Epilepsy & Behavior 112 (2020) 107474

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Long-term efficacy and safety of cannabidiol (CBD) in children with treatment-resistant epilepsy: Results from a state-based expanded access program☆

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ARTICLE INFO

Article history:
Received 13 July 2020
Revised 2 September 2020
Accepted 6 September 2020
Available online xxxx

Keywords:
Cannabidiol
Pediatric epilepsy
Treatment-resistant epilepsy

ABSTRACT

Introduction: An intermediate-sized, multicenter, expanded-access study was opened in 2015 through the support of the State of Georgia. This study provided children with treatment-resistant epilepsy (TRE) access to plant-derived highly purified cannabidiol (CBD; Epidiolex® in the US; Epidyolex® in the EU; 100 mg/mL oral solution). These children had failed to achieve seizure freedom with available treatment options and were ineligible to participate in randomized controlled trials that only included patients with Lennox–Gastaut and Dravet syndromes.

Methods: Cannabidiol safety, changes in seizure type, frequency, and seizure-free days were evaluated for children aged 1–18 years (at time of consent) as an adjunctive treatment for 36 months. The study consisted of a two-month baseline period, a titration period, treatment period, and optional titration period, which occurred after ≥26 weeks of treatment. Cannabidiol treatment was administered up to a targeted dose of 25 mg/kg/day, with an optional secondary treatment up to 50 mg/kg/day. Daily seizure type, seizure frequency, and seizure-free days were recorded in a Web-based diary, and changes in these outcomes were recorded and analyzed for the duration of the study. The occurrence of adverse events (AEs) was also recorded.

Results: The median percentage change in seizures for 45 patients in Months 3, 6, 12, 18, 24, and 36 showed a statistically significant ($p < 0.001$) reduction in major seizures (ranging from 54 to 72% at various time points) and all seizures (61–70%) compared with baseline. A mean increase in seizure-free days per 28 days was >5 in all treatment periods after Month 2, and an average increase of 7.52 ($p < 0.001$) seizure-free days per 28 days was observed at the end of follow-up compared with baseline. All patients experienced ≥1 AE. Children who transitioned to the optional secondary treatment (high-dose group) reported more AEs before increasing their dose to >25.0 mg/kg/day compared with the low-dose group. However, the average rate of AEs was significantly lower after moving to a high-dose regimen ($p = 0.004$). Twelve children reported 20 serious AEs, none of which were considered related to CBD.

Conclusions: This study supports CBD as an adjunctive treatment for children with TRE. Treatment was well tolerated in doses up to 50 mg/kg/day. Patients who did not achieve desired results at a dose of ≤25.0 mg/kg/day reported more AEs when CBD dose increased to >25.0 mg/kg/day. Decreases in major seizure frequency and an increase in seizure-free days compared with baseline were reported during treatment. This supports the efficacy and tolerability of CBD for mixed seizure etiologies.

1. Introduction

Data on the safety and efficacy of cannabidiol (CBD) for treating seizures have been consistently emerging over the past decade. Studies have shown that CBD decreases major seizure frequency both in vivo and in vitro [1], is without psychoactive properties [2], and is generally well tolerated [3]. In addition, owing to increasing numbers of community and patient advocacy groups, there has been strong support for

Abbreviations: AED, antiepileptic drug; CBD, cannabidiol; TESAE, treatment-emergent serious adverse event; TEAE, treatment-emergent adverse event; TRE, treatment-resistant epilepsy.

☆ ClinicalTrials.gov Identifier: NCT02397863.

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https://doi.org/10.1016/j.yebeh.2020.107474
1525-5050/

compassionate use, providing access to CBD therapy among children with treatment-resistant epilepsy (TRE).

Children with TRE have a higher risk for sudden unexpected death in epilepsy [4–6], and the known developmental effects associated with early-age seizure onset and high seizure frequency in these children [7,8] have motivated families to seek alternative treatments. To support families and their children with TRE, the Georgia Governor's Office and Augusta University, in partnership with GW Research Ltd., provided an opportunity for children in Georgia to receive plant-derived highly purified CBD (Epidiolex® in the US; Epidyolex® in the EU; 100 mg/mL oral solution). This state-funded, multicenter, intermediate-sized, expanded-access program gave children access GW Research's federally approved CBD formulation. The study also allowed children with different epilepsy etiologies and complex medical diagnoses—making them ineligible for GW Research-initiated randomized controlled trials—to receive GW Research's CBD, which could potentially improve their seizure frequency, cognition, and overall quality of life.

2. Methods

2.1. Study design and patient population

The study was conducted at three major pediatric epilepsy referral centers in Georgia starting in January 2015, and eligible patients were enrolled consecutively through November 2015. Eligible children were Georgia residents aged 1–18 years with a diagnosis of TRE. Treatment-resistant epilepsy was defined as ≥4 countable seizures per month (28 days) for 2 successive months (with ≥1 seizure in each 2-week period), and a history of trying ≥4 antiepileptic drugs (AEDs), including ≥1 combination of 2 concomitant AEDs. Vagus nerve stimulation and ketogenic diet were included as equivalent to drug therapy.

Patients were excluded if they were eligible to enroll in a CBD randomized controlled trial, had a progressive neurological condition, clinically relevant abnormal blood laboratory levels, unstable AEDs for at least 4 weeks before starting CBD, were unwilling to abstain from current or future cannabis use, or had any abnormalities that would prevent safe study participation. Patients with the following conditions also were excluded: known or suspected hypersensitivity to cannabinoids, impaired hepatic function, cardiovascular conditions that impaired electrocardiography readings, or a clinically significant postural drop in systolic blood pressure at screening or the start of titration. If a child withdrew or was no longer eligible, s/he had an end-of-treatment, in-person visit followed by a taper-down period and safety follow-up.

The study was approved by a central institutional review board or review board at participating institutions and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All children and their parents or legally authorized representatives provided written informed consent, and children with adequate cognitive abilities provided assent. A Data Safety Monitoring Committee reviewed safety data throughout the study. Patients transitioned out of the study in 2019, after CBD gained approval from the Food and Drug Administration (FDA) in June of 2018.

2.2. Study procedures

The study was composed of 4 periods: baseline, titration, treatment, and optional titration. During the 2-month baseline period, seizure type and frequency were reviewed by an independent Epilepsy Study Consortium to ensure consistency of seizure type and eligibility. The 5-week titration period began after confirming eligibility and completion of baseline measurements. During the 26-week treatment period, patients received twice daily, divided doses of an oral solution containing 100 mg/mL CBD (GW Research Ltd., Cambridge, UK) that increased by 5-milligram increments on a weekly basis. Concomitant AED doses remained stable, and this regimen continued throughout the treatment period until the patient reached a maximum dose of 25 mg/kg/day.

Patients were considered for the optional titration period after completing 26 weeks of treatment if the CBD dose ≤25 mg/kg/day had not led to desired improvements. Additionally, local investigators evaluated drug tolerance and safety during the treatment period to determine if the child could potentially benefit from a CBD dose >25 mg/kg/day. Patients who entered the optional titration period increased their CBD dose by weekly increments of 5 mg/kg in divided doses until they reached a maximum of 50 mg/kg/day or until safety and tolerability were achieved. Patients who received CBD doses >25 mg/kg/day at Month 36 were classified as the high-dose subgroup; those who received CBD doses ≤25 mg/kg/day were classified as the low-dose subgroup.

On a daily basis, patients' caregivers logged information on seizure frequency and type, seizure-free days, medication compliance, menses cycle, and use of rescue medication (e.g., valium, lorazepam) into a Web-based application, the Georgia Cannabidiol Study Epilepsy Application (Irody, Inc., Boston, MA). This diary provided cloud-based data aggregation and patient management reports for the study. The application was installed on the caregiver's smartphone or accessed through a Website portal. Caregivers were provided instructions for tracking seizures, treatment-emergent adverse events (TEAEs), and medication compliance.

2.3. Assessments

The primary efficacy endpoint was the percentage change in seizure frequency from baseline to Months 3, 6, 12, 18, 24, and 36 for the overall patient population and for the high- and low-dose subgroups. Major seizures were defined as complex partial with motor involvement, tonic, atonic, epileptic spasm, and generalized (including secondary) tonic–clonic seizures. Minor seizures were classified as complex partial without motor involvement, absence, or myoclonic.

Key secondary endpoints included a responder analysis for major seizures and the mean number of seizure-free days for all seizures in the overall population and for the high- and low-dose subgroups. For the responder analysis, major seizure frequency data at Month 3 were compared with Month 36 to identify patients who had a ≥50% reduction in major seizures (i.e., responders) vs. those who had a <50% reduction in major seizures (i.e., low/nonresponders). The mean number of seizure-free days (every 28 days) at Months 3, 6, 12, 18, 24, and 36 were compared with baseline. All months were counted as 28 days; however, if fewer than 28 days of seizure data were recorded, the frequency was adjusted to reflect the total number of days for which data were collected.

Safety was closely monitored. During the titration periods, patients were seen monthly until a stable dose of CBD was achieved. In-person safety visits also occurred quarterly and progressed to biannually after patients entered Month 36. These visits included a physical examination, neurological examination, vital sign assessment, laboratory values, and a review of online reported seizure activity. Monthly safety calls and access to a 24/7 telephone line provided ongoing monitoring and communication. All TEAEs and serious treatment-emergent adverse events (TESAEs) were counted and rated according to standardized and preferred terms.

2.4. Statistical analysis

Children who received CBD for ≥10 weeks were included in analysis. Patients participated in the study up to a maximum of 54 months of treatment.

The percentage change in seizure (major and all) frequency was calculated as [(seizure frequency per 28 days) − (seizure frequency at baseline)] / (seizure frequency at baseline) × 100. If some days in any given month were missing, seizure frequency was adjusted to 28-day

intervals for baseline and each month by computing these as rates by the observed number of days in the respective time periods. Because missing days most likely correspond to seizure-free days, this is a conservative approach for analyzing this endpoint.

For each prespecified time period, we performed the sign test to assess the changes from baseline in seizure frequency, assuming that the median percentage change in major seizures from baseline was 0. We adjusted for multiple comparisons across the time periods using Bonferroni corrections and adjusted 95% confidence intervals (CIs).

We performed 2 post hoc analyses. We used the Kruskal–Wallis test to determine if response rates were influenced by the epilepsy etiology classification at baseline, and we used the Wilcoxon–Mann–Whitney U test to determine if response rates were influenced by the concomitant use of clobazam at 3 different timepoints (i.e., baseline, Month 13, Month 19) during the study.

Treatment-emergent adverse events reported by >10% of the patients are summarized for the overall patient population. We compared TEAE rates between the high- and low-dose subgroups before some patients transitioned to a high-dose regimen by calculating the total number of TEAEs that occurred in the high-dose subgroup between the start of treatment and just before the patients transitioned to a high-dose regimen, divided by the duration of this follow-up time (exposure-adjusted incidence rate [EAIR]). The mean EAIR of TEAEs in the high-dose subgroup was compared with the mean EAIR of TEAEs in the lose-dose subgroup using a two-sample t-test.

Mean EAIR also was evaluated within the high-dose subgroup before titrating to (>25 mg/kg/day) and after titration to (>25 mg/kg/day) for a pre–post comparison. Treatment-emergent adverse event rates in the high-dose pretitration group were computed as the total number of TEAEs from treatment day 1 to the month of transition to the high dose and computed in the high-dose posttitration group as the total number of TEAEs from the month of transition to the high dose to end of follow-up, divided by duration of follow-up time, respectively. The pre–post TEAE rates were then compared using a paired t-test.

3. Results

3.1. Patient disposition and baseline demographics

Fifty-three patients provided consent, and 50 patients received CBD. No patients were taking artisanal CBD before study enrollment. Three patients withdrew after <10 weeks of treatment (withdrawal of consent [n = 1], lack of perceived efficacy [n = 2]). Forty-seven patients completed 6 months of treatment; 2 patients were excluded thereafter (major seizure not reported during baseline [n = 1], seizure diary reporting noncompliance [n = 1]). Patients in the low-dose subgroup were slightly older than those in the high-dose subgroup. For epilepsy etiology, most patients in the low-dose subgroup (45% [13/29]) had malformations of cortical development; most patients in the high-dose subgroup (69% [11/16]) had a cryptogenic etiology. Baseline demographic and clinical characteristics are presented in Table 1.

3.2. Seizure frequency

There were statistically significant reductions in median major seizure frequency during the first 3 months of CBD treatment, and changes from baseline to Months 6, 12, 18, 24, and 36 also were statistically significant (all p-values <0.001) (Table 2). Median percentage changes in major seizure frequency for all patients and for the high- and low-dose subgroups are shown in Fig. 1. Month-to-month changes in major seizure frequency were not statistically significant (all p-values >0.05). Across all seizure types, the results were similar; all changes from baseline to Months 3 through 36 were statistically significant (all p-values <0.001) (Table 2). Owing to the nature of absence and myoclonic seizures, it is possible that some of these minor seizures were missed and not recorded accurately in the seizure diary.

Table 1
Demographic and baseline characteristics.

Characteristic		Major seizure analysis	
	All patients (N = 47)	High-dose group (n = 29)[a]	Low-dose group (n = 16)[a]
Mean age, years	10.4	10.0	11.5
Median (range)	11.1 (1.3–18.8)	10.5 (1.6–18.8)	12.1 (4.2–17.6)
Male gender, n (%)	27 (57)	16 (55)	10 (63)
Mean BMI, kg/m^2	21.3	20.1	24.1
Epilepsy etiology, n (%)			
Cryptogenic	19 (40)	8 (28)	11 (69)
Malformation of cortical development	15 (32)	13 (45)	2 (13)
Hypoxic–ischemic encephalopathy/stroke	6 (13)	4 (14)	2 (13)
Chromosomal anomaly	4 (9)	1 (3)	1 (6)
Infection	3 (6)	3 (10)	0 (0)
Mean CBD dose (month 36), mg/kg/d	35.9	43.7	22.1
Median (range)	35 (10–50)	47.5 (30–50)	25 (10–25)
Mean (range) number AEDs	4.2 (2–7)	3.2 (2–6)	2.8 (2–5)
AED, n (%)			
Clobazam	30 (64)	19 (66)	11 (69)
Levetiracetam	24 (51)	15 (52)	8 (50)
Lamotrigine	15 (32)	11 (38)	4 (25)
Topiramate	13 (28)	7 (24)	6 (38)
Zonisamide	9 (19)	6 (21)	3 (19)
Rufinamide	9 (19)	6 (21)	3 (19)
Oxcarbazepine	8 (17)	5 (17)	2 (13)
Phenytoin	5 (11)	3 (10)	2 (13)
Lacosamide	5 (11)	4 (13)	1 (6)
Phenobarbital	3 (6)	3 (10)	0 (0)
Vigabatrin	3 (6)	3 (10)	0 (0)
Ethosuximide	2 (4)	0 (0)	2 (13)
Perampanel	2 (4)	2 (7)	0 (0)
Valproic acid	2 (4)	1 (3)	0 (0)
PRN[b]	55 (29)	22 (76)	13 (80)
Other interventions, n (%)			
Vagus nerve stimulation	11 (23)	8 (28)	3 (19)
Epilepsy surgery	10 (21)	3 (10)	7 (44)
Ketogenic diet	1 (2)	1 (3)	0 (0)

AED = antiepileptic drug; BMI = body mass index; CBD = cannabidiol; PRN = pro re nata (as needed).
[a] Two patients were not included in the major seizure analysis (for 1 patient, a major seizure was not reported during the baseline period, and for the other patient, there was noncompliance with diary reporting).
[b] Acetazolamide, clonazepam, diazepam, lorazepam.

Fig. 2 shows the median percentage change in major seizure frequency for all patients and for the high- and low-dose subgroups. Patients represented by the data plotted in green showed a lower median reduction in major seizure frequency during the initial treatment period (n = 31, −46%, p = 0.005). These patients were identified by the Principal Investigators as potentially benefitting from a higher treatment dose and were titrated to a higher dose of CBD. Additional improvements in the median seizure frequency were noted for this group

Table 2
Change in monthly seizure frequency from baseline to Months 3–36 for all patients.

	Major seizures		All seizures	
	Median (95% CI) change	p-Value	Median (95% CI) change	p-Value
Month 3	−62% (−85%, −37%)	0.003	−62% (−77%, −44%)	<0.001
Month 6	−65% (−83%, −39%)	0.001	−62% (−79%, −46%)	<0.001
Month 12	−54% (−70%, −31%)	0.009	−61% (−70%, −39%)	<0.001
Month 18	−65% (−85%, −37%)	<0.001	−69% (−82%, −58%)	<0.001
Month 24	−62% (−78%, −29%)	0.001	−68% (−78%, −53%)	<0.001
Month 36	−72% (−87%, −56%)	<0.001	−70% (−81%, −62%)	<0.001

BL = baseline; CI = confidence interval.

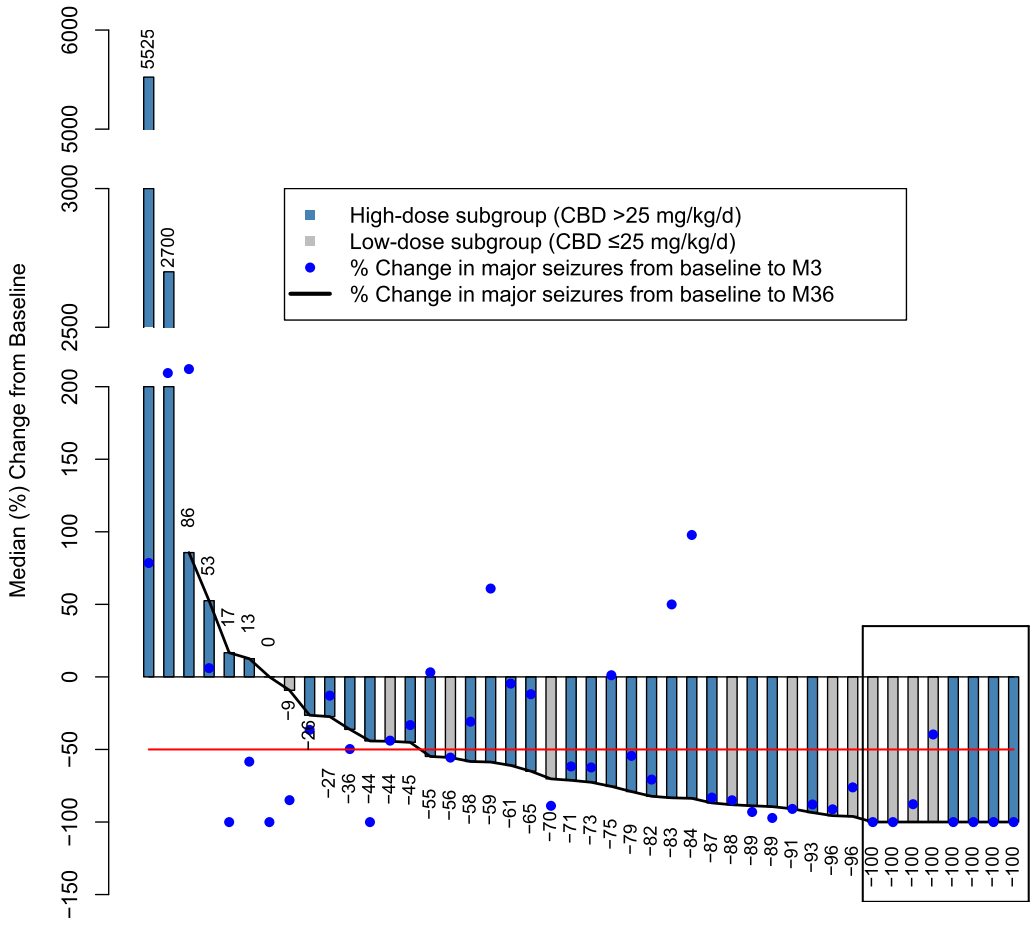

Fig. 1. Major monthly seizure frequency from Month 3 to Month 36.

over time, albeit the relative extent of their seizure reductions was less than the low-dose group. Patients represented by the data plotted in blue showed the largest reduction in major seizure frequency (n = 15, −93%, $p < 0.001$) at the initial treatment dose. These patients did not titrate to higher doses but continued to maintain their initial treatment dose throughout the entire treatment period while also continuing to report sustained treatment responses.

At Month 36, 6 patients (13.6%) had increases in major seizure frequency. Two patients (4.5%) who had a reduction in seizure frequency >50% at Month 3 showed an additional 10–20% increase at Month 36.

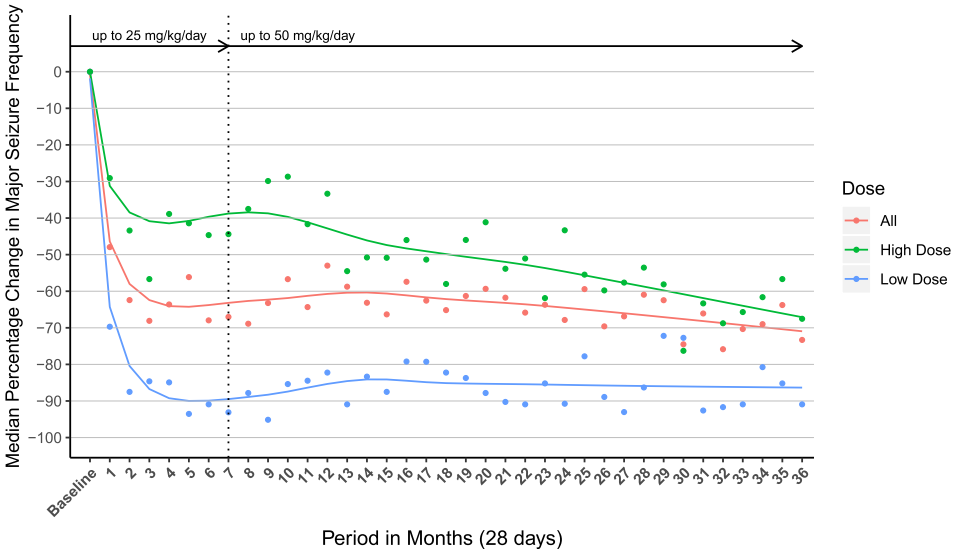

Fig. 2. Percentage change in monthly major seizures from Baseline to Month 36.* [a]n = 44 (1 patient did not experience a major seizure during the baseline period). [a]The percentage change in major seizures from baseline to Month 3 for patients 2 and 3, the second and third blue dots, actual values are outside the first plotting range. These values are 300 and 347 respectively, but are plotted at 200 for illustration.

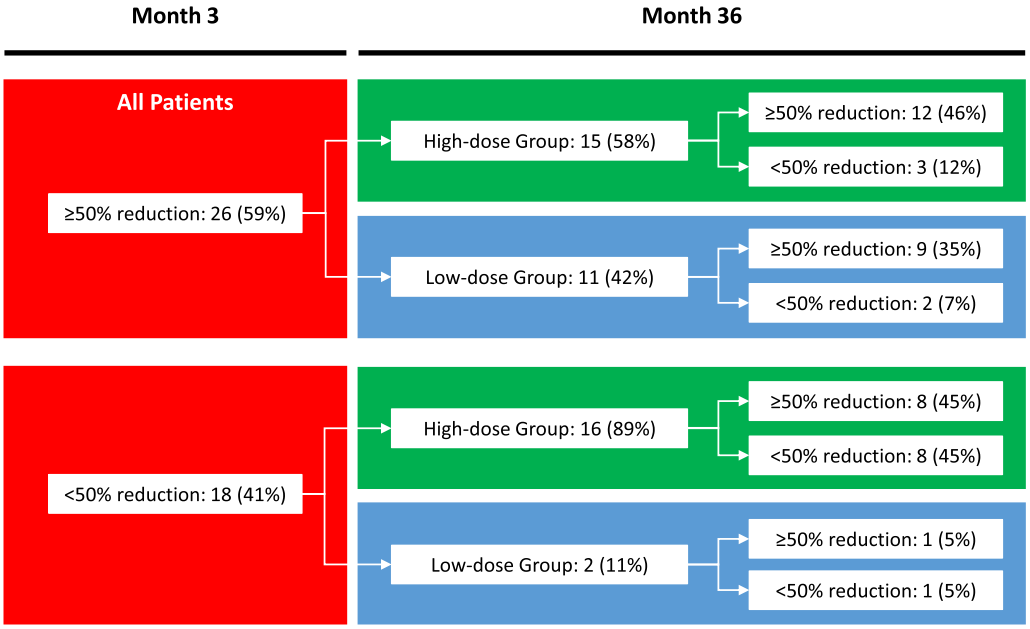

Fig. 3. Results of the responder analysis.

The remaining 4 patients did not achieve a reduction >50% at Month 3. Of these, 2 patients (4.5%) had increases in seizure frequency from 50 to 90%, and 2 patients (4.5%) had increases in seizure frequency of 2700% and 5525% at Month 36. These patients remained on study because their family felt that CBD was still helping them in terms of seizure severity and overall quality of daily living.

3.3. Responder analysis

At Month 3, 59% (26/44) of all patients were classified as responders, as they experienced a ≥50% reduction in seizure frequency (Fig. 1). Forty-one percent (18/44) experienced a decrease in seizure frequency but did not reach the ≥50% responder threshold. Sixteen of these patients transitioned to the high-dose subgroup, and 2 patients remained in the low-dose subgroup. At Month 36, 81% (21/26) of patients remained responders and continued to report seizure frequency reductions ≥50%. This included 80% (12/15) and 82% (9/11) of patients in the high- and low-dose subgroups, respectively. By contrast, 3 patients that transitioned to the high-dose subgroup and 2 that remained in the low-dose subgroup did not maintain a ≥50% reduction in seizure frequency at Month 36. Of the 16 patients that transitioned into the high-dose group, 50% (8/16) became responders, showing a reduction in seizure frequency ≥50%. Of the 2 patients that remained in the low-dose subgroup, 1 patient became a responder. Overall, a reduction in seizure frequency ≥50% at Month 3 had 81% sensitivity for predicting a similar reduction at Month 36 (Fig. 3).

3.4. Seizure-free days

The mean change in the number of seizure-free days from baseline to each of the monthly treatment periods was significantly greater than 0. The mean increase in seizure-free days was >5 during each treatment period, and there was a statistically significant mean increase of 7.77 seizure-free days between baseline and Month 36 ($p < 0.001$) (Table 3).

Four patients each in the low- and high-dose groups achieved 100% seizure-free days by Month 36 (Fig. 1). For these 8 patients, the number of consecutive months with seizure-free days were 27, 26, 24, 20, 15, 11, 1, and 0, respectively. Two patients experienced increases in seizure frequency from baseline (>5000% and 2700%). This was due, at least in part, to the low number of seizures experienced by these patients at baseline and to the adjustments made for the number of missing days. Nevertheless, these patients remained on study, as these patients reported other improvements in quality of life and cognition (data not shown), which were believed to be highly beneficial, particularly for an expanded access study.

3.5. Post hoc analyses

The median percentage changes in major seizure frequency from baseline by epilepsy etiology are presented in Table 4. All *p*-values were >0.05, indicating no evidence of any statistically significant differences in response rates by etiology. However, these findings should be interpreted with caution, as the sample sizes were very low for some classifications. It also should be noted that the medians (Q1, Q3) were much larger for the chromosomal anomaly etiology compared with the others, as the patient with the extreme (highest) increase in seizure frequency was classified by this etiology.

The median percentage changes in major seizure frequency from baseline by patients taking and not taking clobazam during the study are presented in Table 5. All *p*-values were >0.05, indicating no evidence of any statistically significant differences in response rates by concomitant clobazam status.

Table 3
Change from baseline to Months 3–36 in the number of seizure-free days over 28 days.

Month	Mean (SE)	95% CI	*p*-Value[a]	Adjusted *p*-Value[b]
Month 3	5.17 (1.16)	(2.83, 7.51)	<0.001	<0.001
Month 6	6.46 (1.46)	(3.52, 9.41)	<0.001	<0.001
Month 12	6.89 (1.35)	(4.18, 9.61)	<0.001	<0.001
Month 18	7.52 (1.49)	(4.52, 10.51)	<0.001	<0.001
Month 24	7.24 (1.40)	(4.42, 10.06)	<0.001	<0.001
Month 36	7.77 (1.56)	(4.61, 10.92)	<0.001	<0.001

CI = confidence interval; SE = standard error.
[a] *p*-Value for t-test that the mean difference in seizure-free days was 0.
[b] Bonferroni adjusted *p*-value for multiple comparisons.

Table 4
Median (Q1, Q3) percentage change[a] from baseline in major seizure frequency by patient epilepsy etiology.

	Cryptogenic	HIE/stroke	CD	Infection	Chromosomal anomaly	Total	*p*-Value
Month 3	−66 (−91, −29) [n = 20]	−90 (−98, −63) [n = 6]	−31 (−77, −1) [n = 15]	−65 (−98, −7) [n = 4]	1 (−82, 100) [n = 4]	−62 (−91, −5) [n = 49]	0.301
Month 6	−66 (−91, −29) [n = 19]	−70 (−87, −62) [n = 6]	−40 (−81, 3) [n = 15]	−97 (−99, −30) [n = 3]	−93 (−96, 6385) [n = 3]	−65 (−92, −12) [n = 46]	0.622
Month 12	−66 (−91, −29) [n = 19]	−78 (−97, −49) [n = 6]	−34 (−64, −10) [n = 15]	2 (−47, 55) [n = 3]	−100 (−100, 1507) [n = 3]	−54 (−85, −3) [n = 46]	0.457
Month 18	−66 (−91, −29) [n = 19]	−74 (−97, −41) [n = 6]	−57 (−83, −9) [n = 15]	−92 (−96, −48) [n = 3]	−98 (−99, 1329) [n = 3]	−65 (−94, −20) [n = 46]	0.656
Month 24	−66 (−91, −29) [n = 19]	−64 (−92, −34) [n = 6]	−51 (−77, −12) [n = 15]	−7 (−50, 50) [n = 3]	1101 (505, 1696) [n = 2][b]	−62 (−90, −12) [n = 45]	0.633
Month 36	−66 (−91, −29) [n = 18]	−84 (−97, −53) [n = 6]	−63 (−80, −56) [n = 14]	−89 (−95, −67) [n = 3]	−96 (−98, 2714) [n = 3]	−72 (−92, −42) [n = 44]	0.680

CD = coeliac disease; HIE = hypoxic–ischemic encephalopathy.
[a] Kruskal–Wallis one-way analysis of variance on ranks.
[b] One patient with chromosomal anomaly had all 28 days missing at month 24.

3.6. Safety

All 47 patients experienced ≥1 TEAE. Treatment-emergent adverse events reported by ≥10% of patients are presented in Table 6. Twelve children experienced 20 TESAEs, which all required hospitalization (Table 7). Causes for hospitalization were the result of one or more underlying TEAE (n = 29). None of the TESAEs were considered related to CBD treatment and all resolved.

The mean incidence rate of TEAEs in the low-dose subgroup was 0.43 AEs/month. The mean EAIR of TEAEs in the high-dose subgroup – before transitioning to a high-dose regimen – was 0.72 TEAEs/month, corresponding to a mean difference of 0.29 (95% CI: 0.07, 0.52). Patients in the high-dose subgroup experienced a higher mean rate of TEAEs before transitioning to a high-dose regimen vs. patients who remained in the low-dose subgroup ($p = 0.011$). The mean rate of TEAEs after transitioning to the high-dose group was 0.48 TEAEs/month, and the pre- vs. posttreatment difference was 0.24 (95% CI: 0.08, 0.40), indicating a significantly lower mean rate of TEAEs after moving to a high-dose regimen ($p = 0.004$).

4. Discussion

This study investigated the use of CBD for children diagnosed with TRE who failed to achieve adequate seizure management with available treatment options. All patients had previously tried various treatment combinations, including pharmacotherapy, dietary therapy, epilepsy surgery, and vagus nerve stimulation. These patients also were excluded from participating in randomized controlled trials with CBD because of their complex diagnoses. Thus, this intermediate-sized, multicenter, expanded-access program study provided a meaningful and potentially beneficial treatment option for these children.

Table 5
Median (Q1, Q3) percentage change in major seizure frequency from baseline for patients taking and not taking clobazam during the study.

	Taking clobazam at baseline			*p*-Value
	No	Yes	Total	
Month 3	−83 (−93, 1) [n = 17]	−56 (−86, −11) [n = 32]	−62 (−91, −5) [n = 49]	0.487
Month 6	−70 (−93, −38) [n = 16]	−61 (−92, 2) [n = 30]	−65 (−92, −12) [n = 46]	0.473
Month 12	−45 (−76, 5) [n = 16]	−54 (−85, −14) [n = 30]	−54 (−85, −3) [n = 46]	0.764
Month 18	−83 (−99, −38) [n = 16]	−58 (−91, −7) [n = 30]	−65 (−94, −20) [n = 46]	0.146
Month 24	−78 (−92, 5) [n = 16]	−50 (−83, −12) [n = 29]	−62 (−90, −12) [n = 45]	0.255
Month 36	−81 (−95, −58) [n = 16]	−66 (−88, −27) [n = 28]	−72 (−92, −42) [n = 44]	0.221
	Taking clobazam at month 13			*p*-Value
	No	Yes	Total	
Month 18	−67 (−92, −38) [n = 17]	−60 (−95, −14) [n = 29]	−65 (−94, −20) [n = 46]	0.561
Month 24	−77 (−91, −33) [n = 17]	−45 (−83, 25) [n = 28]	−62 (−90, −12) [n = 45]	0.068
Month 36	−77 (−90, −52) [n = 16]	−71 (−94, −23) [n = 28]	−72 (−92, −42) [n = 44]	0.677
	Taking clobazam at month 19			*p*-Value
	No	Yes	Total	
Month 24	−76 (−91, −25) [n = 17]	−50 (−83, 8) [n = 28]	−62 (−90, −12) [n = 45]	0.223
Month 36	−77 (−90, −45) [n = 16]	−71 (−94, −34) [n = 28]	−72 (−92, −42) [n = 44]	0.922

Wilcoxon–Mann–Whitney U test.

Table 6
TEAEs occurring in ≥10% of patients.

TEAE	TEAEs, n	Patients with TEAEs, n (%)
Upper respiratory infection	319	45 (90)
Gastrointestinal disorders (vomiting, diarrhea, nausea)	198	43 (86)
Pyrexia	91	26 (52)
Skin rash or infection	51	26 (52)
Somnolence	42	24 (48)
Bruise, abrasion, laceration, or sprain from fall	59	23 (46)
Increased seizures	41	20 (40)
Irritability/aggression/frustration	31	20 (40)
Pain	18	15 (30)
Headache	32	14 (28)
Broken bone/tooth	11	9 (18)
Eye infection/irritation	12	9 (18)
Constipation	10	8 (16)
Other	8	8 (16)
Urinary tract infection	11	8 (16)
Pneumonia	16	7 (14)
Decreased appetite	12	6 (12)
Respiratory distress/insufficiency	16	5 (10)
Sleep changes	5	5 (10)

TEAE = treatment-emergent adverse event.

The median frequency of seizures decreased significantly during CBD treatment. After 1 month of titration and 2 at a stable dose of CBD, the median reduction was 62% for major seizures and 62% for all seizures, which was deemed to be clinically meaningful [9]. Although there were monthly variations in reduction rates for major seizures, the observed benefit persisted for the remainder of the study without any statistically significant difference between months. This may indicate that early response to CBD is predictive of ongoing responsiveness to this therapy.

Of the 44 patients who experienced major seizures, 59% and 68% showed reductions in seizure frequency ≥50% at Months 3 and 36, respectively. Sixteen patients in the low-dose subgroup for 26 weeks were low/nonresponders. After transitioning into the high-dose subgroup, 50% became responders by showing a ≥50% reduction in seizure frequency. This suggests that some children may achieve improvements in seizure management with longer-term treatment at higher doses of CBD.

Eighteen percent of patients showed 100% seizure-free days at Month 36. This group consisted of 4 children in the low-dose subgroup and 4 in the high-dose subgroup. This is consistent with earlier results [10], although more patients in this study experienced complete seizure-free days.

Findings from our post hoc analyses revealed that neither epilepsy etiology nor concomitant clobazam status influenced response rates for changes in major seizure frequency.

Overall, a consistent safety profile was observed. All patients experienced at least 1 TEAE during 36 months of treatment. The most common TEAEs included upper respiratory infection, gastrointestinal disorders, pyrexia, and somnolence, which are consistent with other recently published studies involving both children and adults treated with this formulation of CBD [9–14]. Treatment-emergent adverse events that resulted in hospitalization were classified as TESAEs. Investigators did not deem any of the increases in seizure frequency to be causally related to CBD. Children who titrated to the high-dose subgroup experienced a statistically significant increase in TEAEs (0.29 TEAEs/month) after transitioning. The decision to increase the dose was based upon real-time clinical judgment, tolerance, and perceptions of potential benefit. This suggests that increasing CBD dose may correlate with an increase incidence of TEAEs for patients with TRE.

This study is not without limitations, including the lack of a control group, providing CBD as an open-label treatment, the small sample size, and treating children with complex and varied epilepsy etiologies. The strengths of this study include treatment with a standardized formulation of CBD, consistent baseline evaluation period, consistent evaluations across all patients and time points, 6 months of sustained, concomitant AED dosing before any AED dosing changes, long-term observation of treatment for 36 months, and an evaluation of the potential response to different doses of CBD. Additionally, the screening criteria and independent review of seizure description by the Epilepsy Study Consortium ensured a consistent classification of seizure type, while the use of the Georgia Cannabidiol Study Epilepsy Application ensured that data reporting was timely with both seizure frequency and seizure-free days accurately recorded. The use of consistent personnel for data monitoring also minimized the risk of missing or inconsistent classification of TEAEs.

5. Conclusions

The results of this study support and extend those from previous research on the safety and tolerability of CBD, demonstrating that CBD was generally well tolerated as a long-term treatment for children with TRE in doses up to 50 mg/kg/day. The treatment effects also appeared to support a reduction in major seizure frequency and an increase in total seizure-free days for many patients, although increasing the treatment dose to >25 mg/kg/day did not appear to provide a sustained improvement in major seizure frequency or increasing

Table 7
TESAEs resulting in hospitalization by underlying TEAE and severity.

TEAE	Severity			TESAEs n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Increased seizures		10 (26)	3 (27)	13 (25)
Respiratory distress/insufficiency		8 (21)	3 (27)	11 (21)
Upper respiratory infection		5 (13)		5 (10)
Pneumonia		4 (10)		4 (8)
Drug concentration increased		1 (3)	1 (9)	2 (4)
Irritability/aggression/frustration		1 (3)	1 (9)	2 (4)
Cardiac disorders: Other		1 (3)	1 (9)	2 (4)
Gastrointestinal disorders		2 (5)		2 (4)
Laboratory value changes		2 (5)		2 (4)
Pyrexia	2 (67)	1 (3)		3 (2)
Constipation		1 (3)		1 (2)
Eye infection/irritation			1 (9)	1 (2)
Hypothermia			1 (9)	1 (2)
Other: bruise, abrasion, laceration, or sprain from fall		1 (3)		1 (2)
Skin rash or infection	1 (33)			1 (2)
Weakness		1 (3)		1 (2)
Total	3 (6)	38 (73)	11 (21)	52 (100)

TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

seizure-free days. A reduction in seizure frequency of ≥50% at Month 3 showed 81% sensitivity for predicting a similar reduction at Month 36. Additional research is needed to clarify the effectiveness of CBD treatment for children with TRE and to investigate changes in the quality of life of affected children and their families.

Funding source

This project was funded by the State of Georgia.

Declaration of competing interest

Yong Park, MD served as a speaker and consultant for Greenwich Biosciences, Inc. All other authors have no conflicts of interest relevant to this article to disclose.

Acknowledgments

We would like to thank the GW Pharmaceuticals team that provided feedback on the study design and supported the State of Georgia in the development of this treatment approach and provided the investigational drug at no cost. We also would like to thank Georgia Governor Nathan Deal and the Governor's Office for providing financial support for the study. Linda Goldstein, PhD, CMPP of The Write Source MSC, LLC provided medical writing and editing assistance funded by Augusta University.

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