pure CBD use for the treatment of drug resistant epilepsy in Sturge-Weber syndrome in this open-label dose-finding observational study. A baseline seizure frequency will be recorded for each subject in a diary for eight weeks prior to investigational drug initiation and parents/caregivers will document seizures on a daily basis throughout the study period (see seizure log). Investigational drug (CBD) will be administered as an adjunct to all current anti-epileptic drugs. All subjects will, at minimum, be clinically evaluated at screening, baseline, weekly for the first 6 weeks after drug initiation, then 4 weeks and 8 weeks later during the Core Phase. During the Optimization Phase they will be followed every 6-12 weeks (see Study Visits Table for precise timeline).

Method of administration: Cannabidiol oral solution 100 mg/ml will be administered orally. The participants will be treated on an outpatient basis and will not require inpatient hospital admission.

Dose / titration schedule: Initiation of treatment will begin with 2 mg/kg/day given in two divided doses. The dose will be increased by 3 mg/kg/day after seven days and then by 5 mg/kg/day every seven days up to a maximum dose of 25 mg/kg/day given. The dosing schedule will be as follows, as tolerated:

- Start of study : 2 mg/kg/day; subject will be evaluated here
- Week 1: Increase dose by 3 mg/kg/day for total daily dose of 5 mg/kg/day; subject will be evaluated here
- Week 2: Increase dose by 5 mg/kg/day for total daily dose of 10 mg/kg/day; subject will be evaluated here
- Week 3: Increase dose by 5 mg/kg/day for total daily dose of 15 mg/kg/day; subject will be evaluated here
- Week 4: Increase dose by 5 mg/kg/day for total daily dose of 20 mg/kg/day; subject will be evaluated here
- Week 5: Increase dose by 5 mg/kg/day for total daily dose of 25 mg/kg/day; subject will be evaluated here

If a subject responds well to an intermediate dose during the Core Phase, he or she may be maintained at that dose and does not need to complete escalation. Escalation may resume during the Optimization or Extension Phase if there is a temporary increase in seizures. If escalation resumes, the dose will be increased by 5mg/kg/day at each visit up to a maximum of 25mg/kg/day.

The dose of concomitant anti-epileptic drugs will remain unchanged **during the first 14 weeks** of CBD treatment (or until 8 weeks after steady state at final dose), unless symptoms of toxicity and/or significant changes in blood levels are observed.

Measurement of changes in seizures (Routine)
Change in seizure frequency is the primary outcome measure for this pilot trial. All seizure types will be classified before study entry. Seizure frequency for each seizure type will be recorded during a baseline of 8 weeks before administration of CBD. Seizure type, frequency will be monitored during baseline and treatment as recorded in a patient diary (see seizure log). For assessing the efficacy of CBD, the investigator will count the change in the frequency of seizures (i.e., tonic seizures, clonic seizures, tonic-clonic seizures lasting more than 3 seconds, focal motor seizures, focal seizures with impaired consciousness, atonic seizures, myoclonic seizures including myoclonic absences). In addition, parents/caregivers will report the following **secondary outcome measures**:

- Change in average seizure duration by seizure type
- Change in the number of episodes of status epilepticus, defined as convulsive seizure lasting longer than 10 minutes
- Change in the number of uses of rescue medication
- Change in the number of ER visits/ hospitalizations

Laboratory tests and clinical procedures

- Weight, vitals and orthostatics will be monitored at baseline and at each visit. For subjects who are physically unable to complete standing orthostatics, only supine orthostatics will be collected. (Routine care)
- Neuroscores will be assigned at each visit by Dr. Comi as per her clinical routine. Neurologic exam and general physical exam will also be performed at each visit. (Routine care)
- Participants will be asked at each clinic visit about migraine frequency, severity (scale of 1-10) and duration, and any change in neurologic symptoms
- CBC, LFT, BUN, creatinine levels, electrolytes, will be measured at baseline, one month after baseline, one month and two months after maintenance dose steady state is reached, every 2-3 months during the Optimization Phase, and every three months (at each visit) during extension phase. Urine analysis will be performed at each of the extension phase visits (every three months).
- For subjects with a facial port-wine birthmark, frontal and profile photograph will be taken under standardized conditions with scoring of the port-wine birthmark for percent of face covered, thickness of birthmark, and darkness of birthmark color. Subjects without any facial port-wine birthmark will only need photographs taken at a single visit to confirm the lack of birthmark. (Research, See Study Visit Table)
- Concomitant AED plasma concentrations will be measured at baseline, one month after baseline, at steady state maintenance CBD dose, one month and two months after maintenance dose steady state is reached, every 2-3 months during the Optimization Phase, and at each extension phase visit.
- CBD plasma concentrations will be measured twice, at 6 and 10 weeks after baseline.
- hCG urine pregnancy test will be used for all female participants Tanner stage 2 and above (see Study Visit Table). We will tell subjects that they must be using effective birth control (for example, abstinence, birth control pills, contraceptive implants, condoms) and confirm that this is the case at each study visit. We will inform female subjects that they should not become pregnant or breastfeed a baby while on this study or for 30 days after taking Cannabidiol. We will also inform male subjects that they should not get their partners pregnant while on this study or for 30 days after taking Cannabidiol. Anyone who becomes pregnant while on the study will be removed immediately.
- Forms generated for use as case report forms will also be used as source documents. Forms will be filled out during the study visit with data. *Immediately* after the visit, the form will be photocopied and one copy will *immediately* have the study subject ID# written on it (case report form). The other copy will *immediately* have the subject name written on it (source document).

b. Study duration and number of study visits required of research participants.

1. **Duration of therapy:** Once optimal dose is found (25 mg/kg/day or maximal tolerated dose; expected to be reached within 5 weeks), participants may continue on the **Core Phase** for a minimum of 8 weeks after reaching steady state; during this time the dose of their other anticonvulsants will not be changed unless signs of toxicity or significant changes in blood levels are observed. This will be followed by 28 weeks of an **Optimization Phase** during which the subject will be followed every 6-12 weeks (see Study Visits for details) and doses of other anticonvulsants may be changed to optimize seizure control. After the Optimization Phase, subjects will be offered the opportunity to enter the **Extension phase** and continue on CBD with clinical follow-up every 3 months. Optimal dosing is proposed by GW Pharm Inc, based upon their preclinical studies and clinical experience to date.

2. **Study Visits:**
   - Study Visit 1: Screening Visit: Informed consent process, eligibility criteria, provide seizure diary and instruct on use.
   - Study Visit 2: Baseline Visit: Confirm eligibility and begin drug at dose 1 (see Visit Table and Dose Schedule). Provide study drug dosing record and instruct on use.

During the following Study Visits (see Visit Table), the participants will undergo clinical assessments, a neuroscore, have pictures taken, blood draws for laboratory tests, study drug accountability, concomitant medication survey, adverse event reporting, and study drug administration (see Visit Table for details).

An additional blood draw will also be necessary within 72 hours of a previous blood draw if the most recent result indicates a clinically significant (>3xULN) elevation of ALT or AST. At minimum, the following tests should be repeated: ALT/AST, total bilirubin, and alkaline phosphatase. A GGT test will also be performed at that time. This bloodwork (ALT/AST, total bilirubin, and alkaline phosphatase and GGT test) will also be necessary if: 1) the dose of your study drug dose is increased after the escalation phase, 2) another drug which affects liver function is added, stopped, or has a dose change, or 3) you have one or more of the following symptoms without another explanation: fatigue, encephalopathy, nausea, vomiting, right upper quadrant pain or tenderness, abdominal pain or distension, fever, excessive bruising, excessive nose or gum bleeds, or petechia. All trial subjects with elevated LFTs will be followed closely until all abnormalities return to the baseline state as assessed by the investigator with AST/ALT < 3x ULN and will be followed until ALT/AST have normalized and symptoms resolve.

At the end of the Core Phase (Visit 10) and Optimization Phase (visit 14), participants will have the option between continuing in an extension study or weaning off of the study drug. Those who decide to continue will remain on the same dosage of medication and return for labs and clinical visits at least every three months or as deemed clinically necessary, and drug will be provided free of cost to the subject for at least one year, or until the drug is approved for clinical use for the treatment of epilepsy in patients with Sturge-Weber syndrome. Those who decide to wean off of the study will return for a final follow-up visit in 1 month (Week 52).

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

During this pilot expanded access study, where the primary objectives are to assess tolerability and dose, blinding is not appropriate. There is no placebo or non-treatment group that would require blinding.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive routine care and will not have to stop any of their current anticonvulsants. They will be clinically managed by Dr. Comi who will respond to side effects or worsening of the participants' care in a manner consistent with the participants' best interest, including the removal of the participant from the trial.

e. Justification for inclusion of a placebo or non-treatment group.

Not applicable for this first small expanded access study.

f. Definition of treatment failure or participant removal criteria.

Treatment failure will be defined as less than a 50% reduction in seizure frequency compared to baseline seizure frequency. Treatment failure will be initially assessed 14 weeks after starting drug (or 8 weeks after reaching steady state) and will be reassessed at every visit thereafter. A subject may continue with only a 30% reduction in seizure frequency if the drug is well tolerated compared to previously tried anticonvulsants. If the subject experiences a temporary increase in seizures at the time treatment failure is assessed, Dr. Comi may take the temporary nature of the increase into account. She may also look at the overall reduction in seizure frequency since treatment initiation in determining whether a subject should be withdrawn. If the subject has had other benefits to mood, behavior, or neurologic exam that outweighed the risk from an increase in seizures, then Dr. Comi may decide to decrease the dose of the study drug since it has been observed that some subjects do well at doses lower than 25mg/kg/day.

Participant removal criteria: If a participant experiences a significant decline in his or her health or wellbeing, the PI will remove the participant from the study. This could include a significant worsening of seizures, or the occurrence of intolerable side effects.

Treatment will continue until any of the following take place:

1. Loss of seizure control defined as an increase of 50% in the average weekly number of seizures for a minimum of 4 weeks as compared to the average weekly number of partial-onset seizures during the 8 weeks baseline period. At this point, the subject's CBD dose can be decreased without requiring immediate withdrawal. The subject does not need to be withdrawn unless the seizure frequency does not drop below the 50% increase on the lowered dose.
2. Use of rescue medications longer than the maximum duration determined during the Baseline period.
3. Intolerable toxicity.
4. Treatment failure as defined above.
5. Pregnancy.
6. Withdrawal of consent.
7. Treatment duration completed as per protocol: completion of the Core phase (if patients do not accept to start the extension phase) or completion of the Extension phase.
8. Laboratory results indicate that the subject's liver function test (ALT or AST) has increased in any of the following ways:
   - >8xULN
   - >5xULN for more than 2 weeks
   - >3xULN **and** either (TBL >2xULN **or** INR >1.5)
   - >3xuLN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

At study's end GW Pharmaceuticals will continue to provide drug to any patient doing well on Epidiolex and wanting to remain on it (extension study), at least until they have obtained an indication for pediatric epilepsy and it can be billed to the patient's insurance company. All others will be weaned off of the study drug over a month and seen back for one final follow-up visit one month later. For those discontinued specifically due to elevated liver function tests, they will continue to be followed until all abnormalities return to the baseline state as assessed by the investigator with AST or ALT <3xULN. Any patient removed early from the study, and all participants at the end of the study wishing to remain

Dr. Comi's patient will continue to be cared for by Dr. Comi and seen at the Hunter Nelson Sturge-Weber Center.

5. Inclusion/Exclusion Criteria

Inclusion criteria: Participants with Sturge-Weber syndrome brain involvement as defined on neuroimaging (n=10 subjects, male and female, ages 1 month to 45 years of age) and the following:

1. Documentation of a diagnosis of drug resistant epilepsy as evidenced by failure to control seizures despite appropriate trial of two or more AEDs at therapeutic doses. **Drug resistant epilepsy for this study is defined as:** At least 1 reported quantifiable (no cluster or innumerable) defined seizure with motor signs per month for at least 3 months prior to initial visit and during the period between Visit 1 (Screening Visit) and Visit 2 (Baseline Visit), as per data captured in daily seizure diaries. These can be focal seizures, focal seizures with impaired consciousness, myoclonic seizures, generalized, and secondarily generalized seizures.
2. Between 1-5 baseline anti-epileptic drugs at stable doses for a minimum of 4 weeks prior to enrollment. Vagus nerve stimulator (VNS), ketogenic diet and modified Atkins diet do not count toward this limit.
3. VNS must be on stable settings for a minimum of 3 months prior to enrollment.
4. If on ketogenic or Atkins diet, must be on stable ratio for a minimum of 3 months prior to enrollment.
5. Previous subjects who failed at any point to meet continuation criteria and withdrew early may be considered for re-enrollment under a new subject ID as long as the above inclusion criteria are met. The determination of whether to re-enroll will be made by the PI and sponsor on a case-by-case basis. Re-enrollment can occur no earlier than 4 weeks after the final, post-weaning follow-up visit under the old subject ID.

Written informed consent obtained from the patient or the patient's legal representative must be obtained prior to beginning treatment.

Exclusion Criteria:

1. Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness.
2. Presence of only non-motor partial seizures (without limb or facial movements, eye deviation or head turning)
3. Patients who require rescue medication during the Baseline Phase for more than 6 days.
4. Patients with any severe and/or uncontrolled medical conditions at randomization such as:
    a. Liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA)
    b. Uncontrolled diabetes as defined by fasting serum glucose > 1.5
    c. Active (acute or chronic) or uncontrolled severe infections
    d. Active, bleeding diathesis
5. Patients who have had a major surgery or significant traumatic injury within 4 weeks of study entry. Patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia), or patients that may require major surgery during the course of the study.

6. Patients who change the dose of the AEDs during 4 weeks before screening or during the baseline period.
7. Prior treatment with any investigational drug or use of any other cannabis product within the preceding 4 weeks prior to study entry.
8. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study. Those in foster care, unable to keep follow-up appointments, maintain close contact with Principal Investigator, or complete all necessary studies to maintain safety.
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Epidiolex is a pharmaceutical grade purified version of cannabidiol which has been extensively studied in many *in vivo* and *in vitro* models. These studies suggest neuroprotective benefit (da Silva VK et al, Molecular Neurobiol, 2014), effects on abnormal angiogenesis (Solinas M et al, British J Pharmacol, 2012), and anti-inflammatory effects (Mecha M et al, Neurobiol Dis, 2013). These effects would be expected to be beneficial in SWS. Furthermore, preclinical (Shirazi-zand Z et al, Epilepsy Behav, 2013; Jones NA et al, Seizure, 2012) and recent anecdotal experience, (Porter BE et al, Epilepsy Behav 2013; see above), demonstrate anti-epileptic effects which require further study in children.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Not applicable.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable.

7. Study Statistics

a. Primary outcome variable.

Seizure frequency

b. Secondary outcome variables.

Neurologic score
Port-wine score
Frequency and severity of side effects
Seizure duration
Number of episodes of status epilepticus, defined as convulsive seizure lasting longer than 10 minutes
Number of uses of rescue medication
Number of ER visits/ hospitalizations

c. Statistical plan including sample size justification and interim data analysis.

Since this is a small Expanded Access study no sample size calculation has been done. The results of this study, if promising, will be used to perform a sample size calculation for follow up studies.

Interim data analysis: Since this is a very small open label study there will not be a formal interim analysis. However, each patient will be assessed at each visit and at phone or email contact and the decision made whether to continue them on study drug.

If three subjects are removed from the study because of side effects or lack of benefit then enrollment (if not already complete) will stop, and those already enrolled will be given the choice to stop taking the drug. If any subject has a major unexpected negative event (serious injury or death) attributable to the drug, this information will be shared with the other subjects who will have the choice to come off the drug and further enrollment will cease.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The medical risks involve the use of Epidiolex which has not been used for the treatment of Sturge-Weber syndrome before. The side effects, which have been previously reported, are generally mild and tolerable. They include: drowsiness, fatigue, conjunctival hemorrhage, change in vision, diarrhea, flatulence, gastric reflux, joint pain, muscle pain, difficulty concentrating, abnormal mood and trouble sleeping. The significance and impact of side effects versus the benefit (if any) needs to be carefully assessed.

There is a time commitment for participants attending the required appointments and maintaining seizure diary/records. The first appointment will take 1.5 hours, with all subsequent visits lasting 1 hour. Participants will also be asked to maintain a seizure diary and study drug dosing record, requiring a maximum time commitment of 5-10 minutes per day.

The only procedures involved are the taking of peripheral blood samples and this is part of the routine care of these participants, as is the history and physical exam used to obtain the neurologic score.

b. Steps taken to minimize the risks.

1. The Principal Investigator, Dr. Anne Comi, will review all data relating to safety and tolerability throughout the study. The subjects will be known to Dr. Comi and the study will benefit from her decade of experience treating participants with Sturge-Weber syndrome as the director of the Hunter Nelson Sturge-Weber Center. We realize that participation in this study is a significant time commitment; therefore we will do our best to schedule at their convenience. Dr. Comi will work closely with GW Pharmaceuticals, and the participants, to both anticipate any possible side effects, and ensure that the side effect is reported, evaluated, and do not inordinately compromise the health of the patient. Any subject experiencing significant side effects or medical concerns during the course of study treatment will be responded to appropriately by Dr. Comi. If the subject is not doing well clinically and the patient, parent or Dr. Comi thinks that it is in the best interest of the subject to stop the study drug, then they will be removed from the study. Subjects will have Dr. Comi's cell phone number, email and office and will be encouraged to contact her directly with any concerns.

2. In order to ensure safe use at higher doses, subjects receiving more than 600 mg of daily CBD will be evaluated at least monthly until they achieve steady state at their final fixed maintenance dose. Once at their maintenance daily dose they will be evaluated one month after achieving the final steady state dose and every three months thereafter.
3. The investigator will be available by telephone or email throughout the entire study.
4. Data on safety and tolerability of pure CBD is limited. According to the GW Pharma CBD Investigator's Brochure side effects reported as greater than placebo with highly purified CBD in one clinical trial were conjunctival hemorrhage, change in vision, diarrhea, flatulence, gastric reflux, joint pain, muscle pain, difficulty concentrating, abnormal mood and trouble sleeping.
5. The participants will be closely monitored for side effects during the titration and treatment period and the dose and/or frequency may be adjusted as appropriate.
6. CBD is an inhibitor of CYP 2C19[6], CYP 2C9[7], and other cytochrome P450s belonging to the 2C and 3A subfamilies[8]. The effects of CBD administered concomitantly with anti-epileptic drugs that are metabolized by this enzyme system are unknown. Plasma levels of CBD and its metabolites will be measured at study visits 8 and 9 (see Visit Table). Concomitant anti-epileptic drug plasma levels will be measured at baseline, at study visits 2, 6, 9, 10, 12, 13, and at all extension phase visits if participating (see Visit Table). Anti-epileptic drug doses will be adjusted as needed based on signs and symptoms of toxicity and / or changes in drug levels (routine care).
7. We realize that participation in this study is a significant time commitment; therefore we will do our best to schedule at their convenience.

c. Plan for reporting unanticipated problems or study deviations.

All adverse events, unanticipated problems, protocol deviations or other concerns will be promptly reported to the principal or co-investigator who will have primary responsibility for notifying the IRB and the KKI Office of Research Compliance. As stated previously, no serious risks are anticipated. All side effects or adverse events problems of a medical nature will also be reported to GW Pharmaceutical.

Study deviations will be reported to the Johns Hopkins IRB as below. Study deviations which impact the interpretation of the data with regards to drug safety of efficacy also will be reported to GW Pharmaceuticals.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

The legal risks are minimal as all proper steps will be taken to maintain subject confidentiality and to make the subject feel comfortable and aware of any risks. Photographs will be stored in a digital, locked research database. Participants will have the option to select on the consent form between having these photographs destroyed at the end of the study once all data has been analyzed and published, or allowing the photographs to be relocated to our general data collection photographic database.

e. Financial risks to the participants.

In the event that this study leads to complications requiring hospitalization or medical treatment outside of being seen by Dr. Comi, the participants, parents, or their insurance company will be responsible for any further treatment that may result from being involved in this Expanded Access study. There are no other financial risks in this study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There are no individual medical benefits from participating in the study. The enrolled subjects have epilepsy refractory to multiple anti-convulsants. Epidiolex is a promising new approach to the treatment of refractory pediatric epilepsy. If successful, this expanded access study would open the door to a completely new treatment option for these participants. Because poor seizure control in SWS is linked with poor neurologic outcome and worse cognitive outcome, obtaining seizure control would have positive consequences for the family and for the costs they and society bear as a result of the uncontrolled seizures.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will not be any financial remuneration for subject participation in this expanded access study. There will also not be any penalty for not completing the study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The drug is provided by GW pharmaceuticals. The cost of the visits and labs will be covered by the study.