University of Nebraska Medical Center

LB390 Scientific Report

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Introduction:

The use of cannabis related derivatives has long been a target of interest in the treatment of epilepsy, particularly certain varieties of refractory epilepsy that are not adequately responsive to traditional medical therapies. Recently, Epidiolex®, a pharmaceutical derived from the cannabis plant, has been approved for sale in the US by the FDA, and determined by the DEA to be a Schedule V medication (Corroon and Kight 2018). Epidiolex® is a highly purified and concentrated component of the cannabis plant, called cannabidiol (CBD). CBD has garnered significant interest in the treatment of severe childhood epilepsies. Recent randomized, placebo controlled trials (RPCTs) have demonstrated a significant effect of Epidiolex® in the treatment of two specific childhood epilepsies, specifically Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS) (Devinsky, Cross et al. 2017, Thiele, Marsh et al. 2018). DS and LGS are seizure disorders with onset in early childhood and very difficult to control seizures that can be numerous and long lasting, despite optimal medical therapy. Children with these disorders can also have significant developmental delays, which can be exacerbated by ongoing seizure activity. In the above-mentioned studies, Epidiolex® reduced 'drop' seizures in the LGS population by 44% (compared to 22% in placebo). In the DS trial, 43% of patients had at least a 50% decrease in overall seizure activity (compared to 27% in the placebo group). Based on the findings of the phase III RPCTs in DS and LGS, the FDA has approved Epidiolex® for treatment of these two specific conditions. In addition to these trials, several open-label studies (where all subjects receive the drug without placebo) of Epidiolex® were conducted through state based expanded access programs (EAPs) for treatment of epilepsies beyond those with LGS and DS. The focus of the EAPs was on expanding the understanding of tolerability and side effect profiles associated with Epidiolex® initiation (Szaflarski, Bebin et al. 2018). Through the EAP mechanism, data collected in a number of states was encouraging that Epidiolex® may be effective in the control of seizures in other childhood genetic epilepsies, such as Aicardi Syndrome, Doose Syndrome, and CKDL5 deficiency disorder (Devinsky, Verducci et al. 2018). In Nebraska's state sponsored EAP, we conducted a small open label study of Epidiolex® at the University of Nebraska Medical

Center. This communication describes the study and the specific finding, including its impact on seizure control and the types, frequency, and severity of side effects.

Methods:

The EAP program at the University of Nebraska Medical Center was initiated with the support of the State of Nebraska, in conjunction with LB390, enacted in 2014 by the Nebraska State Legislature. GW Research Ltd. provided Epidiolex® at no cost to the patients enrolled in the study, committing enough medication for 25 patients to be on study drug for the expected two-year period of study. Broad public announcements were released and letters were sent to neurologists across the state to include potential patient candidates, adults and children, who had a history of medically refractory epilepsy and were residents of Nebraska. The study defined refractory, or drug resistant epilepsy, as failing treatment of at least four separate drugs or treatments, including at least one combination of two concomitant drugs, without successful seizure control. Patients were required to be on treatment with between 1-4 anti-seizure drugs at baseline, with the intention of adding Epidiolex® as an adjunctive medication to their existing drug regimen. Inclusion and exclusion criteria are listed below:

Inclusion Criteria:

- Age: 1-60 years.
- Having 4 clinically countable seizures per month and prior concomitant video-EEG evidence documenting the diagnosis of epilepsy. Seizure history to include a documented history of generalized seizures ('drop' attacks, atonic, tonic-clonic and/or myoclonic), focal seizures without loss of consciousness with a motor component, focal seizures with loss of consciousness, or focal seizures with secondary generalization.
- Drug resistant epilepsy defined as trials of at least four drugs, including one trial of a combination of two concomitant drugs, without successful seizure control. Vagal nerve stimulation (VNS), RNS deep brain stimulation, or the ketogenic diet can be considered equivalent to a drug trial and documented evidence of drug and other therapeutic failures.
- Taking between 1-4 anti-epileptic drugs at time of enrollment. VNS, ketogenic diet and modified Atkins diet do not count toward this limit and are not contraindicated for inclusion.
- VNS, if in use, must be used on stable settings for a minimum of 4 weeks.
- If on ketogenic diet, on a stable ratio for a minimum of 12 weeks.
- Subject and/or family able to sign assent /research authorization and meet the study expectations for appointments for the duration of the study
- Patients or their caregivers able to consistently maintain a seizure diary for at least 2 months prior to enrollment and during the course of the study period.
- Nebraska resident

Exclusion Criteria:

- Renal, hepatic, pancreatic, or hematologic dysfunction as evidenced by: values above upper limits of normal for BUN/creatinine, or values twice the upper limit of normal for serum transaminases (ALT/SGPT, AST/SGOT), values twice the upper limit of normal for serum lipase and amylase, platelets <80,000 /uL, WBC<3.0 $x10^3$ /uL.
- Less than 4 countable seizures per month; absence seizures and myoclonic seizures are non-countable seizures.
- Use of cannabis-related product within the last 30 days.
- Active substance abuse/addiction.
- Pregnancy and breastfeeding because CBD is contraindicated in pregnancy and breastfeeding. Female subjects able to become pregnant will be tested with a urine pregnancy test before entry into the study and must agree to a double barrier method of contraception or abstinence for the duration of treatment. If pregnancy occurs, CBD will be stopped in the most clinically appropriate manner and a maternal-fetal medicine specialist will be consulted.
- Allergy to CBD or any cannabinoid.
- Unable to provide consent and no legally authorized representative (LAR) available to provide consent.
- Unable to comply with study visits/requirements.
- Drinking any alcohol.
- Unable to take liquid without a J tube, or using a G tube made with polyvinyl chloride (PVC) material.

Potentially eligible participants were referred by their primary physician or neurologist. Their patient information was then reviewed by an internal Approval Committee to determine whether the subject met the eligibility criteria for the study.

Data collection and subject study visits were scheduled in the Clinical Research Center (CRC) at Nebraska Medicine. Following informed consent, seizure frequency was documented during an 8-week baseline period, by the participant or guardian using a seizure calendar. If the threshold seizure frequency criteria was confirmed, the dose of Epidiolex® was titrated at every two week visits. The dose was started at 5mg/kg/day, taken in two divided doses approximately 12 hours apart. At each two-week follow-up clinical visit, the dosage was increased by 5mg/kg/day, until subjects reached a goal dose of 25 mg/kg/day. Titration was paused if the subject achieved a 2-week seizure-free period or the subject could not tolerate this titration schedule. In those cases the titration schedule was slowed and/or goal dose to be achieved was reduced.

At each visit, participants received a medical and neurological examination, and completed a variety of questionnaires that addressed the participant's/guardian's global impression of change after being on escalating doses of medication. Additionally, participants or guardians filled out seizure diaries from which average monthly seizure frequency was calculated.

Statistical Methods:

A generalized linear mixed model (GLMM) with log-link was used to compare the patient reported average daily number of all seizures over the first year of the study over time. The log transform of the average daily seizures was needed due to a mean variance relationship evident in the fit plots when analyzed on the data scale. The use of the log-link, means that the comparisons were done between model estimated geometric means rather than model estimated means. Since the data were right skewed, the geometric mean was closer to the median than it is to the arithmetic mean of the raw data. The model estimated geometric means (95% confidence interval), the sample median (interquartile range), and the sample mean (standard deviation) at each visit (time point) are presented in Table 2 under the heading *Seizure Activity*. For the geometric means, Dunnett's adjustment was applied to the post-hoc t-tests that compared each time point beyond day 14 back to reported seizure activity on day 14 (labeled p-value in Table 2).

The total number of adverse events across all participants per time point are reported in Table 2 under the heading *Adverse Events*. The mean number and standard deviation as well as the median and interquartile range of adverse events per participant are provided.

Because there was a large variation in numbers of seizures between participants, comparison was also made in relative reduction in seizure activity. Relative reduction (RR) in seizure activity was calculated for each person by dividing the difference in seizure activity at 14 days and each subsequent time point divided by the seizure activity at 14 days multiplied by 100. Table 3 summarizes the percentage of subjects experiencing a RR in seizure activity of 25% or more, 50% or more, 75% or more and 100% at each study reporting period. All statistical analyses and calculations were conducted using SAS software, Version 9.4, copyright 2016. Unless otherwise specified, a significance level of 0.05 was utilized.

Results:

Initial recruitment was projected to be 25 because of drug available, but total enrollment during the course of the study was 27 patients because two were added when two initial participants dropped out. All individuals had medically refractory seizures but the causes were diverse, including one with DS and five with LGS. At the time of this analysis, 23 patients are still participating in the open-label study. Four withdrew due to the development of adverse events (14.8%). Of those screened (n=32), five did not meet criteria for study. Demographics of the enrolled participants are listed in Table 1.

Table 1. Demographics of study participants. Age is reported in years at Baseline Visit. STD: standard deviation

	Aggregate	Female	Male
n	27	11	16
Average Age +/- STD	20.3 +/- 11.8	19.1 +/- 11.6	21.07 +/- 12.3
Age Range	3.2 – 58.1	3.2 – 40.0	8.3 – 58.1
Median Age (IQR)	18.4 (12.0 – 26.2)	20.1 (9.5 – 27.5)	17.3 (13.5 – 25.9)
Ethnicity			
Non-Hispanic	26	11	15
Hispanic	1	0	1
Race			
Caucasian	25	11	14
Other	2	0	2
Diagnosis			
Lennox-Gastaut Syndrome	16	4	12
Dravet Syndrome	1	1	0
Complex Partial Epilepsy	1	0	1
Other	9	6	3

Aggregated seizure response is shown in Table 3. A marginally detectable difference in the geometric mean of average seizures per day was observed by the fifth visit (56 days), where the reference visit was considered visit 2 (14 days). There was no further decrease over the remaining visits indicating a bottoming effect. Thus, from visit 5 (56 days) to visit 9 (270 days), estimated seizure reduction from baseline was 61.1% based on mean percentage reduction between visits 2-9. No participant experienced a complete cessation of seizure activity.

Table 2: Seizure activity by day and adverse events. Seizures were evaluated by generalized linear mixed model (GLMM) to estimate geometric means (95% confidence interval), medians (IQR), and arithmetic means (standard deviation).

Seizure Activity	14 Days	28 Days	42 Days	56 Days	70 Days	90 Days	180 Days	270 Days
Visit #	2	3	4	5	6	7	8	9
N	28	26	26	26	26	25	25	24
Geo mean (95% CI)	6.3 (2.6, 15.7)	4.4 (1.8, 10.8)	3.1 (1.3, 7.7)	2.8 (1.1, 7.0)	2.4 (1.0, 6.0)	2.4 (1.0, 6.0)	2.9 (1.2, 7.2)	2.1 (0.8, 5.3)
Median (IQR)	9 (3.0, 20.5)	7 (2.5, 16.0)	5.8 (1.5, 18.5)	2.8 (1.1, 7.0)	2.4 (1.0, 6.0)	2.4 (1.0, 6.0)	2.9 (1.2, 7.2)	2.1 (0.8, 5.3)
Mean (Stdev)	16.7 (27.6)	10.9 (10.6)	10.1 (10.9)	9.5 (10.6)	9.1 (12.0)	10.7 (13.0)	11.4 (14.8)	6.5 (8.5)
p-value[a]	Reference	0.7377	0.1245	0.0625	0.0146	0.0179	0.0774	0.005
Adverse events								
N	6	8	9	5	11	4	19	12
Mean (Stdev)	1.1 (0.3)	1.3 (0.5)	1.6 (0.8)	1.3 (0.5)	1.5 (0.8)	1.5 (1.2)	2.7 (2.2)	1.9 (1.3)
Median (IQR)	1 (1, 1)	1 (1, 1.3)	1 (1, 2)	1 (1, 1.3)	1 (1, 2)	1 (1, 1)	2 (1, 4)	1 (1, 3)
Total count	10	10	19	5	20	9	46	23

[a]Dunnett-Hsu corrected; reference is average seizure activity reported on day 14 visit. Geo mean: geometric mean. IQR: interquartile ratio; Stdev: standard deviation

Adverse Events and Severe Adverse Events.

Adverse events (AEs) were defined in this study as any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings), a new diagnosis, or worsening of a pre-existing condition, which presented following Epidiolex® administration, which may or may not be considered to be related to Epidiolex®. Serious adverse events (SAEs) were defined as AEs that results in death, were considered life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect (if the subject became pregnant) or deemed medically significant by study personnel.

Table 3: Percentage of subjects with relative (to day 14) seizure reduction at or above stated quartile.

	28 Days	42 Days	56 Days	70 Days	90 Days	180 Days	270 Days
25% RR	50.0	57.7	61.5	57.7	50.0	57.7	68.0
50% RR	19.2	30.8	50.0	42.3	46.2	42.3	56.0
75%RR	11.5	23.1	26.9	26.9	23.1	34.6	40.0
100%RR	7.7	11.5	11.5	15.4	19.2	15.4	12.0
N	26	26	26	26	26	26	25

RR: risk reduction

AEs are shown in Tables 2 and 4. A total of 142 AEs were reported between visit 1 (day 0) and visit 9 (day 270) over all the subjects. AEs were experienced by 24 (88.9%) out of the 27 subjects that received at least one dose of Epidiolex®. Of the 142 AEs reported, 125 (88.0%) and 17 (12.0%) were classified mild or moderate severity, respectively. Fifteen AEs (10.6%) AEs were classified as probably (10) or definitely (5) related to Epidiolex® by the principal investigator. These occurred in 8 subjects (29.6%) of the subjects enrolled.

Table 4: Summary count (percentage) of adverse events by classification.

Adverse Event Category	Number of Subjects Experiencing AE (out of 27)	Total Number of Occurrences (out of 142)
Appetite Disturbances	7 (25.9)	7 (4.9)
Falls	2 (7.4)	3 (2.1)
Decreased Platelets	4 (14.8)	4 (2.8)
Gait Disturbances	7 (25.9)	8 (5.6)
GI Disturbances	5 (18.5)	7 (4.9)
Increased ALT and/or AST	2 (7.4)	6 (4.2)
Infections	12 (44.4)	33 (23.2)
Menstrual Disturbances	2 (7.4)	4 (2.8)
Nausea/Vomiting/Dizziness	2 (7.4)	3 (2.1)
Sleep Disturbances	17 (63.0)	28 (19.7)
Miscellaneous	18 (66.7)	39 (27.5)

AE: adverse event GI: gastrointestinal; ALT: alanine aminotransferase; AST: aspartate aminotransferase

A total of five serious adverse events (SAEs) have been reported through Day 270 on study. These SAEs were experienced by 3 (8.1%) of the 27 subjects given at least one dose of Epidiolex®. The SAEs that were reported included the following:

- Suicidal Ideation
- Dehydration
- Fluid Refractory Septic Shock
- Community Acquired Pneumonia
- Decreased Platelets

The last three SAEs above were all experienced by a single subject. The three subjects experiencing SAEs withdrew. One additional subject withdrew because of a perceived lack of improvement in seizure activity.

Discussion:

In this small, open label study of Epidiolex®, a now FDA approved medication that represents highly concentrated and purified, pharmaceutical grade of cannabidiol (CBD), we treated a small cohort of adults and children with medically refractory epilepsy. Our overall goal was to determine the tolerability and adverse reactions to the medication, as well as the ability of the medication to reduce seizure rates. Overall, there appeared to be an aggregate reduction of seizure frequency of 61.1% in our study population, with the majority of adverse events (side effects) classified as mild severity. These numbers are consistent with the previously published phase III trials, with the important distinction that this was conducted as an open-label study with no placebo arm for comparison).

These results should be interpreted cautiously even though they are encouraging. One limitation of this open-label study is the potential that part of the benefit could have occurred because of a placebo effect, as all study subjects are assured of receiving actual medication, that could have been reduced if this were a randomized control trial with one group taking only placebo. However, placebo effects tend to be more prominent in the initial phases of drug initiation, and less over time. As there was a sustained reduction in seizure response in this study suggests there is likely a benefit of Epidiolex® on seizure frequency, not just a placebo effect.

There are no published placebo-controlled trial results of efficacy of Epidiolex® in conditions beyond LGS and DS, which is both the gold standard of efficacy, and what FDA requires to determine whether Epidiolex® is efficacious for other types of epilepsy. Our study population includes subjects with causes of refractory seizures beyond LGS and DS, and some appeared to receive benefit. However, this study cannot conclude that individuals with seizure disorders other than LGS and DS will benefit from this therapy because the number of subjects is small and not conducted as a placebo-controlled trial.

The majority of patients encountered adverse events, but most were mild. Somnolence was common as this drug was added to others and other drugs needed to be adjusted due to expected or unexpected drug-drug interactions. Speed of dose titration and

maximum dose tolerated had to be modified in some. Four participants encountered adverse effects substantial enough to warrant their withdrawal from the study. Some of the adverse events were related to changes in liver function tests and thrombocytopenia. These adverse events confirm the need to regularly check liver function tests and blood counts while on Epidiolex® to identify these potential side effects as early as possible.

The data from this open-label trial contributed to the growing scientific evidence of a benefit in seizure reduction as well as anecdotal reports of improved quality of life. Additionally, it was a vehicle to make the drug available to Nebraskans prior to commercial availability and provided Nebraska clinicians with experience prescribing and dosing Epidiolex®. Research focused on causes of epilepsy beyond those of LGS and DS will be required to better understand and evaluate the efficacy of this medication in epilepsy types beyond those of LGS and DS.

It is important to emphasize that Epidiolex® is an FDA approved, pharmaceutical grade medication that has been studied extensively and is manufactured in a reliable and consistent fashion. CBD products available through non-pharmacy locations, on the other hand, are not equivalent, cannot be assumed to have the same active ingredients, and may not have either the same benefits on seizure activity or safety profile. Many patients with seizures are treated with multiple medications simultaneously, and concomitant use of several medications can lead to interactions in safety and efficacy. These other nonprescription CBD formulations have not been systematically studied for interactions, so while they may be safe, they also have the potential to cause unintended harm.

Finally, Epidiolex® is not the same as 'medical marijuana'. It is made of a chemical derived from the cannabis plant, but these results should not be used to confirm the benefits of 'medical marijuana' or that marijuana has the same impact as this medication. Cannabis as a whole contains over 300 psychoactive compounds. Because Epidiolex® is an isolated, highly concentrated and purified substance its impact cannot be compared to marijuana. In particular, Epidiolex® does not have the risk of intoxication associated with marijuana use, and in a recent trial, Epidiolex® has demonstrated significantly low abuse potential in a highly sensitive population of polysubstance abusers (Schoedel, Szeto et al. 2018).

With this report, our data is consistent with other studies suggesting Epidiolex® expands the portfolio of medications available as epilepsy therapeutics to more effectively control seizures in the most difficult patients with the goal of improving overall quality of life.

This study represents an interim scientific report with a planned final report following conclusion of the trial.

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