Official Title of the Study: Novel Cognitive Treatment Targets for Epidiolex in Sturge-Weber syndrome: A phase II trial

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Importance: With this phase II drug trial, we hope to better understand the utility of cannabidiol (CBD/Epidiolex) for improving the treatment of cognitive impairments in Sturge-Weber syndrome.

Problem: Sturge-Weber syndrome (SWS) is a vascular malformation disorder occurring in about 1 in 20,000 live births, and one of the most common neurovascular disorders. Those affected have vascular malformations in the brain, skin and eye. SWS is associated with lifelong epilepsy and cognitive issues; children develop a range of cognitive impairments, including intellectual disability, ADHD, learning disabilities and autism. Patients often develop anxiety, depression and behavioral issues, as well as migraines and motor impairments.

Dr. Comi led and published on an Investigator Initiated trial of Epidiolex for medically refractory seizures in 5 patients with Sturge-Weber syndrome (Kaplan et al, Pediatric Neurology, 2017). Three of the 5 subjects had sustained improvement in their seizures; one became seizure-free. Interestingly, cognitive, mood and behavioral improvements were also noted by these patients and their families. It is possible that these improvements resulted from improved seizure control. However, these improvements were first seen between 1-3 weeks after starting Epidiolex, and occurred sooner than would be expected as a result of improved seizure control. In addition, these anecdotal improvements have been sustained. The following clinical improvements were reported qualitatively in these subjects: 1) improved cognitive function, 2) improved social function, 3) improved mood and behavior, 4) improved motor function and 5) reduced migraine frequency and severity. Therefore, we are interested in doing a follow up study to quantify the improvements noted in the initial study.

Please note that Epidiolex is FDA approved for the treatment of seizures in Lennox-Gestaut syndrome and Dravet syndrome and is clinically used for the treatment of seizures in Sturge-Weber syndrome and many other medically refractory seizure disorders[1-3]. Epidiolex is **no longer** scheduled and can be prescribed clinically for patients seen remotely. We are studying Epidiolex here in Sturge-Weber syndrome for different indications.

Hypothesis: Cannabidiol (Epidiolex) improves SWS brain function resulting in improved cognitive function, social interactions, mood, motor function and behavior, as well as reduced migraines.

2. Objectives (include all primary and secondary objectives)

We propose a follow up to the initial SWS Epidiolex study which suggested improvements in SWS cognitive, social, and behavioral function and in other neurologic issues. **Primary outcome measure:** Quantify cognition 6 months after initiation of Epidiolex compared to baseline. **Secondary outcome**

measures: The following at 6 months compared to baseline: Social function and mood, frequency and severity of seizures, migraine frequency and severity, and motor outcomes.

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)

SWS is associated with cognitive impairments. By school age, cognitive impairments are common in SWS, even among patients that perform at or slightly below their age level. In a retrospective study of 29 SWS patients who underwent neuropsychological testing, 36% demonstrated no intellectual impairment, 32% performed in the "borderline/low average" range, and the final 32% displayed impaired intellectual functioning.[4] In addition, the study found that 58% displayed impaired performance in adaptive functioning. Adaptive functioning has been associated with executive dysfunction, externalizing and internalizing behavioral disorders, and borderline intellectual functioning.[5] Interestingly, hemiparesis was found to be independently associated with adaptive functioning. [6-8] Neuropsychological testing is recommended for patients that display hemiparesis in order to introduce early interventions (occupational therapy, cognitive rehabilitation) and accommodations (extra school support). On MRI, increased brain calcification over time is associated with a longer duration of epilepsy, a younger age of seizure onset, as well as a lowered IQ. Additionally, neuronal loss, gliosis, and decreased perfusion often surround calcium deposits.[9 10] The brain-involved hemispheres, as well as half of the uninvolved lobes also displayed significant reductions in glucose metabolism on positron emission tomography (PET) scans.[9]

Cognitive impairments in SWS are likely related to impaired vascular function and blood flow. In a normal brain, venous blood from the cerebral cortex and subcortical white matter drains through surface veins, whereas blood from deep white and grey matter drains through deep medullary veins.[11-13] The leptomeningeal venous malformations that characterize SWS induce the destruction of effective superficial venous pathways. As a result, venous pressure increases, prompting the blood to seek an alternate route for drainage. This unusual blood flow likely contributes to the strokes and stroke-like episodes observed in SWS patients.[14 15] Thus, modulation of blood flow in the brain may improve neurological symptoms of SWS.

GNAQ and signaling in SWS. In 2013, Shirley, Comi and Pevsner *et al.* identified a somatic nonsynonymous single-nucleotide variant R183Q in *GNAQ*, the gene that encodes G protein subunit αq.[16] G αq is part of a trimeric G protein complex that binds to the cytosolic side of an inactive G-protein-coupled receptor (GPCR).[16],[17 18] Several important GPCRs signal through Gαq including: 5-HT_2 serotonergic receptors, Alpha-1 adrenergic receptor, Vasopressin type 1 receptors 1A and 1B, Angiotensin II receptor type 1, Calcitonin receptor, Histamine H1 receptor, and the Metabotropic glutamate receptor. This mutation exists in SWS-related and isolated port-wine birthmarks alike, and is enriched in endothelial cells in SWS brain lesions and in other skin capillary malformations.[19 20]

GPCR engagement induces the exchange of GDP to GTP on the Gα subunit, which facilitates the release of the G protein heterotrimer from the GPCR, as well as the dissociation of the activated Gα from the β/γ dimer. This process results in downstream activation of the Ras/Raf/MEK/ERK pathway, which in turn regulates the PI3-K/AKT/ mammalian Target of Rapamycin (mTOR) pathway.[17 18] These pathways have essential regulatory functions in vascular growth and organization, and are activated in endothelial cells from SWS capillary malformations as indicated by increased phosphorylated-S6 expression,[21] and in SWS leptomeningeal tissue as shown by increased p-ERK.[22] The R183Q mutation in *GNAQ* is predicted to hyperactivate downstream pathways.

Both the Ras/RAF/MEK/ERK and PI3K/AKT/mTOR pathways modulate vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1α expression, and SWS brain tissue shows increased expression

of these and other vascular factors. VEGF expression is increased in cortical neurons and glia underlying the abnormal leptomeningeal vessels, whereas VEGF receptor 2 (VEGFR2), HIF-1α, and HIF-2α expression are increased in endothelial cells lining the abnormal leptomeningeal vessels.[23] Expression of VEGFR2 in endothelial cells is mediated by activated GNAQ,[24 25] and likely drives vascular remodeling that has been observed in SWS.[23]

Cannabidiol for SWS. SWS can be viewed as a model for testing the impact of Epidiolex upon Gαq, an important regulator of pathways downstream of crucial GPCRs. Furthermore, if Epidiolex improves SWS treatment targets such as anxiety, migraine or cognitive impairments, then this drug may prove more generally useful for these symptoms.

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: The proposed study will be a phase II trial in 10 participants with Sturge-Weber syndrome brain involvement and cognitive impairments at the Hunter Nelson Sturge-Weber Center at the Kennedy Krieger Institute, led by Dr. Comi. We may need to consent additional subjects (N=11) to meet our goal of 10 accrued subjects on study drug. In response to the COVID-19 Pandemic Crisis, all visits and assessments will now be conducted remotely by utilizing a video conference application. If medically required, such as for an adverse event that requires an in-person exam, the subject will be seen on-site in our out-patient neurology clinic. We do not anticipate needing to see subjects on-site, but include this in case it is medically necessary.

After screening, written consent will be obtained remotely (see process below), with baseline measures completed before starting on the study drug. All scheduled visits and assessments will be done remotely.

Done remotely as part of routine care (but in this setting NOT billed as clinical care): History, neurological exam, home weight (families to be sent digit scales to be used), home blood pressure and heart rate (families to be sent digital blood pressure and heart rate equipment) labs (outside lab, see process below), SWS neuroscore, Neuropsych testing and psychiatric exam. The following will also be done remotely and only done for research: Port-wine score, picture taken, NeuroQoL (Neurologic Quality of Life Scale), quantitative measurements of motor, behavior, and social function, and migraine scale.

The study drug will be initiated at the baseline visit with Dr. Comi reviewing instructions for its use. If a subject lives outside of Maryland, a script will be written and sent to Pharmacord, a pharmacy hub working with Greenwich who will ship the Epidiolex directly to the subject's home within 1 week. If a subject resides in the state of Maryland, a script will be written and sent to the Johns Hopkins Investigational Drug Research Pharmacy, who will ship the Epidiolex directly to the subject's home within 1 week. Receipt of the epidiolex will be confirmed with the subject by the research coordinator and instructions for its use reviewed and any questions answered by Dr. Comi if needed.

Follow-up remote visits consisting of lab work (done by script to outside labs), seizure/adverse event reports, an exam (including home reporting of weight, blood pressure and heart rate), neuroscore, , NeuroQoL, and medication review will be held after 1 and 3 months on Epidiolex. After 6 months on Epidiolex, the subjects will undergo follow up remote repeat testing for all the above initial measurements.

If the subject had significant improvements, they will have the option to continue the drug as a part of the extension phase. During the extension phase, the PI will have the ability to change (increase and decrease) dose of Epidiolex and other anti-seizure medications as clinically indicated. The extension phase will involve at least 4 visits (one every 3 months) but subjects may continue on the extension phase until

insurance company coverage is obtained. Study drug will be provided by Greenwich Biosciences until insurance coverage is obtained or other arrangements made to cover the cost of the study drug. At the end of one year, if insurance coverage has not been obtained then Greenwich Biosciences will work with the family through the Greenwich Drug Coverage Program to ensure that subjects benefitting from the drug can continue to receive it. Subjects who did not improve, or do not wish to continue taking Epidiolex, will wean off the drug at this time. If at any point the subject leaves the study, they will be asked to have a follow up remote visit one month after weaning has commenced.

Serious adverse events include those events that: result in death; are life-threatening; require hospitalization or prolongation of existing hospitalization; or create persistent or significant disability, or birth defects.

An unexpected adverse event is defined as any adverse event, the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with participation in the study.

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 developed and maintained by CTEP at National Cancer Institute.

Dosing: Epidiolex will be started at 5 mg/kg/day and titrated to maximum dose of 20 mg/kg/day, increasing the dose by 5 mg/kg/day weekly over the next three weeks. The investigational drug (Epidiolex/CBD) will be administered as an adjunct to all current anti-epileptic drugs.

Visit Schedule (see Figure): Subjects will be seen remotely for Screening Visit for Consent and initial studies, at Baseline Visit to start on CBD, then at 1 month, 3 months, and 6 months after initiation. Phone and/or email communication will take place bimonthly.

Lab work: CBC, chemistries including LFTs, urinalysis, Cannabidiol (CBD)/ Tetrahydrocannabidiol (THC) ratio, and trough levels of all seizure medications will be done at each visit. All labs tests will be completed remotely at an outside lab site local to the participant and charged to the study budget.

Database: A Redcap database will be used to organize data which will be analyzed with SPSS.

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

Dose / titration schedule: Initiation of treatment will begin with 5 mg/kg/day given in two divided doses. The dose will be increased by 5 mg/kg/day after seven days and then by 5 mg/kg/day every seven days up to a maximum dose of 20 mg/kg/day given. Study drug supply will be mailed to the participants (see process outlined above). The dosing schedule will be as follows, as tolerated:

Start of study: 5 mg/kg/day; subject will be evaluated here

Week 1: Increase dose by 5 mg/kg/day for total daily dose of 10 mg/kg/day

Week 2: Increase dose by 5 mg/kg/day for total daily dose of 15 mg/kg/day

Week 3: Increase dose by 5 mg/kg/day for total daily dose of 20 mg/kg/day

Week 4: Subject will be evaluated at stable dose of Epidiolex. If a subject has side effects thought to be due to study drug on 20 mg/kg/day, or a lower dose, then the dose will be decreased to the maximal dose tolerated in this dose range (5-20 mg/kg/day)

Seizure Medications: The dose of concomitant seizure, mood or behavioral drugs will remain unchanged during CBD treatment unless there are symptoms of toxicity, significant changes in blood levels, or an increase in seizures requiring an increase in a seizure medication. If seizure or mood issues require the *addition* of a seizure medication, the subject will be taken out of the study.

Recruitment of Participants

Recruitment will be from Dr. Comi's patients at the Hunter Nelson Sturge-Weber Center database at the Kennedy Krieger Institute. Patients who are in research databases (NA_00043846, NA_00038014) and have given the study team at the Kennedy Krieger Institute permission to contact them regarding research will be sent information regarding the trial and invited to contact the study team for more information if interested. Patients coming for clinical visits to Dr. Comi will be pre-screened for meeting inclusion criteria. A log will be kept of patients pre-screened for this trial and results of the pre-screening process.

Information about the pilot study will also be posted on the center websites, clinicaltrials.gov, and offered for posting on the websites of relevant advocacy foundations. If interested, individuals will contact Dr. Comi from the website postings. Subjects may also be referred to Dr. Comi for research purposes by treating clinicians not on the study team. The investigational nature and objectives of this trial, the procedures, the treatments involved, the attendant risks, and discomforts, as well as potential alternative therapies, will be carefully explained to the patient or their parents or guardian if he/she is a child. A signed informed consent document will be obtained after the entirety of the pilot study is explained. Consent will be obtained by the PI on the trial. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial. Assent will be obtained from all children able to provide assent according to our local IRB guidelines. Our consent contains an assent statement on the second-to-last page. The goal is to recruit ten participants total in this study.

Retention Strategies

When recruiting participants, the frequent visit schedule will be reviewed with the participants to ensure they are aware of the time commitment required to be in this study. All visits will be scheduled as far in advance as possible and will occur remotely by utilizing a video conference application Participants will receive reminders via email or phone before their appointments. All appointments surrounding holidays and travel will be scheduled far in advance.

Anticipated numbers of subjects to be enrolled and on study drug:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	0	1	1	0	3		5
Male	1	0	0	1	3		5
	1	1	1	1	6		10

Total							

Written Informed Consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant or legal guardian with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Process of Consent

The investigational nature and objectives of this trial, the procedures, the treatments involved, the attendant risks, discomforts, and potential benefits, as well as potential alternative therapies, will be carefully explained to the patient or their parents or guardian if he/she is a child. A signed informed consent document will be obtained after the entirety of the pilot study is explained. Consent will be obtained by the co-investigator designated to obtain consent on the IRB and delegation log for the trial. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and assent obtained where appropriate.

Virtual Written Consent Process: A copy of the IRB approved Informed Consent document will be provided to the participant prior to the teleconsent meeting either via email, fax or previously provided during an in person visit. The person conducting the consent process will conduct the process via telephone or video. The following is a step-by-step teleconsent / remote consent process: After the consent designee and participant or LAR review the consent form, the participant or LAR will be offered the opportunity to ask any questions and have those questions answered. The consent designee will verify the participant or LAR physically signed the consent document either by viewing via video conference, obtaining a photo of the complete signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically. The participant or LAR will sign and date/time the informed consent document. The signed document will then be mailed, emailed or faxed to the consent designee. If the signed consent is emailed or faxed or returned via photo, the participant or LAR will be asked to return the original signed document on their first in person visit. If the informed consent form is mailed to the consent designee by the participant or LAR, the IRB-approved consent designee will sign the copy which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document. Once received, the IRB-approved consent designee signs, dates/times the informed consent document. A copy of the fully signed written consent will be sent to the participant by mail, email or fax.

Estimated Time Commitments for Visits

Baseline Evaluations- Done on Visit 1 or 2 prior to starting drug. Can also be done between Visit 1 and 2 if more convenient for subject. Cognitive testing/assessments: 1 1/2 hours. Psychiatric/Mood: 3 hours. Neurologic Exam, history, picture, neuroscore, birthmark score: 1 hour. Labs: 30 minutes. **Total=6 hours.**

Visits 3 and 4. Neurologic Exam, history, and neuroscore: 1 hour. Labs: 30 minutes. **Total: 1 ½ hours each remote visit**

Final Evaluations: Done on or close to Visit 5 (within a 7-day period of time) and while still on Epidiolex. Cognitive testing/assessments: 1 1/2 hours. Psychiatric/Mood: 1 hour. Neurologic Exam, history, picture, neuroscore, birthmark score: 1 hour. Labs: 30 minutes. **Total=4 hours.**

Outcome Measures

Primary Outcome Measure: *The primary outcome* will be a **change in cognitive function** defined as change in score on the List Sorting Working Memory test. This cognitive test in the NIH Toolbox was suggested by our data in another study to yield the most actionable data. The NIH has provided guidance on the remote application of the NIH Toolbox Changes in cognitive function (from pre-treatment baseline to 6 months on study drug) will be assessed. Each subject measured at baseline will serve as his/her own control. Other cognitive function tests (below) which will be measured were selected because they also assess working memory and processing speed.

The NIH Toolbox for the Assessment of Neurological and Behavioral Function (NIH-TB).[26 27] Cognitive measures are computer-based tasks used for assessing a number of cognitive domains, including executive functioning, memory, language, etc. Because the tests were developed and normed for use with a very broad age range (ages 3-89), the NIH-TB is appropriate for the range of ages proposed for this research application (childhood, adolescence, and early adulthood). The NIH-TB has also been shown to be appropriate for use with individuals with lower or impaired cognitive functioning.[28] These are published tests which are widely used. From amongst the measures of the NIB-TB Cognitive measures, two measures were selected for use both which we have already utilized in subjects (and patients) with SWS:

The List Sorting Working Memory subtest is a test of working memory which will be used to assess the study outcome of working memory. Approximate time: 10 minutes

Secondary Outcome Measures

Change in other cognitive outcomes: The Picture Vocabulary subtest is a single-word receptive vocabulary/auditory comprehension task. When administered: Single words are presented via an audio file, paired simultaneously with 4 screen images of objects, actions, and/or depictions of concepts. The task is to pick the picture that matches the spoken word.77 This subtest was selected as one less likely to be treatment responsive, as compared to the other two above. Approximate time: 10 minutes

In addition, subscales were selected from several other assessments which also assess working memory and processing speed from the **Wechsler Intelligence Scale for Children**, Fifth Edition (WISC-V) (Wechsler, DL. (2015). *Wechsler Intelligence Scale for Children, Fifth Edition* (Fifth). San Antonio, TX: The Psychological Corporation.). Subtests from the WISC-V will be used to assess working memory and processing speed in all participants ages 6 to 15. Specific subtests will be used to measure primary outcome variables of this study. (1) The Digit Span subtest is verbal working memory task that presents participants with requirements to repeat digit strings verbatim, repeat digit strings backwards, and sequence digit strings numerically and alphabetically. (2) The Coding subtest is a nonverbal processing speed task that presents the participant with speeded visual scanning and discrimination requirements, and requires a degree of pencil control and visuo-motor coordination. (3) The Symbol Search subtest is also a nonverbal processing speed task that requires speeded visual scanning and discrimination, but has lesser visuo-motor coordination requirements relative to the coding subtest. The Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Wechsler, DL. (2008). Wechsler Adult Scale is similar. Administration time: 10 minutes

NeuroQoL (NIH Tool Box Neurological Quality of life scale) has been shown in SWS that the cognitive function quality of life domain is significantly lower than in controls and that it is associated with extent of brain involvement and age of seizure onset (manuscript in preparation). Time: 15 minutes

Checklists: The following symptom-report checklists are outcome measures that will be completed (while waiting for procedures/visits) by parents/caregivers in order to more fully assess executive function, social function and behavior:

Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2; Gioia, G., Isquith, P., Guy, S., & Kenworthy, L. (2015), Behavior *Rating Inventory of Executive Function, Second Edition.* Lutz, FL: WPS.) is a caregiver report questionnaire designed to assess the behavioral manifestations of executive functions in children ages 5-18 years. Raters assess the child's behavior on a 3-point Likert scale and scores are obtained on the scales such as: Initiate, Working Memory, Plan/Organize, Organization of Materials, Self-Monitor, Task-Monitor, Inhibit, Shift, and Emotional Control. Administration time: 10 mins.

The Social Responsiveness Scale, Second Edition (SRS-2; Constantino, J. N., & Gruber, C. P. (2012). *Social Responsiveness Scale–Second Edition (SRS-2).* Torrance, CA: Western Psychological Services) enquires about a child's ability to engage in emotionally appropriate reciprocal social interactions in naturalistic settings and includes items that ascertain social awareness, social information processing, capacity for reciprocal social responses, social anxiety/avoidance, and characteristic autistic preoccupations/traits. The SRS-2 generates a singular score that can be used as a measure of severity of social function and which can be used to screen for ASD. Approximate time: 15 – 20 minutes.

Change in Migraine Severity: Change in migraine severity is a secondary outcome measure for this trial. At pre-treatment baseline and after 6 months on the study drug, the subject will complete the "Migraine Specific Quality of Life Questionnaire," reflecting on how migraines affect their daily living. The MSQ has 14 questions and been shown to be a psychometrically valid tool that can be used to reliably measure the impact of migraine among chronic migraine patients.[29] Administration time: 10 minutes

Psychiatric Evaluations: Subjects will undergo baseline behavioral assessments including a semi-structured diagnostic interview in order to obtain DSM-V diagnoses. The diagnostic interview instrument will be tailored for the age and cognitive level of the participant. For pediatric participants, the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) will be used. The KSADS is a semi-structured diagnostic interview well established in clinical psychiatric research as the standard method for objectively identifying DSM diagnoses, suitable for clinical research purposes.

Baseline behavioral profiles will also be obtained by using age-appropriate, well-established standardized instruments commonly used in neuropsychiatry clinical practice. These instruments may include the Behavioral Assessment System for Children (BASC), The Screen for Child Anxiety Related Disorders (SCARED) or Children's Depression Rating Scale (CDRS). A quality of life scale is also expected to be obtained such as the Quality of Life in Epilepsy Scale for adolescents (QOLIE-ad-48).

The use of these instruments will reveal a sophisticated behavioral and psychiatric profile that is the state of the art in clinical behavioral science research. Baseline behavior function and psychiatric diagnoses will be well established prior to treatment and compared to ratings from behavioral profile scales obtained at a follow up stage (Approximate time-3 hours at baseline, 1 hour at follow-up).

Safety of Epidiolex: as measured by the number of adverse events and serious adverse events resulting from study drug.

Change in Seizure Severity: All seizure types will be classified before study entry (most common seizure type are partial motor and partial with impaired consciousness). Seizure frequency for each seizure type will be recorded retrospectively for the month prior to enrollment and at each visit during the study using diaries. In addition, at each visit the parents/caregivers will report the following secondary outcome measures: seizure duration by seizure type, number of episodes of status epilepticus (defined as convulsive seizure lasting longer than 10 minutes), number of uses of rescue medication, and the number of ER visits/ hospitalizations.

Change in motor function, as defined by Modified House Classification and selected scales from EDPA and parent-report measures: PEDI-CAT and ABILHAND/ABILHAND-KIDS (as previously described).[30] Video recordings of the Modified House Classification and selected scales from EDPA will be taken for each subject at baseline and at six months follow-up. The video recordings will be reviewed and scored blind by a study team occupational therapist. Administration time: 20 minutes

Laboratory tests and clinical procedures

1) Weight and vitals will be monitored at baseline and at each remote visit. (Routine care).

2) **Neuroscores** (as previously described)[31-33] will be assigned at each visit by Dr. Comi as per her clinical routine. The SWS neuroscore is comprised the frequency of seizures, extent of hemiparesis, assessment of visual field cut, and degree of cognitive functioning with a total score of 15 possible points. Neurologic exam and general physical exam will also be performed remotely at each visit. (Routine care)

3) Participants will be asked at each remote visit about any change in neurologic symptoms. (Routine care)

4) 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 **(Port-wine birthmark score)** for percent of face covered, thickness of birthmark, and darkness of birthmark color. Families will be mailed a color chart (see appendix) to hold up next to the subject while photos are being taken. 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).

Table of Remote Visits	Screening	Baseline	Core Phase		Endpoint 6 months
Visit Number	1	2	3	4	5
Study Week	-2 ← ± 14 days →	0	4 ←	12 ± 7 days →	24
Consent	X				
Physical Exam	X	X	X	X	X
Neuroscore	X	X	X	X	X
Neuro QoL	X	X	X	X	X
Incl/Excl Criteria	X	X	X	X	X
Past Medical History	X				
Diagnosis of SWS	X				
Seizure Hx	X	X	X	X	X
Previous AED Hx	X				
Current Med Hx	X	X	X	X	X
Picture Taken		X			X
Rescue Meds	X	X	X	X	X
AEDs	X	X	X	X	X
Motor, NP, psychiatric Assessments	←	→			**X ± 7 days**
Labwork					
AED Levels	X		X	X	X
CMP (renal, hepatic)	X		X	X	X
CBC	X		X	X	X
CBD/THC Ratio			X	X	X
Urinalysis	X		X	X	X
Pregnancy Test (if applicable)	X		X	X	X
Safety					
Adverse Events check		X	X	X	X
Safety Calls:		←		Bi-monthly →	
Continue or Remove?	X	X	X	X	X
Patient Reported Outcomes			X	X	X

5) CBC, LFT, BUN, creatinine levels, electrolytes, and urinalysis will be measured at each visit (screening, 1, 3, and 6 months on drug). Concomitant AED plasma concentrations will be measured at the same visits. CBD/THC ratio in urine will be measured three times; at the one month visit, at the three month visit, and at the 6 month visit. All lab tests will be done remotely at a site local to the participant and charged to the study budget.

6) 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 12 weeks after taking Cannabidiol. We will also inform male subjects that they should not get their partners pregnant while on this study or for 12 weeks after taking Cannabidiol. Anyone who becomes pregnant while on the study will be removed immediately.

Case Report Forms: 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.

Duration of therapy: Study duration for subjects will be between 6 months to 2 years depending on the age at enrollment. During the study, subjects will be seen at 1 month, 3 months and the every 3 months until they are 2 years of age. Therefore the number of study visits will range from 4 to 8, again depending on the age at enrollment. Total length of study for completion of all subjects will be 4 years as outlined in the Milestones Table attached. Once the optimal dose is found (20 mg/kg/day or maximal tolerated dose; expected to be reached within 4 weeks), participants will continue on the Core Phase until 2 years of age. At the end of the core phase, cognitive and all other testing will be repeated. **Total duration for each subject= until 2 years of age, a minimum of 6 months and 5 visits.**

Study Visit 1: Screening Visit- Informed consent process, eligibility criteria reviewed. The following tests are done at *visit one, or at or before visit 2* (maximum of two weeks between visits 1 and 2): baseline developmental testing, baseline labs sent, neurological exam, and baseline motor testing, Quality of life measures, motor testing video, Neuroscore and Port-wine birthmark score.

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. History, exam, Quality of life measurs, have picture taken, and Port-wine birthmark score.

During visits 3 and beyond (see Visit Table)- the participants will undergo clinical neurologic assessments, blood draws for laboratory tests, study drug accountability, concomitant medication survey, adverse event reporting, and study drug administration (see Visit Table for details). Also, Quality of life measures and neuroscore.

Final Study Visit- Repeat all assessments- developmental testing, labs, neurological exam, motor testing, Quality of life measures, motor testing video, Neuroscore, have picture taken, and Port-wine birthmark score. Determine whether subject will continue on Epidiolex or will be weaned off.

Clinical Follow Up: Subject will be seen one month later for clinical follow up whether on or off Epidiolex.

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 will 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 the 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) the subject has 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.

Sharing of test results: This study involves tests, labwork, that could be useful for the clinical care of the subject. We will share this information with the subject if clinically significant abnormalities are seen. If for example, if the labwork is significantly abnormal, then Dr. Comi will contact the subject tell them what to do. If the evaluation of mood suggests that urgent treatment is required, then Dr. Salpekar or Dr. Comi will speak with them about what the next step should be. The other research tests are not expected to produce results that would be relevant for clinical care, so we will not share these results with the subject.

Data Management
The trial PI will review the study progress weekly. Patients entered on the trial and adverse events will be reviewed to ensure that the study is implemented as outlined in the protocol. Data will be collected on case report forms. Monthly reports will be generated to assess completeness of data. There will be monthly phone conferences to address quality assurance (QA) issues.

The trial database will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a research identifier by the KKI.

Study Records Retention
Patient files will be kept until at least seven years after completion of the study.

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

During this phase II trial, where the primary objectives are to assess novel treatment targets and tolerability, blinding is not appropriate.

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

Participants will otherwise receive routine care and will not have to stop any of their current anticonvulsants or other medications. 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 trial.

f. Definition of treatment failure or participant removal criteria.

Early stopping rules: If a participant experiences a significant health decline or a loss of seizure control (defined as a need to add a new seizure medication), ending assessments will be done, and the subject removed. If the subject experiences a temporary increase in seizures, Dr. Comi may take the temporary nature of the increase into account. If the subject has had other benefits to mood, behavior, or neurologic exam that outweigh the risk of 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 20 mg/kg/day. Other removal criteria include: death, lost to follow-up, withdrawal of consent for any further data submission, or any other reason the patient, parent, PI or caring physicians think that the subject should be removed. Early withdrawals within the first two months will be replaced.

Study cessation rules. The study will be stopped if any of the following occur: (1) more than 4 subjects drop out because of adverse events probably or definitely **due to study drug** or (2) more than two subjects experience a SAE probably or definitely **due to study 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 while the event is being fully assessed.

Treatment will continue until any of the following take place:

1. Loss of seizure control defined as need to add another seizure medication or other seizure treatment (diet or surgery).

2. Intolerable toxicity.

3. Pregnancy.

4. Withdrawal of consent.

5. Six month treatment duration completed as per protocol.

6. 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.

Extension Phase:
Those who do not demonstrate a clear benefit after six months of treatment will be weaned off of the study drug over a month, and seen back for one final follow-up visit one month later. All subjects removed early from the study will be requested to complete the end of study assessments while still on study drug; but only if safely possible and with subject consent.

At study's end, any patient doing well on Epidiolex and demonstrating improvement on cognitive, neurologic, mood and/or behavioral assessments may continue on the drug (extension study). Every effort will be made to obtain insurance authorization based on the cognitive and medical improvements

demonstrated by the trial; if required the drug will be provided free of cost to the subject until the drug is approved for clinical use for the treatment of cognitive impairments (or other measured indications) in patients with Sturge-Weber syndrome.

They will then be followed and seen about every 3 months, at which time interim history, including evaluation of side effects and patient reported outcomes, neuroscore, photographs of the port wine birthmark, and the Neuroquality of Life questionnaire will be collected. During the extension phase, the PI will have the ability to change dose (increase and decrease) dose of Epidiolex and other anti-seizure medications as clinically indicated. The maximum dose of Epidiolex will not exceed 20 mg/kg/day. The extension study will consist of at least 4 visits, with the option to remain on the extension study until insurance company approval is obtained for Epidiolex. Study drug will be provided by Greenwich Biosciences until insurance coverage is obtained. The study coordinator will contact the family once per month to ensure the subject is taking the Epidiolex. The study coordinator will ask how much of the Epidiolex the subject has remaining and will ask to see the bottle(s) to confirm.

Lab work (CBC, anticonvulsant levels, and chemistries about every 3 months) will be done as part of clinical care. At all extension study visits, there will be a urine pregnancy test. If the subject is under the age of 18, these results will be given to the parents.

Every six months, an interim analysis will be done of adverse events and outcome measures. Results will be discussed by the Research Investigators and a summary sent to Greenwich Biosciences.
Study cessation rules. Consideration for stopping the study will occur if any of the following occur. (1) more than 4 subjects drop out of the extension study because of adverse events probably or definitely due to study drug, (2) more than two subjects experience a SAE probably or definitely due to study drug. All subjects will be informed of any SAE due to the study drug.
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 enrolled and on study drug, male and female, ages 3 to 50 years of age) and the following:

1. Cognitive impairment defined as a cognitive neuroscore of ≥2 at screening.

2. Anti-epileptic, mood or behavioral drugs (if on) at stable doses for a minimum of 4 weeks prior to enrollment.

3. If present, 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 fail at any point to meet continuation criteria and withdraw 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.

6. 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 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

2. 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.

3. Patients who start or discontinue a seizure, mood or behavioral medication in the 4 weeks leading up to screening.

4. Prior treatment with any investigational drug or use of any other cannabis product within the preceding 4 weeks prior to study entry.

5. 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. This includes those in foster care, or those unable to keep follow-up appointments, maintain close contact with Principal Investigator, or complete all necessary studies to maintain safety.

6. 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. Dr. Comi has previously studied use of Epidiolex in Sturge-Weber patients with medically refractory seizures. 3 of the 5 patients in this cohort had sustained improvement in their seizures, with one patient achieving seizure freedom. Of interest, these patients and their families also noted cognitive, mood, and behavior improvements.[1] Other studies suggest anti-depressant like effects,[34] and reduced social anxiety symptoms[35] associated with Cannabidiol use. In addition, other studies suggest cannabidiol has neuroprotective benefit,[36] effects on abnormal angiogenesis,[37] and anti-inflammatory effects;[38] these effects would be expected to be beneficial in SWS.

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.

Epidiolex is currently FDA approved only for treatment of medically refractory seizures in Lennox-Gastaut syndrome, Dravet syndrome with a dose range of 5-20 mg/kg/day. It is no longer a scheduled drug.

An earlier study of Epidiolex for medically refractory seizures in Sturge-Weber syndrome suggested improvement in cognition, social, and behavioral outcomes. The side effects experienced were mild and transient.

The proposed trial will be assessing the impact of Epidiolex upon cognitive impairment in Sturge-Weber patients.

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.

Change in cognitive impairment: Combined score of two NIH Toolbox subtests.

b. Secondary outcome variables.

Change in the following:
SWS neuroscore
Port-wine score
Adverse Events
Seizure severity
Social, behavioral, and mood function
Migraine severity
Motor function

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

Statistical Plan: Results of the above tests will be compared to age normed values. In addition, the difference in results between final test results and initial test results will be obtained for the cognitive functioning score of each subject. Mean and standard deviation of this difference for all 10 subjects on study drug will be calculated. These results will be used to determine whether individuals and the group as a whole demonstrated age normed changes in their cognitive functioning over the course of the six month trial. There is no control group in this study of subjects who are not receiving study drug. The published test-retest standard deviations will be used to determine whether changes in testing results exceed expected test-retest changes in results.

Sample Size Calculation: Since these outcomes will be done for the first time with this drug in SWS, a sample size calculation was not done. Rather, we are estimating that 10 subjects enrolled and on study drug will be sufficient to do the proposed pilot trial and show improvements (or trends for improvement) sufficient to design a future larger clinical trial, or to guide clinical care. This estimate is based on our experience with another trial using the same primary outcome measure.

Interim data analysis: Every week Dr. Comi and the study coordinator study will review data for safety. Each month, a formal review of recruitment, safety, data completion and study progress will be made. An

assessment of progress as it relates to study milestones (see **Milestone Table** below) will be made, and a summary report prepared for Greenwich Biosciences.

One year into the study, an interim analysis will be done of adverse events and outcome measures. Results will be discussed by the Research Investigators and a summary sent to Greenwich Biosciences.

d. Early stopping rules.

Study cessation rules. The study will be stopped, if any of the following occur: (1) more than 4 subjects drop out because of adverse events probably or definitely **due to study drug**, (2) more than two subjects experience a SAE probably or definitely **due to study drug**, or (3) if sufficient milestones are not being met. 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 while a full analysis is completed and a decision is made whether to continue the study.

Milestone Table. Including new timeline because of COVID shutdown.

Milestones	By June 2019	Aug 2019	Oct 2019	Dec 2020	Feb 2020	Oct 2020	Dec 2020	Feb 2021	Aug 2021	Sept. 2021	Oct 2021	Nov 2021
Contract signed	**X**											
Protocol approved	**X**											
Subject 1 consented and on drug		**X**										
Subjects 2&3 consented and on drug			**X**									
Subjects 4&5consented and on drug				**X**								
Interim Analysis Completed (Subjects 1-5) Go/No Go decision made					**X**							
Subjects 6&7 consented						**X**						
Subjects 8&9 consented							**X**					
Subjects 10 &11 consented								X				
All subjects Completed (subjects 1-11)									**X**			
Data Analysis Completed										**X**		
Write NIH/DOD Grant applications											X	
Submit Abstract and prepare Manuscript												**X**

8. Risks

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

Epidiolex: As a part of Dr. Comi's first Investigator Initiated trial of Epidiolex for treatment of medically refractory seizures in SWS, 5 patients with Sturge-Weber syndrome used Epidiolex to reduce the frequency and severity of seizures. All adverse events reported in this trial were transient, and resolved on their own or with adjustments to their anticonvulsant or CBD doses. The adverse events considered possibly related to CBD in this initial study were: a temporary increase in seizures (n= 1), transient behavioral issues (n=2), transient increased aspartate aminotransferase liver function test (n=1, indirectly related), tiredness (n=1) and transient exotropia/redness of the right eye (n=1).

Other side effects, which have been previously reported in other populations using CBD, are also generally mild and tolerable. They include: diarrhea, fatigue, pneumonia, drowsiness, increased levels of aspartate aminotransferase, gamma glutamyl transferase, alanine aminotransferase, and transamines, abnormal liver function tests, weight loss and decrease in appetite, lethargy, drooling, irritability, aggression, trouble sleeping, hypersensitivity reactions sometimes requiring the use of corticosteroids, and rashes.

Risks to Pregnancy: The effects of Cannabidiol on an embryo or fetus are not known. Subjects able to become pregnant or to father a child will be instructed to avoid pregnancy.

Drug Interactions: Epidiolex can interact with other medications, particularly with valproate and with clobazam in our patients with SWS. Being on these seizure medications can increase the risk of having adverse events such as increased liver function tests, and sedation. Subjects who are also on these seizure medications will be monitored closely and may have the dose of their seizure medication or their Epidiolex decreased by Dr. Comi.

Blood draws: Also included is the taking of peripheral blood samples, which is part of the routine care of these participants. Blood draws may result in discomfort, bruising, or transient pain at the site of needle entry into the vein. There is a remote risk of fainting. Infection could occur at the place where the needle goes into the arm.

Incidental Findings: As a part of this research study, subjects will undergo laboratory testing. There is a possibility that while reviewing the labs results we may see and unexpected abnormality called and "incidental finding." We will let subjects know if we see such an incidental finding, and will contact them by mail, email, or phone. In the case of a potential serious emergency, someone may go to their home. An incidental finding may cause the subject to feel anxious. A report of the incidental finding will be part of the subject's medical record, it will be available to those accessing your medical record for their clinical care, and may affect their current or future life or health insurance coverage. The costs for any care that may come from the incidental finding, such as the need to see a doctor to diagnose or treat an incidental finding, will not be paid for by this research study. These costs would be responsibility of the subject or their insurance company.

Other Assessments: Procedures involved in this study include cognitive testing, motor, mood, behavior, and social function evaluations, assessment of migraine severity. All of the above procedures may be considered boring or tiring to the participant, especially children.

Time Commitment: There is a time commitment for participants attending the required appointments and maintaining seizure diary/records. The first two appointments will take about 3 hours, follow up visits 1-2 hours and the final visit 3-4 hours. Participants will also be asked to maintain a seizure diary and study drug dosing record, requiring a time commitment of about 5-10 minutes per day.

Confidentiality: There is also the risk of loss of confidentiality in allowing us to see medical information and use it for research purposes.

b. Steps taken to minimize the risks.

PI Oversight: The Principal Investigator, Dr. Anne Comi, will review all data relating to safety and tolerability throughout the study. The study will benefit from her two decades of experience treating participants with Sturge-Weber syndrome as the director of the Hunter Nelson Sturge-Weber Center. The investigator will be available by telephone, text, or email throughout the entire study.

Training: Training will be provided by Dr. Comi and the other clinician investigators to all nursing and research staff who will be involved in the drug trial. This training will be documented and updated as needed.

Managing Adverse Events: Dr. Comi will work closely with Greenwich Biosciences, and the participants, to both anticipate any possible side effects, and ensure that side effects are reported, evaluated, and do not inordinately compromise the health of the patient. 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. Any subject experiencing significant side effects or medical concerns during the course of study treatment will be responded to appropriately by Dr. Comi. Additional clinic visits with Dr. Comi required for medical reasons during the study will be provided at no cost to the subject. Appropriate referrals for evaluations will be made as needed. If the subject is not doing well and the patient, parent or Dr. Comi thinks that it is in the best interest of the subject to stop the study drug, they will be removed from the study. Subjects will have Dr. Comi's cell phone number, email and office numbers and will be encouraged to contact her directly with any concerns.

Study Oversight: Dr. Comi will meet with study staff weekly to review clinical trial subjects, issues and concerns. Trial oversight will be provided by compliance and quality assurance monitors who perform periodic reviews of all study documents to ensure the study is being carried out as stated in the protocol. In addition, monthly review of the data with all trial Investigators will be made by meeting/conference call to review recruitment, subject issues and safety, and review data analysis and completion. A summary of these meetings/calls and data will be provided to Greenwich Biosciences.

Data Safety and Monitoring Plan: The Study Chair (Anne Comi, MD) has primary oversight responsibility of this clinical trial. Dr. Comi and the sub-investigators will comprise the Safety Monitoring Committee. The Safety Monitoring Committee will review accrual, patterns and frequencies of all adverse events, and protocol compliance every month. They will review data together every month for this small pilot trial by 1) Reviewing and analyzing the progress of the study; 2) Monitoring the safety of the study treatments and diagnostic procedures; 3) Ensuring data quality; 4) Recommending early stopping or continuation of the trial (if applicable); and 5) Reviewing recruitment and event rates. They will assess the proportion of enrolled versus projected enrollment and proportion of subjects who have completed the trial. The Study Chair will provide Safety Monitoring Committee reports and meeting summaries to Greenwich Biosciences regarding the continuation status of the protocol.

The research coordinator at will make safety calls and/or email/text contact with each participant bimonthly to ensure follow-up and assessment of any adverse events. Also, subjects will be asked to keep daily diaries of any side effects or concerns and asked to email or fax them in on a bimonthly basis. If any adverse events have occurred, the PIs will be notified immediately and corrective actions will take place. While patients with Sturge-Weber syndrome can have serious medical issues, we do not expect any serious adverse events (SAEs) directly attributable to the study drug. Occurrence of an SAE directly attributable to the study drug will trigger a review to consider stopping the participant on the study within one month of

the event. Based on a prior study, an adverse event rate of approximately 1 event /subject/month is expected. An adverse event rate more than double this event rate will trigger an in-depth review to consider whether to consider continuing the participant on the study; an important consideration in this decision will be whether the adverse events are considered to be due to the study drug or not.

The trial PIs and clinical coordinators will review the study progress regularly. Adverse events will be reviewed to ensure the safety of the patients. Internal reviews carried out quarterly by clinical trials specialists to ensure that all protocol specifications are being followed and issues addressed promptly. Quarterly reports will be generated by KKI to assess completeness of data.

Data provided must be treated with the strictest confidence. No information provided from individual patient's records may be discussed with anyone other than those individuals mentioned in the collaborative research agreement. Data may not be released in any form except as provided in the agreement.

Each subject enrolled will, from that point forward, be identified by a unique identifier. All records generated will be stored in a locked office area, only accessible to study personnel. Clinical information will be accessed, according to HIPAA requirements, by study personnel to complete study documents, as needed.

Managing Pregnancy Risks: Subjects will be instructed that if they become pregnant, father a child, or breastfeed while on this research study there is the potential for very serious harmful effects to an embryo or fetus or infants. Female subjects will be told not become pregnant or breastfeed a baby while on this study or for 12 weeks after taking Epidiolex. If they become pregnant during the study they will have to leave the study and we ask to will follow the progress of the pregnancy and its outcome. Subjects able to become pregnant or make someone become pregnant will be instructed to us effective birth control (for example, abstinence, birth control pills, contraceptive implants, condoms) in order to avoid pregnancy during the study and for at least 12 weeks after the last dose of Epidiolex.

Professional Staff: All testing and medical procedures will be conducted by nurses and trained professional staff at Kennedy Krieger and Johns Hopkins or at outside lab facilities (for blood draws). This will greatly reduce the chances of pain, infection, or bruising associated with the blood draw and any other assessments. Efforts will be made to make potentially stressful tests, a comfortable experience for the subjects, including using of child life staff as applicable.

Scheduling: We realize that participation in this study is a significant time commitment for subjects; therefore we will do our best to schedule at their convenience. For the convenience of families, paper evaluations for mood, behavior, and social function will be mailed to the families to complete, and then will be reviewed with them at the time of their visits. Breaks for food or relaxing will be taken into consideration during scheduling for the baseline and 6 month visits to reduce subject stress and fatigue.

Protection of Confidentiality: All subject information will be de-identified prior to being shared with Greenwich Biosciences or collaborators, or organized into research databases for analysis and publication. Research data will be kept in locked cabinets or on a password protected computer in a locked office. All members of the research team have been trained in confidentiality law and methods. If the subject asks to have their photographs destroyed at the end of the study, we will digitally delete all electronic files and shred all hard copies.

Drug Interactions: CBD is an inhibitor of CYP 2C196, CYP 2C97, and other cytochrome P450s belonging to the 2C and 3A subfamilies. CBD/THC ratio in urine will be measured at study visits (see Visit Table). Concomitant anti-epileptic drug plasma levels will be measured at all visits. Anti-epileptic drug

doses will be adjusted as needed based on signs and symptoms of toxicity and / or changes in drug levels (routine care). Epidiolex can interact with other medications, particularly with valproate and with clobazam. Being on these seizure medications can increase the risk of having adverse events such as increased liver function tests, and sedation. Subjects who are also on these seizure medications will be monitored closely and may have the dose of their seizure medication or their Epidiolex decreased by Dr. Comi.

The medical risks associated with joining the study are believed to be similar to continuing clinical care. All medications used to treat Sturge-Weber syndrome have associated risks and side effects.

c. Plan for reporting unanticipated problems or study deviations.

Adverse Events: All adverse events, unanticipated problems, protocol deviations or other concerns will be promptly reported to the principal who will have primary responsibility for notifying the IRB, the KKI Office of Research Compliance and the sponsors.

Reporting Timeline:

- Within **<u>24 hours</u>** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:

    1. Is considered life-threatening/disabling or results in death of subject

    -OR-

    2. Is Unexpected/Unanticipated

- Investigators must report all other reportable SAEs within **<u>5 working days</u>** (of learning of the event).
- All other (suspected) reportable AEs must be reported within **<u>14 working days</u>** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

Protocol deviations: that constitute unanticipated problems involving risks require prompt reporting to the JHM IRB. Protocol deviations which impact data results or integrity will also be reported to Greenwich Biosciences.

A protocol deviation that constitutes an "unanticipated problem involving risks to subjects or to others" for the definition of an unanticipated problem) must be reported <u>promptly</u> to the IRB, as follows:

a. *Emergency deviations:* When a deviation occurs in an ***emergency situation*****,** such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The sponsor and the reviewing IRB must be notified <u>as soon as possible</u>, but not later than 5 days after the ***emergency*** situation occurred. The PI must submit a report to the JHM IRB.

b. *Major, non-emergent deviations without prior approval:* A planned deviation that is non-emergent and represents a major change in the protocol as approved by the IRB. The IRB must approve the request <u>before</u> the proposed change is implemented. The PI must submit non-emergent deviations to the IRB for review in eIRB under the Further Study Action

activity, and use the Change in Research activity; for paper studies, submit a Change in Research form.

Protocol deviations that are only minor or administrative

At JHM, minor or administrative protocol deviations are defined as those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." If a protocol deviation occurs which meets this definition, the deviation should be reported to the JHM IRB at the time the continuing review application is submitted. In eIRB and for paper studies, we use the Protocol Deviation Summary Sheet (R.F. 4) to report these deviations. Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

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

All proper steps will be taken to maintain subject confidentiality and to make the subject feel comfortable and aware of any risks. All subjects will be encouraged to ask her any questions they may have. Data on mood and behavior will be gathered. All research databases created with this data will not include subject name or other identifying information.

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 longitudinal SWS IRB-approved research database (NA_00043846), for use in future studies examining extent of the port-wine birthmark and its correlation to other clinical outcomes.

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 study. The subject/family is responsible for costs related to travel for visits. There are no other financial risks in this study.

9. Benefits

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

The enrolled subjects have cognitive impairments that affect their ability to independently receive education or to work. Epidiolex may have positive effects on SWS cognitive problems, social impairments, mood, migraines, or motor function. If successful, this study would lay the foundation for a completely new treatment option for patients with SWS and cognitive impairment. It is likely that this study will result in new information regarding the usefulness of Epidiolex for Sturge-Weber syndrome cognitive impairments and other neurologic issues.

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 phase II trial. There will also not be any penalty for not completing the study. Any decisions to not participate or to withdraw will not affect the patient's care.

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 study drug and study funding will be provided by Greenwich Biosciences. The costs of the motor testing will be covered by funding provided by the Faneca 66 Foundation..

Limitations: The main limitations of this study are its size and lack of a placebo group. However at this point, when the best outcome measures for assessing the improvements need to be ascertained, the proposed trial is most appropriate. A larger, randomized, placebo-controlled trial can be done after this trial is completed. All of the outcome measures proposed are familiar to the investigators; most of them have previously been utilized here in subjects with SWS. Dr. Comi has previously successful drug trials in SWS and is expected to successfully complete the proposed drug trial.

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