Clinical Research Protocol -

Cannabinoid therapy in medically refractory pediatric epilepsy – Phase 1: Dosing and tolerability study of a Cannabidiol-rich whole Cannabis plant extract.

Study Site:

The Hospital for Sick Children

Toronto, Ontario

Principal Investigator:

[redacted]

Lead Co-Investigator:

[redacted]

Co-Investigators:

[redacted]

Study product:

TIL-TC150 Oil

Study product Vendor:

Tilray

Study Funding:

Tilray, the Little Rocky Fund (via Sick Kids Foundation)

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List of Abbreviations

AED	Anti-epileptic drug
CBD	Cannabidiol
CBG	Cannabigerol
CBDV	Cannabidivarin
CBC	Cannabichromene
CYP	Cytochrome P
GABA	Gamma-aminobutyric Acid
LFP	Local field potential
LFT	Liver function tests
MES	Maximal Electroshock
PESQ	Pediatric Epilepsy Side Effects Questionnaire
PTZ	Pentylenetetrazol
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire
SUDEP	Sudden Unexplained Death in Epilepsy
THC	Delta-9-Tetrahydrocannabidiol
VNS	Vagus nerve stimulator

Study Summary

Title	Cannabinoid Therapy in Medically Refractory Pediatric Epilepsy – Phase 1: Dosing and Tolerability Study of a Cannabidiol-Rich Whole Plant Extract of Cannabis.
Short Title	Cannabinoid Therapy for Pediatric Epilepsy
Phase	1
Methodology	Open-label Intervention
Study Duration	20 weeks to primary analysis with continued follow-up until 64 weeks completed
Study Center	The Hospital for Sick Children, Toronto Ontario
Objectives	To determine the tolerability and optimal dose of 50:1 ratio CBD:THC Cannabis extract as an adjunct treatment in children with severe drug resistant epilepsy
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Patients with Dravet Syndrome Between ages of 1 and 18 years old male or female Must have failed 2 AEDs at therapeutic doses and be on current regimen of 1-4 AEDs which have been stable doses for 4 weeks
Study Product, Dose, Route, Regimen	TIL-TC150 Oil is the study product The active ingredients in TIL-TC150 Oil are THC and CBD, present in a 1:50 ratio. These active ingredients are derived from *Cannabis sativa* L. strains produced by Tilray and suspended in a grape seed oil. This suspension is administered at a dose of 2mg/kg/day CBD divided BID and titrated up to a maximal dose of 16mg/kg/day CBD (or maximal tolerated).
Duration of Administration	Study period: primary safety and outcome data at 20 weeks with longer follow-up of safety and tolerability in those who chose to continue after the 20-week period and will be followed up to 64 weeks.
Reference Therapy	None
Statistical methodology	The primary aims of this study are to determine the maximal tolerated dose of TIL-TC150 Oil Cannabis Extract in children with drug resistant epilepsies. Descriptive statistics will be used to quantify the frequency and severity of adverse events that are

	reported for the various dosages that are employed

1. Background

1.1 Introduction

This is a single center study to ascertain dosing and tolerability of add-on (i.e., in addition to their standard anti-epileptic therapy) Cannabidiol in children between 12 months and 18 years with treatment-resistant epilepsy due to Dravet syndrome. Dravet syndrome is a devastating syndrome which causes medication resistant epilepsy associated with significant cognitive morbidity and frequent seizures [1-7]. In addition to the significant morbidity, children with refractory epilepsy are at risk of seizure-related mortality and Sudden Unexpected Death in an Epilepsy Patient (SUDEP) [8]. The risk of SUDEP in treatment resistant epilepsy is 1 in 150 [9]. The current armory of anti-epileptic drugs, dietary therapy and the Vagal Nerve Stimulator (VNS) device are not always successful in achieving seizure control. The healthcare costs of childhood-onset treatment resistant epilepsy are well established [10, 11]. In Dravet syndrome the severity of the epilepsy often requires frequent emergency department attendances, and hospital admissions.

Rationale for this study

The availability of a treatment to reduce the seizure frequency in children with Dravet syndrome (thus reducing hospital admissions) and to provide the chance of improved long term cognitive outcome, hence reducing the need for lifelong neurodisability service availability, would lead to significant savings in healthcare expenditure [12].

In addition, it is scientifically plausible that this study product would have efficacy in treating seizures in Dravet syndrome. In 80% of cases of Dravet syndrome a causative genetic mutation is detected in a Sodium channel coding gene (SCN1a mutation). Cannabinoids CBD and CBG have been shown to be potent sodium channel blockers in both human and animal models.

1.2 Investigational Product

The physiochemical characteristics of THC and CBD are detailed in Table 1.

Table 1: Drug Substance Common Name	delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
Chemical Name	THC: IUPAC ID: (−)-trans-Δ9-tetrahydrocannabinol; IUPAC ID: (−)-(6aR,10aR)-6,6,9-trimethyl- 3-pentyl-6a,7,8,10a-tetrahydro- 6H-benzo[c]chromen-1-ol. CBD: IUPAC ID: 2-[(1R,6R)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol.
Appearance	THC: Light yellow resinous oil; CBD: Light yellow resinous oil
Molecular Formula	THC: C21H30O2; CBD: C21H30O2
Molecular Mass	THC: 314.47; CBD: 314.47
Solubility	THC: Soluble in methanol, ethanol, acetone, chloroform, and dichloromethane. Insoluble in water. CBD: Soluble in methanol, ethanol, acetone, chloroform, light petroleum, and dichloromethane. Insoluble in water.

Tilray TIL-TC150 is formulated with THC and CBD in grape seed oil at strengths of 2 mg/ml and 100 mg/ml, respectively. The product is formulated with standard pharmaceutical excipients.

TIL-TC150 Oil is packaged in 25 ml Type III amber glass stopper bottles with a polypropylene cap and a fill of 20.0 ml. The oil drug product is stored at room temperature with a 6 months expiration.

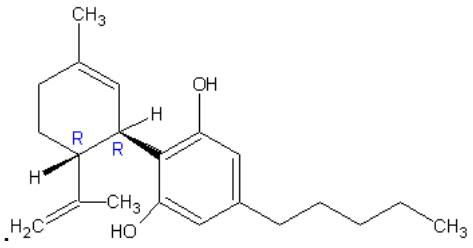

Figure 1. Cannabidiol Structure

CBD is highly lipid soluble and is a potent inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. The effects of other concomitant drug levels metabolized by these enzyme systems are not known. CBD is excreted in the urine and faeces. The plasma peaks vary significantly between individuals but are typically between 1 to 2 hours. The CBD levels are detected up to 8 hours post administration. The adverse drug reactions of CBD that have been indicated in trials include headache, dizziness, fatigue, loss of appetite, oral numbness, dry mouth, neck pain, feeling strange, depression, lack of taste or changed taste, gastrointestinal disturbances, feeling weak, falls, shakiness, muscle stiffness, unusual dreams, nose bleeds, hot or cold flashes, and heartburn.

Cannabinoids: Increases in systolic BP over time (Sativex = 3 hrs), and decreases in diastolic BP with noted heart rate increase (Sativex = 4-8 hrs) [1] However, this is anticipated to be due to the THC content. Much of the published data refers to Sativex which contains 50% THC and many of the adverse effects are considered in keeping with the psychoactive THC effects.

Phytocannabinoids exhibit very low mammalian toxicity, and mixtures of cannabinoids are *less toxic* than pure THC. [2] Therefore, a mixture of other cannabinoids (terpenoids, etc.) may also reduce any potential toxicity issues due to having a high CBD product.

The following are the most common side effects of AEDs and/or high-THC cannabis. However, since our product is very low in THC we anticipate that these will be minor or rare:

- Dizziness, somnolence, fatigue, irritability, ataxia, blurred vision, diplopia vision, rashes, and motor incoordination / falls.
- Gastrointestinal (anorexia, loss of appetite, nausea, vomiting, and weight loss).Psychiatric and behavioural adverse reactions such as aggression, hostility, irritability, anger, and homicidal ideation / threats.

1.3 Preclinical Data

There have been a number of studies published reporting the anti-convulsant effect of CBD using the mouse model. Izquierdo et al used a maximal electroshock (MES) model to induce seizures in mice and found CBD to be protective against the maximal electroshock (MES) model of generalized seizures with an ED_{50} (effective dose for 50% of group) of 3 mg/kg CBD [13]. Chesher et al used the MES model and Pentylenetetrazole (PTZ) induced seizure model in mice and found CBD of 50-200 mg/kg orally exhibited no anti-convulsant effects in either model [14, 15]. However, there was no data on the pharmacokinetics for oral CBD making the results difficult to interpret. In mice, CBD has been found to be an effective and relatively potent anti-convulsant in the MES model with ED_{50} values of 12 mg/kg. In these mice models, CBD enhanced the anti-convulsant potencies of phenytoin and phenobarbital. However, CBD diminished effects of clonazepam and ethosuximide.

Karler et al studied the occurrence of tolerance in CBD's (120 mg/kg) anti-convulsant effects in electrically-induced seizure models [16]. Mice were dosed repeatedly for 3-4 days with CBD, phenytoin, and phenobarbital and no change in their anti-convulsant sensitivity was found in MES models compared to those dosed acutely. Repeated dosing increased sensitivity of CBD in 6 Hz electroshock-threshold test.

Another study found that CBD (0.3-3 mg/kg) raised the threshold required to produce epileptic after-discharges recorded by chronically implanted electrodes in electrically kindled limbic seizures in rats [17]. This is consistent with the known effects of phenytoin in this model. However, CBD also decreased the after-discharge amplitude, duration, and propagation in this model, similar to the effects of ethosuximide. The group concluded that "CBD was the most efficacious of the drugs tested against limbic after-discharges and convulsions."

CBD was evaluated in many different seizure models and found to be an effective anti-convulsant in MES and all of the GABA inhibition-based models [18].

Recently, Jones et al reported significant anti-epileptiform and anti-convulsant activity with *in vitro* and *in vivo* models [19, 20]. Using spontaneous epileptiform local field potentials (LFPs) models they found that in vitro CBD decreased epileptiform LFP burst amplitude and duration. In addition, CBD had significant anti-convulsant effects against PTZ- induced acute, generalized seizures, pilocarpine-induced temporal lobe seizures and penicillin-induced partial seizures in their rats.

1.4 Clinical Data to Date

A Cochrane Report from 2012 compiled studies on cannabinoids for epilepsy [21]. This report included 4 clinical studies where CBD was used to treat epilepsy. In 1978, a study by Mechoulam et al randomized 9 adult patients to either 200mg of CBD (4 patients) or placebo (5 patients) [22]. All patients had uncontrolled temporal lobe epilepsy and had failed treatment with multiple medications. Two of the four patients treated with CBD over the 3 month trial became seizure free for duration and 1 patient showed partial improvement. However, none of the 5 patients receiving placebo experienced a reduction in seizures. There were no toxic effects observed.

Cuhna et al studied 15 adult patients with treatment resistant secondary generalized epilepsy [23].Each participant had at least 1 generalized convulsion per week. They were randomly divided into 2 groups and treated with either placebo (8 patients) or 200-300 mg of CBD (7 patients) daily up to 18 weeks. One patient was transferred to the treatment group after one month. Four of eight patients in the CBD group became almost seizure free, and three of the eight experienced a partial reduction in seizures. Only one of seven patients in the placebo group experienced seizure reduction. The most commonly reported side effect was somnolence and no patients reported psychotropic effects. All patients remained on their previously prescribed anti-epileptic drugs (AED) throughout the trial.

Ames et al performed a placebo-controlled trial of 12 institutionalized, intellectually disabled patients with frequent seizures uncontrolled on conventional AEDs [24]. The

patients were divided into 2 groups by unclear method. The treatment group was given 300 mg cannabidiol daily for 1 week then 200 mg daily for 3 weeks. At the study's conclusion there were no statistically significant differences between the 2 groups. The only immediate side effect reported was mild drowsiness. The specific details of the study were lacking on seizure frequencies and other parameters. There was no indication that patients continued on their AED medication during the study.

Trembly et al [25] conducted a cross-over design in which 12 patients with incompletely controlled epilepsy received their standard AEDs for 3 months and then a placebo for 6 months. Patients' AEDs could change in this period only. The 12 patients were then randomized to placebo or cannabidiol 100 mg 3 times a day for 6 months. After this period, those on the active treatment switched to the placebo and those on the placebo switched to the active treatment for another 6 months. The study concluded with all patients receiving neither placebo nor treatment for 3 months. The study's published abstract did not report any statistical analysis. The only reported results were no discernible effect on the Minnesota Multiphasic Personality Inventory (MMPI), Beck depression inventory, trail making test, and finger tapping test. This same study was later summarized in a book chapter by Consroe in 1992 [26]. This summary reported that there were only 10 patients and that Trembly reported no effects on seizure pattern, character, or frequency. Cochrane was unsuccessful in contacting Trembly's group for clarification.

Dr. Porter and Dr. Jacobson of Stanford University conducted a survey of parents to learn about their experience with CBD. They surveyed 19 parents to determine their observations about the effect or lack of effect of CBD on their children's seizure frequency. The children ranged in age from 2 to 16 years old and had Dravet syndrome (13), Doose syndrome (3), and one each with myoclonic astatic epilepsy, Lennox-Gastaut syndrome, and idiopathic epilepsy. The children experienced a wide variety of seizure types and had unsuccessfully trialed an average of 12 AEDs before their parents began cannabidiol-enriched cannabis treatment. The doses of cannabidiol the parents reported administering to their children ranged from less than 0.5 mg/kg/day to

28.6 mg/kg/day. The doses of THC contained within those samples were reported to range from 0 to 0.8 mg/kg/day. The parents obtained dosage information by having their preparations tested at commercial medical cannabis testing facilities. Seizure frequency prior to administered cannabidiol-enriched cannabis ranged from 2 per week to 250 per day.

Validation of the survey was achieved by giving the same survey to a similar group of parents to enquire about effects of an AED approved in Europe for Dravet Syndrome, stiripentol (STP). Sixteen of 19 parents (84%) reported a reduction in their child's seizure frequency. Two parents reported their child become seizure-free after more than 4 months on cannabidiol-enriched cannabis. Of the remaining 14 parents, 8 reported greater than 80% reduction in seizure frequency, 3 reported greater than 50% reduction, and 3 reported greater than 25% reduction. Three parents reported no change in seizure frequency. Twelve parents were able to wean their child off of another AED after starting cannabidiol-enriched cannabis. Other beneficial effects of cannabidiol-enriched cannabis included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%), and decreased self-stimulation (6/19, 32%). The only negative effects reported were drowsiness (7/19, 37%) and fatigue (3/19, 16%). While this data does contain some limitations, such as lack of control data, lack of randomization and blinding, and uncertainty of artisanal preparation dosages, it does lend hope that CBD may be a useful pharmaceutical alternative to existing therapies in drug resistant epilepsy and sheds light on what tolerated doses are being used experimentally.

There have also been clinical studies on chronic dosing of CBD in other disease states. CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with Huntington's Disease. Oral CBD (10 mg/kg/day) or placebo (sesame oil) was administered for 6 weeks and the effects were evaluated weekly under a double blind, randomized crossover design. The CBD was found to show no significant or clinical difference compared to placebo in Cannabis side effect inventory, clinical lab tests, or other safety outcome measures [27]. A published case report of a 19-year-old

diagnosed with schizophrenia had severe side effects after treatment with conventional antipsychotics, but showed significant improvement of symptoms with no adverse effects after 4 weeks of inpatient treatment with CBD in increasing doses up to 1500 mg/day [28]. CBD monotherapy was administered to 3 patients with treatment-resistant schizophrenia with starting dose at 40 mg/day and increased to 1280 mg/day up to 4 weeks with no side effects reported [29]. Lastly, 2 patients with bipolar affective disorder received CBD of 600-1200 mg/day for up to 24 days with no side effects at any dose [30].

GW Pharma has a product called Sativex ® Oromucosal Spray that has been approved in over 20 countries as an adjunct medication for symptom improvement in patients with spasticity from multiple sclerosis (MS). These patients had not shown an improvement in spasticity with other anti-spasticity medications and showed significant improvement during initial trials with Sativex. It contains 27 mg/mL of THC and 25 mg/mL of CBD. The dosing is administered as a spray (each spray is 0.1 ml and contains 2.5 mg of CBD/ 2.7mg of THC). The recommended dosages are one spray twice daily (5mg of CBD/ 5.4mg of THC per day) at initiation and titration according to effect to 4-8 sprays per day (10 mg CBD/ 10.8 mg THC – 20 mg CBD / 21.6 mg THC). The most common adverse reactions to Sativex are dizziness, nausea, fatigue, dry mouth, and somnolence. While it is believed that most of these adverse effects are mostly like from the THC component of the Sativex, it has still been approved as safe and effective. Sativex was originally approved in Canada in 2005 and since then there have been 16 periodic safety update reports (PSURs). During that time, 5,472 patients were exposed to Sativex and the benefit-risk evaluation for Sativex continues to be unchanged. There have been no safety concerns identified and Sativex continues to remain well tolerated. Therefore, even in the presence of THC, CBD-containing compounds have been proven to be well tolerated and safe.

Recently a retrospective review was undertaken in an attempt to provide guidance on the safety and efficacy of CBD [31]. 11 patients with intractable epilepsy (Dravet, Doose and similar) were identified ranging in age from 6 months to 21 years. All 11 patients

were observed to have significant reduction in seizures after 3 months. The range of seizure reduction was found to be 55% to 100% with a mean of 90%. 10 of 11 patients experienced 80% or more seizure reduction, and 3 of 11 patients were seizure free after 3 months of therapy. The average dose giving maximal improvement at 3 months was 5 mg CBD/lb/day (range: 2-8 mg CBD/lb/day or 1-3.6 mg/kg/day). Families reported no adverse effects attributed to the high CBD, low THC extract therapy. Several families reported an increase in adverse events from concurrent AEDs, including irritability and increased seizure activity, when therapy was added. Families reported that titrating down doses of concurrent AEDs while continuing therapy resolved adverse events and improved seizure control.

The CBD/epilepsy landscape was further changed dramatically in December 2015 with the publication by Devinsky and colleagues [32] of an open-label trial of CBD, in over 200 patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment resistant epilepsy, in 11 epilepsy centers across the United States. Open label add-on study, 11 centers across US between 2014-2015. The CBD used in this study was a 99% pure oil-based cannabidiol extract of constant composition (Epidiolex, GW Pharmaceuticals, London, UK), in a 100 mg per mL preparation, so 100:1 ratio of CBD: THC. Their results showed an average reduction from 30 seizures a month to 16 seizures a month. There were 5 participants who were free from motor sz at the end of the 12 weeks. They titrated doses up to 25mg/kg/day without patients withdrawing due to side effects. They noted that side effects of GI disturbance (diarrhea) were more likely at higher doses, and they titrated up to 25mg/kg/day.

Health Canada has approved a cannabis extract oil of 18:1 ratio CBD:THC and 20:1 CBD:THC for sale to patients of all ages (Cannimed licensed producers). Given the recent data on CBD:THC at a 100:1 ratio from Devinsky et al (Epidiolex)[32], we feel dosing and safety for a 50:1 CBD:THC cannabis extract product in our study product is the appropriate next step. This ratio allows us to maximize the CBD dosing, while ensuring exposure to lower THC dosing than products currently licensed for sale to patients in Canada.

1.5 Dose Rationale

Chronic CBD dosing up to 1500 mg/day is described in published literature with no adverse effects. In addition, the report by Drs. Porter and Jacobson from a parent survey of children (2-16 years of age) receiving Cannabinoid with high CBD content up to doses of 28.6 mg/kg/day showed that it was well tolerated. In addition, a recent pediatric report [31] described a good clinical effect with doses between 1-3.6 mg/kg/day. In Devinsky et al study they descried tolerance of up to 25mg/kg/day of their Epidiolex compound. Somnolence was reported in 25%. At doses of CBD above 15mg/kg/day diarrhea (19% at any dose) and weight loss (6%) were reported. No patients wanted to discontinue despite the frequent side effects. Therefore, we feel the dosing titration protocol of up to 16 mg/kg/day of CBD is reasonable and safe in this population of children with treatment-resistant epilepsy.

Study investigators will review all data relating to safety and tolerability throughout the study, after every third patient has been treated, to monitor study conduct and assess patient safety throughout the dosage period of 4 months. This review of data will be conducted by regular clinical evaluations at baseline, every 2 weeks for the first month, monthly for 4 months (to interim outcome stage) then once every 3 months thereafter (for those choosing to continue therapy). CBD will be started at 2mg/kg/day CBD and titrated slowly by 2mg/kg/day CBD every 7 days until 16mg/kg/day CBD is reached (or maximal tolerated dose clinically). Patients will also be assessed for concomitant AED levels at baseline and maximal tolerated CBD dose. These concomitant AEDs will be adjusted by the study team as necessary based on the level and signs/symptoms of toxicity or decline in seizure control. Patients will also be monitored via telephone or email in between in-person visits.

1.6 Study Population

Our target population is children with treatment-resistant epilepsy due to Dravet syndrome. Dravet syndrome may be clinically suspected by evaluation of the clinical

history and EEG (sleep recording within 12 months of study enrollment), and the diagnosis will be confirmed genetically (up to 80% of children with Dravet syndrome are positive for a mutation in the SCN1A gene).

Clinical features suggestive of Dravet syndrome –

Normal early development prior to seizure onset

Seizure onset in the first year of life

Febrile and afebrile seizures – often prolonged and unilateral clonic or tonic-clonic

Seizure types evolve to include myoclonic, atypical absence, and focal clonic seizure types

Seizures typically refractory to AED

Cognitive delay begins typically during second year of life, with marked slowing of development typically between 2-4 years, which may plateau thereafter.

EEG features suggestive of Dravet syndrome –

Early EEG may be normal

As epilepsy progresses EEG shows focal, generalized and multifocal interictal epileptiform discharges.

The background may show generalized slowing in line with clinical seizure frequency.

In order to recruit patients, we will forward study information to all hospital pediatric neurologists at our institution by email. In addition, we will write to the referring community neurologists in the Greater Toronto Area (GTA) or local referring centres who care for children with complex epilepsy inviting them to refer children with Dravet syndrome for consideration for enrollment to attend a clinic visit with the study investigator team at our institution to learn more about the study and potential

enrollment. Referring physicians will be asked to confirm that referred families have ascertained to hear more about the study. When seen at a clinic visit the study details will be explained to them by one of the investigator team (a physician or NP)

1.7 Research Risks and Benefits

1.7.1 Risk of Study Product

Cannabinoids have not been extensively studied and therefore like with any drug, not all risks are known. The possible adverse drug reactions may include headache, dizziness, fatigue, drowsiness, somnolence, loss of appetite, oral numbness, dry mouth, neck pain, feeling strange, depression, lack of taste or changed taste, GI disturbances, feeling weak, falls, shakiness, muscle stiffness, unusual dreams, nose bleeds, hot or cold flashes, and heartburn. All patients will be closely monitored for adverse events during titration and treatment period. Dose and/or frequency may be adjusted as appropriate.

From the study recently published by Devinsky et al, [32] their prominent side effects were somnolence (25%), diarrhea (19% at least one episode however only 2% were classified as a serious adverse event of diarrhea), weight loss, weight gain, fatigue (13%). Status epilepticus was reported in 6% (9 participants) during their study, however it is difficult to ascertain whether this was related to therapy or in keeping with their inherent risk of status epilepticus due to their refractory epilepsy

Potential drug interactions may occur as CBD is a potent inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. The effects of other concomitant AED and other drug levels metabolized by these enzyme systems are not fully known, but it may increase their levels leading to potential toxicities. Therefore, AED plasma levels will be measured at baseline and at day 28 following first CBD dose. AEDs may be adjusted as needed based on signs and symptoms of toxicity and/or changes in drug levels.

1.7.2 Potential Benefits

The potential benefits of this study include the possibility of reduced seizure frequency due to the addition of a high CBD low THC whole plant extract option to the patient's current AED regimen. We hope that knowledge gained about high CBD and low THC whole plant extract dosing and tolerability during this study will benefit all study participants' quality of life by reducing their seizure frequency. The data from Devinsky et al open-label study [32] suggest that CBD might significantly "reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy". Epidiolex is now an orphan drug in the United States to be used for medically refractory childhood onset epilepsy. However, to date this compound is not available in Canada.

1.8 Compliance Statement

This document is a clinical research protocol for a human research study. This study will be conducted in accordance with the protocol, applicable Health Canada regulatory guidelines, international standards of Good Clinical Practice, and institutional research policies and procedures.

2. Study Objectives

The primary objective is to establish the safe dosing and tolerability of TIL-TC150, a CBD rich cannabis plant extract administered as an oral solution for children with severe refractory epilepsy. Dosing safety will be measured by blood work evaluation of renal, hematologic and hepatic function and of AED levels, by parent/caregiver report, by physician assessment, and by assessing caregiver reported tolerability and the Pediatric Epilepsy Side Effects Questionnaire (PESQ).

As secondary measures we will also assess:

1. The impact of therapy on quality of life using the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire and on everyday behaviours using the Vineland Adaptive Behavior Scales, Second Edition.

2. Change in seizure frequency from baseline using the following measures:

   Parent-reported seizure diary

   24 hour Ambulatory EEG study (measurements: (a) percentage change in electrographic seizure frequency and (b) using spike detection software we will measure the percentage change in interictal activity during the recording)

   Number of episodes of Status Epilepticus – defined as convulsive seizure lasting longer than 10 minutes

   Frequency of use of rescue medications (Lorazepam, Midazolam, or Diazepam).

   Number of visits to emergency department / hospitalizations with seizures

3. Study Design

The study is a Phase 1 dosing and tolerability study of TIL-TC150. TIL-TC150 will be administered to 20 children with Dravet syndrome by the investigator team who will closely follow them for the duration of the study.

3.1 Pre-intervention period (4 weeks)

This period is the first four weeks after the patient is enrolled. Once enrolled, the participant's legal guardian will be educated about maintaining a detailed seizure diary during this 4 week period to allow baseline analysis of seizure frequency. As an objective measure of seizure frequency, during this 4 week period all enrolled

participants with undergo a 24 hour ambulatory EEG study to also assess ictal and interictal epileptiform activity.

3.2 Intervention period (20 weeks)

Following the pre-intervention assessment of baseline seizure frequency, the participant will commence TIL-TC150 product. The initial dose is 2mg/kg/day CBD divided twice daily with weekly titration as described below in section 5. Study treatment will be increased each week as tolerated by 2mg/kg/day CBD. Week 8 should be the last increase if the participant increases by this schedule. The maximal dose is 16/mg/kg/day CBD.

During this time there will be regular communication and clinic visits with the investigator team, as detailed in section 5. Once 16 weeks of therapy have been completed, participants will enter a 4 week interim analysis period, during which time they continue the TIL-TC150 at an unchanged does and a 4 week seizure diary and a 24 hour ambulatory EEG recording will be performed and compared with the pre-intervention seizure frequency.

This primary outcome data regarding safety, tolerability, dosing and secondary seizure outcomes will be reported at this time point.

3.3 Longitudinal safety and tolerability (44 weeks)

For those participants who chose to continue TIL-TC150 therapy after the initial intervention period, they will be followed by the investigator team in clinic at 3 monthly intervals to assess for any tolerability and safety issues that arise with more prolonged therapy. They will be followed to 64 weeks.

Once the participant is stable on the therapy the frequency of visits and phone calls may be reduced at the discretion of the investigator team in conjunction with discussion with participant family.

3.4 Primary Study Endpoint

The primary endpoint is establishing the maximal safely tolerated dose of TIL-TC150 in our study population.

4. Selection and Withdrawal of Participants

4.1 Inclusion Criteria

Participants selected for the study must meet the following criteria:

1. Age between 12 months and 18 years
2. Parent/ legal guardian informed consent obtained
3. Clinical and EEG (sleep recording within 12 months of study enrollment) characteristics of Dravet Syndrome and confirmatory genetic mutation result
4. Medication-resistant epilepsy – with failure to achieve seizure control with at least 2 appropriate AEDs at therapeutic doses
5. Clinically apparent seizures (excluding myoclonic and absence) occurring at least twice per week
6. Agreed diary compliance and clinical compliance with current prescribed therapy
7. Concomitant AED medication dosing stable during 4 week pre-intervention period. Ketogenic diet regime and VNS device settings must be stable for 3 months prior to pre-intervention period.
8. Ability to tolerate administration of medication orally or via percutaneous feeding tube (PEG).
9. Negative urinary pregnancy test for all female participants of child bearing age

10. Was never on Cannabinoid therapy or have not been treated with Cannabinoid products for at least last 60 days (confirmed by negative urine test for Tetrahydrocannabidiol (THC), only for those who had been treated with CBD).

4.2 Exclusion Criteria

Children may not be included in the study if:

1. Under 12 months, over 18 years
2. Co-morbid renal, liver or cardiac disease
3. Any evidence of underlying inborn error of metabolism (mitochondrial disease)
4. No clinically apparent seizures, or less than 1 per week
5. Previous significant drug reaction (i.e. Stevens Johnson Syndrome, Significant angioedema causing airway compromise)
6. Any known or suspected family history of schizophrenia or other psychotic illness, or known schizophrenia in a first degree relative
7. Known sensitivity or allergic reaction to cannabinoids.
8. Currently taking any Cannabinoid products.
9. Any planned surgical or other intervention or travel during the intervention period.
10. Any inability to understand/speak English.

4.3 Recruitment

20 participants will be recruited by the study investigators from their epilepsy clinics at The Hospital for Sick Children. During a routine visit, patients/parents/caregivers that meet criteria for the study will be asked if they would like to participate in the study. If they are interested in participation then eligibility will be assessed using our inclusion

and exclusion criteria. Patients who have previously been treated with a Cannabinoid product, must have stopped taking it at least 60 days before enrolment, and they will be asked for a urine test (5-10 ml) to assess for the presence of Tetrahydrocannabidiol (THC) in urine. A negative urine test for THC will confirm their eligibility to the study. There is published clinical trial evidence for epidiolex (a cannabinoid product) as an anti-epileptic agent, and Health Canada approved Cannabinoid product use over a year ago, therefore many families have tried this product, and it is not feasible to expect CBD naïve participants, nor is it necessary. A washout period is sufficient. A wash out period of 60 days allows for all of the administered cannabinoid products to be eliminated from the participant's body. All genders and ethnicities will be included between ages of one and eighteen years. The physician will explain the study during the routine visit. If the patient/parent/caregiver agrees, they will be given the informed consent documents to read and sign. Only the Principal Investigator, Sub-Investigators, and other research personnel listed on the study will have access to participant's research files.

4.4 Withdrawal from the study

4.4.1 When and How to Withdraw

Study participant may withdraw or be withdrawn from the study at any time if the participant, parent/caregiver, or Investigators feel it is not in the participant's best interest to continue. Study participation may be discontinued in the following circumstances:

1. Parent/ legal guardian withdrawal of consent
2. Participant non-compliance with study procedures
3. Serious adverse events, including significant toxicity, impaired liver or renal function, or impaired hematopoeisis
4. Exacerbation of seizures not attributable to another factor

5. Interaction with participant concomitant AED regimen causing unacceptable toxicity

Once the study withdrawal is decided, the termination of treatment is determined based on reason for withdrawal. For example if participant has a severe allergic reaction with rapidly progressive rash the treatment would be abruptly stopped, whereas if the participant experiences excessive somnolence, the treatment may be withdrawn in a gradual way. This determination will be made on an individual basis by study team in consultation with participant and participant's parent/caregiver.

4.4.2 Data Collection

For all participants who withdraw from the study we will invite them to attend a clinic evaluation within 4 weeks of withdrawal +/- 2 weeks. During this visit we will document: their dose reached, reasons for withdrawal, adverse events, seizure diary and PESQ will be assessed, patients will have a physical and neurological examination and AED trough levels and routine bloodwork (CBC, LFT, Renal profile).

4.4.3 Replacement

Participants will not be replaced following withdrawal in the study

4.4.4 Follow-up

Every participant will be followed closely throughout the study and if a withdrawal occurs contact will be made with participant and they will be invited to attend a final clinic visit as described above. If the participant cannot be contacted after 4 phone calls, a letter requesting the participant's parent / legal guardian to contact the study investigator team will be sent to participant household.

5. Study Treatment

5.1 Study Drug

Tilray TIL-TC150 is formulated with THC and CBD in grape seed oil at strengths of 2 mg/ml and 100 mg/ml, respectively. The product is formulated with standard pharmaceutical excipients. The active ingredients in TIL-TC150 Oil are THC and CBD, present in a 1:50 ratio. These active ingredients are derived from *Cannabis sativa* L. strains produced by Tilray, a federally-licensed producer and distributor of medical cannabis under Health Canada's Marijuana for Medical Purposes Regulations. The details of extraction and formulation are laid out in the Tilray investigators brochure (part of submission)

5.2 Treatment Regimen

Each participant will start the treatment with a dose of 2mg/kg/day CBD given in two equal doses each day. The first dose will be given during the Baseline (Week 0) visit. Following this dose the participant will be observed by study personnel for a period of 2 hours. The participant's parent/legal guardian will increase the participant's dose by 2mg/kg/day CBD every 7 days as tolerated, to a maximal dose of 16mg/kg/day CBD. Once optimal dose is determined for each participant they may continue the treatment for the duration of study follow-up and thereafter it will be continued if wished by participants.

5.3 Concomitant treatments

Participants will be taking concomitant AED, perhaps 1-4 AEDs. In addition they may have a VNS device inserted or be on the ketogenic diet. We require that their current regime is stable prior to initiation – 4 weeks for AED and 3 months for VNS and ketogenic diet. All concomitant anti-epileptic treatments are to be continued during the intervention period. Participants who are currently taking AEDs where trough levels can

routinely be assessed, will have levels assessed at interval throughout the study intervention period (as per the detailed schedule) to ensure safety.

5.3 Compliance Monitoring

Study drug compliance will be assessed by clinic evaluations and the follow-up phone calls and emails as outlined in earlier section. In addition we will ask dispensing hospital research pharmacist to measure the mls remaining in their bottle of Cannabinoid when they return to collect a next prescription. Any participant who is not compliant with the study treatment regime will be withdrawn from the study.

5.4 Enrollment

All participants meeting inclusion and exclusion criteria will be invited to enroll during a clinic visit at The Hospital for Sick Children with the study investigator team. The participant's legal guardian/parent will be given a consent form to read and the study will be explained to them by a physician member of the study team. Given the level of intellectual impairment associated with Dravet syndrome, we do not anticipate a participant will have capacity to consent or assent to participation in the study and thus a single parent/legal guardian consent form has been created.

5.5 Pre-Intervention Period (4 weeks)

Once enrolled, the pre-intervention period begins. Participants will be seen and baseline physical and neurological examination performed. Medical information regarding seizures, medications, birth and development will also be collected. Participant parent / legal guardian will be instructed to keep a daily seizure diary for the next four weeks which will be used as a measure of baseline seizure frequency. Seizure diary will be kept by participant's parent/ legal guardian for the duration of the study follow-up period also. Seizure frequency for each seizure type will be recorded at baseline. Seizure types will be classified prior to study entry.

A. Diary: Seizure frequency and type will be monitored and recorded in a participant's daily diary. Participant's parent/caregiver will report the seizure frequency, type, number of episodes of Status Epilepticus, use of rescue medication and attendance to ER/ hospitalizations.

B. Prolonged EEG study: During the pre-intervention period each participant will have a 24 hour ambulatory EEG recording performed to enable objective measurement of a 24 hour sample of electrographic activity – ictal and interictal, which will be reported by a certified experienced Clinical Neurophysiologist who is not part of the investigator team.

C. Vineland Adaptive Behaviour Scale, Second Edition: this is a standardized parent interview that will take 20-60 minutes to complete either in person at the clinic or by telephone prior to starting the TIL-TC150. The interview will also be completed again at the primary evaluation period (week 16-20) and again during the longitudinal follow-up (52-64 weeks). This will be done by a clinical research assistant, under supervision of a clinical neuropsychologist (Dr. K Sinopoli, CPsych). Parents will be provided with a research report detailing the assessment findings at study completion.

5.6 Intervention Period – and Primary Evaluation (20 weeks)

Week 0: (Baseline): A neurological and physical exam (including measurement of vital signs) will be performed and the participant will be weighed. The parent / legal guardian will complete the QOLCE. During this visit their seizure diary will be evaluated and bloodwork will be performed for baseline measures (Complete blood count, LFT (AST ALT, gamma GT, bilirubin), renal profile (electrolytes, creatinine and urea), and AED trough levels). The participant's parent/legal guardian will be instructed on dosing and twice daily administration of TIL-TC150. Each participant will start TIL-TC150at an initial dose of 2mg/kg/day CBD in 2 equally divided doses, this will be added to their current anti-epileptic drug therapy regimen. They will be advised to increase the dose of the study treatment after 7 days by 2mg/kg/day CBD. The study pharmacist will be present

at the first clinic visit to review dosing schedule, administration and pharmacy dispensing procedures. In addition study pharmacist will be available during the study period to provide education and support to families. The first dose will be administered in clinic and the participant will be observed for a period of 2 hours by study personnel to evaluate for any adverse events.

Week 2: Participant to return to The Hospital for Sick Children. Study treatment increased as tolerated by 2mg/kg/day CBD, neurological and physical exam will be performed and the participant will be weighed, and seizure diary evaluated. Medical history including concomitant medications will be reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant's parent/legal guardian to assess for any adverse events and tolerability.

Week 4: Participant to return to The Hospital for Sick Children. Study treatment increased as tolerated by 2mg/kg/day CBD, neurological and physical examination will be performed, weight recorded, seizure diary evaluated. Bloodwork performed (CBC, LFT, Renal profile, AED trough levels). Medical history including concomitant medications will be reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant's parent/ legal guardian to assess for any adverse events and tolerability.

Week 8: Participant to return to The Hospital for Sick Children. Study treatment increased as tolerated by 2mg/kg/day CBD, neurological and physical examination will be performed, weight recorded, seizure diary evaluated. Medical history including concomitant medications will be reviewed. If at maximally tolerated study treatment dose as determined by study team, then bloodwork will be performed (CBC, LFT, and Renal profile and trough AED levels) and QOLCE completed by caregiver/parent. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by parent/legal guardian to assess for any adverse events and tolerability.

Week 12: Participant to return to The Hospital for Sick Children for clinical evaluation, which includes an interview to assess current clinical condition, any participant, parent/

legal guardian concerns related to TIL-TC150and assess for any adverse effects and tolerability by interview. A neurological and physical examination will be performed, weight recorded, seizure diary evaluated. Medical history including concomitant medications will be reviewed. Participant should be on maximal dose of 8mg/kg/day or max tolerated dose now, or on maximally tolerated dose (as determined by study team). If at maximally tolerated study treatment dose as determined by study team, then bloodwork will be performed (CBC, LFT, and Renal profile and trough AED levels). The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant parent / legal guardian to assess for any adverse events and tolerability.

Week 16: Participant to return to The Hospital for Sick Children for clinical evaluation, neurological and physical examination will be performed, weight recorded, and seizure diary will be evaluated. Medical history including concomitant medications will be reviewed. If target dose only reached at this stage blood work to be done now, if previously performed at target or maximally tolerated doses no need to repeat. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant parent/legal guardian to assess for any adverse events and tolerability and QOLCE completed by caregiver/parent between weeks 16 – 20. In addition, the family will be contacted by clinical psychology to complete a follow-up Vineland adaptive behaviour assessment to measure any changes in behaviour.

Between week 16 and 20 an ambulatory EEG study will be performed at maximal study treatment doses and the completed seizure diary will be collected.

5.7 Longitudinal safety and tolerability phase (44 weeks)

This is a continuation of the study beyond the initial 20-week intervention to continue to assess participants who chose to continue with TIL-TC150therapy beyond the primary analysis period.

Week 28: Participant to return for clinical evaluation (including physical and neurological examination) as they have decided to continue TIL-TC150. Their dose will be 16mg/kg/day CBD divided twice daily or their individual maximally tolerated dose during

the intervention period. Their seizure diary will be reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed to assess for any adverse events and tolerability and QOLCE completed by caregiver/parent.

Week 40: Participant to return for clinical evaluation (including physical and neurological examination) and seizure diary reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant parent/legal guardian to assess for any adverse events and tolerability. Bloodwork will be performed once to check CBC, LFT, and Renal profile and trough AED levels during weeks 40-64.

Week 52: Participant to return for clinical evaluation (including physical and neurological examination) and seizure diary reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed by participant parent/ legal guardian to assess for any adverse events and tolerability and QOLCE completed by caregiver/parent. Bloodwork will be performed to check CBC, LFT, and Renal profile and trough AED levels. If the blood work is done at week 40, then no need to repeat.

Week 64: Participant to return for clinical evaluation (including physical and neurological examination) and seizure diary reviewed. The Pediatric Epilepsy Side Effect Questionnaire (PESQ) will be completed to assess for any adverse events and tolerability by caregiver/parent. For families who choose to continue therapy for the longer term, they will be invited to complete a Vineland assessment during 52-64 weeks by the psychology team in our study to measure any changes in behaviour. Bloodwork will be performed to check CBC, LFT, and Renal profile and trough AED levels. If the blood work is done at week 40 or 52, then no need to repeat.

After this time point participants will resume care with their regular pediatric neurologist. Written communication regarding their therapy and current dosing will be forwarded by the study investigators to this physician. In addition, the study team will be available by telephone or email to provide support to physicians as participants' transition back to their care; in particular should they have any questions about TIL-TC150.

For the weeks of the study that the participants are not being evaluated in person at The Hospital for Sick Children, follow-up emails and/or phone calls will be made. This communication will occur in between the clinical visits for the intervention period - week 1, 3, 5, 6, 7, 10, 14, and 18. Participant's parent/ legal guardian will be asked about their child's dosage to ensure correct titration or if already at maximal study protocol dose (as determined during the intervention period) how they are tolerating it. Adverse events and concomitant medications will always be assessed and any concerns participant, parent/caregiver may have will be addressed.

The study participant will be given a window of +/- 3 days around the timing of each study visit during the intervention period and +/- 14 days for the post-intervention longitudinal visit scheduling.

5.8 Schedule of Events table:

Study Period	**Week #**	**Participant/ study team interaction**	TIL-TC150**Dose**
Pre-Intervention Period	-4	Clinic visit – education, baseline physical and neurological review and urine test for THC for those only who have not been on cannabinoids for at least last 60 days.	None
Baseline analysis	-4 to 0	Participant parent/legal guardian completion of seizure diary; 24 hour ambulatory EEG, psychologist will arrange for parent/caregiver to complete a Vineland assessment	None
Intervention period	0	Clinic visit – education, weight, physical and neurological review; baseline bloodwork; collection of baseline seizure diary; education regarding dosing of study product; parent to complete baseline QOLCE	Starting at 2mg/kg/day CBD divided in 2 equal doses; first dose given in clinic with 2 hours of observation post-dose.
	1	Telephone and/ or email contact by study team to determine dosing and tolerability	Once tolerance ensured, increase dose to 4mg/kg/day CBD divided twice daily

	2	Clinic visit – tolerance review, adverse events,; physical and neurological exam; parent/legal guardian to complete PESQ; seizure diary review	Once tolerance ensured, increase to 6mg/kg/day CBD divided twice daily
	3	Telephone and/ or email contact by study team to determine dosing and tolerability	Once tolerance ensured, increase to 8mg/kg/day CBD divided twice daily
	4	Clinic visit – tolerance review, adverse events; physical and neurological exam; parent/legal guardian to complete PESQ; seizure diary review; bloodwork	Once tolerance ensured, increase to 10mg/kg/day CBD divided twice daily
	5	Telephone and/ or email contact by study team to determine dosing and tolerability	Once tolerance ensured, increase to 12mg/kg/day CBD divided twice daily
	6	Telephone and/ or email contact by study team to determine dosing and tolerability	Once tolerance ensured, increase to 14mg/kg/day CBD divided twice daily
	7	Telephone and/ or email contact by study team to determine dosing and tolerability	Once tolerance ensured, increase to 16mg/kg/day CBD divided twice daily
	8	Clinic visit – tolerance review, adverse events; physical and neurological exam; parent/legal guardian to complete PESQ and QOLCE; seizure diary review; bloodwork performed once child is at target / maximal tolerated dose (any stage from week 8-16)	If tolerated, dose to continue at 16mg/kg/day CBD divided twice daily
	10	Telephone and/ or email contact by study team to determine dosing and tolerability	If tolerated, dose to continue at 16mh/kg/day CBD divided twice daily
	12	Clinic visit – tolerance review, adverse events; physical and neurological exam; parent/legal guardian to complete PESQ; seizure diary review; bloodwork performed once at target / maximal tolerated dose (if not done previously)	If tolerated, dose to continue at 16mg/kg/day CBD divided twice daily
	14	Telephone and/ or email contact by study team to determine dosing and tolerability	If tolerated, dose to continue at 16mg/kg/day CBD divided twice daily

	16	Clinic visit – tolerance review, adverse events; physical and neurological exam; parent/legal guardian to complete PESQ and QOLCE; seizure diary review; bloodwork performed once at target / maximal tolerated dose (if not done previously)	If tolerated, dose to continue at 16mg/kg/day CBD divided twice daily
Primary Analysis	16-20	Telephone and/ or email contact by study team at 18 weeks to determine dosing and tolerability Psychologist will arrange for parent/caregiver to complete a Vineland assessment Participant parent/legal guardian completion of seizure diary during this 4 weeks; 24 hour ambulatory EEG. Collection of seizure diary reported seizure frequency.	If tolerated, dose to continue at 16mg/kg/day CBD divided twice daily
	20	If tolerated, and participant parent/legal guardian wishes to continue study product dose to continue at 16mg/kg/day CBD divided twice daily	
Longitudinal follow-up period	28	Clinic visit – tolerance review; physical and neurological exam; parent/legal guardian to complete PESQ and QOLCE; seizure diary review;	If tolerated, and participant parent/legal guardian wishes to continue, dose to continue at 16mg/kg/day CBD divided twice daily
	40	Clinic visit – tolerance review; physical and neurological exam; parent/legal guardian to complete PESQ; seizure diary review; Follow up bloodwork performed once (any stage from week 40-64)	If tolerated, and participant parent/legal guardian wishes to continue, dose to continue at 16mg/kg/day CBD divided twice daily
	52	Clinic visit – tolerance review; physical and neurological exam; parent/legal guardian to complete PESQ and QOLCE; seizure diary review; Follow up blood work performed once (if not done previously) During 52-64 weeks psychologist will arrange for parent/caregiver to complete a Vineland	If tolerated, and participant parent/legal guardian wishes to continue, dose to continue at 16mg/kg/day CBD divided twice daily

		assessment	
	64	Clinic visit – tolerance review; physical and neurological exam; parent/legal guardian to complete PESQ; seizure diary review Follow up blood work performed once (if not done previously)	If tolerated, and participant parent/legal guardian wishes to continue, dose to continue at 16mg/kg/day CBD divided twice daily

NB* At all periods during the study there will be study personnel available 24 hours through the main hospital switch board by telephone pager system for participant, parent/legal guardian should they have any concerns or queries out of hours or outside of these contact times.

NB Should clinical concern arise during reviews about potential toxicity (clinical evidence of accentuated AED action such as somnolence, change in mentation etc), a further blood draw may be performed to evaluate trough AED level (for AED where trough routinely assessed).

6. Assessment of Efficacy

6.1 Specification of Efficacy Parameters

This is a phase 1 dosing and tolerability study. Efficacy of CBD is not a primary outcome. However, as a secondary outcome we will report change in seizure frequency, severity by parent/caregiver reporting and change in EEG by objective prolonged 24 hour recording prior to and at maximal dose of intervention.

6.2 Methods of Assessing

Seizure frequency is measured by parent/caregiver in a daily diary. This will be reviewed at each clinic visit and during each phone call/email to track change and ensure compliance with reporting. Seizure severity will be measured by frequency of

rescue medication administration, frequency of status epilepticus and frequency of ER attendance /hospitalization, recorded in a daily diary. In addition to this baseline analysis of EEG will be performed for each participant using an ambulatory EEG recording for 24 hours. Pre-intervention ictal and interictal EEG patterns will be compared with a post-intervention study (once maximal dose of treatment has been achieved). EEG analysis will be performed by 2 board certified electroencephalographers (part of the study team) at the end of the primary intervention period. They will report all EEG studies blinded to whether the recording is performed pre- or post therapy. They will record the number of electrographic seizures during the study and use spike detection software to provide an objective measure of the percentage of interictal activity during each study.

7. Assessment of Safety and Adverse Events

7.1 Specification of Safety Parameters

Each participant will be carefully screened for suitability prior to commencement of the intervention. If the study team feels that any pre-existing conditions place the participant at risk they will be excluded from participation. Once enrolled in the study each participant and parent/legal guardian will receive education regarding the administration, dosing and schedule of the study treatment from the study investigator physician, study nurse and the study pharmacist. This information will be reviewed and dosing schedule re-evaluated at every clinic visit and phone call / email follow up. During each clinic visit there will be an evaluation of tolerability of the study treatment and of possible adverse events.

If at any stage during the study any adverse events are suspected they will immediately be evaluated by study team. The adverse event reporting period is from the initiation of the study treatment until the end of study treatment follow-up.

An *adverse event* is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illness or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered

adverse events, if the abnormality leads to study withdrawal, is associated with clinical signs or symptoms, leads to additional treatment or diagnostic tests, is considered by the study team to be of clinical significance or is considered a serious adverse event.

A *serious adverse event* is one which is:

- fatal
- life-threatening
- requires hospitalization or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event (not immediately life-threatening but of significant clinical importance)

All adverse events that do not meet the criteria for seriousness should be considered *non-serious adverse events*.

7.2 Methods of assessing

During the intervention period and follow-up there will be regular clinic review and telephone/email evaluation of the participant to assess tolerability of the study treatment and screen for any adverse events. This will be done by direct questioning of participant, parent/caregiver at each review. In addition the study team will perform a physical and neurological examination of participant at each clinic review. Every clinic visit we will ask parent/ caregiver to complete a side effect questionnaire (PESQ questionnaire) and study team will review the daily seizure diary. In addition at regular

intervals during the study the participant will have bloodwork to evaluate hematopoeisis, liver and renal function and trough AED levels.

7.3 Recording Procedures

At each contact with study participant the study team will evaluate for potential adverse events as specified above. Information on all adverse events will be recorded immediately in source document (medical chart) and in the specific adverse event case report form (CRF). All relevant symptoms, signs, and abnormal diagnostic tests will be recorded in the source documents also.

7.4 Reporting Procedures

Adverse Event Reporting to the SickKids REB and to Health Canada

All adverse events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements. All serious, unexpected adverse drug reactions (S-UADR) will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days. Adverse reactions will be managed according to The Hospital for Sick Children's standard clinical management practices. Each ADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: Clinical Safety Data Management Definitions and Standards for Expedited Reporting.

7.5 Adverse Event Follow-up

The clinical course of each adverse event encountered will be followed by the study team until resolution, stabilization, or until determined that study participation is not

causative. Serious adverse events that are ongoing at the end of the study period will continue to be followed until they are either resolved, or in the opinion of the Principal Investigator, the participant is medically stable and does not require further follow-up or the participant is deemed lost to follow-up. Any serious adverse event that occurs after the intervention period, but is deemed by the study team as possibly related to participation will be recorded and reported also.

8. Statistics

8.1 Statistical Method

This is an observational study. The primary aims of this study are to determine the tolerability of the study treatment in a cohort of children with mediation resistant epilepsy due to Dravet syndrome. As such, there are no formal statistical methods required, rather descriptive statistics will be presented to quantify dosing tolerability and frequency of adverse events. All participants will be analyzed regardless of dose achieved or duration of study completed, according to intention to treat analysis. The study data will be entered into the REDCap database for analysis.

8.2 Sample Size

No sample size calculation was employed. An intermediate sample size of convenience is selected, with 20 participants expected to be recruited from a single site.

9. Source Data/Documents Access

The study investigator team will permit trial-related monitoring, audits, REB review, and regulatory inspections, providing direct access to source data/documents.

10. Quality Control Procedures

The study pharmacist will oversee the dispensing of the study treatment to the participant parent/caregiver and keep documentation of this. Study investigators will document all clinical details throughout the study in CRFs and in source documentation. Principal investigator will make time to review the documentation, source documentation and ensure that it is readily available for any reviewing agency at any time. In addition study investigator team will ensure confidentiality is maintained throughout the data process. This will be overseen by study Principal Investigator as detailed below.

11. Study Ethics

This study is conducted in accordance with applicable Health Canada regulations and international standards of Good Clinical Practice, and applicable institutional policies and procedures.

12. Data Handling and Record Keeping

12.1 Confidentiality

Study participant medical information will be recorded for this study. Any participant identifier information and personal health information will be stored in a locked filing cabinet in a locked office at The Hospital for Sick Children and only the investigational team will have access to this.

12.2 Data Storage

Relevant study records will be archived for 25 years following completion of the study, as per the requirements of Health Canada's Food & Drug Act, Division 5.

13. Trial Registration

This trial will be registered with the U.S. National Institutes of Health ClinicalTrials.gov, which is a registry of federally and privately supported clinical trials conducted in the

United States and around the world. The registration will not include any identifiable participant data.

14. Publication policy

On completion of the study the enrolled participant data will be reported and this report submitted for publication in an appropriate medical journal.

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