



## Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results

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### ABSTRACT

**Background:** Since 2014, patients with severe treatment-resistant epilepsies (TREs) have been receiving add-on cannabidiol (CBD) in an ongoing, expanded access program (EAP), which closely reflects clinical practice. We conducted an interim analysis of long-term efficacy and tolerability in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) who received CBD treatment through December 2016.

**Methods:** Children and adults with LGS/DS taking stable doses of antiepileptic drugs (AEDs) at baseline were included from 25 EAP sites across the United States. During the 4-week baseline period, parents/caregivers kept diaries of all countable seizure types. Patients received a pharmaceutical formulation of highly purified CBD (Epidiolex®; 100 mg/mL) in oral solution at 2–10 mg/kg/day, titrated until tolerability limit or a maximum dose of 25–50 mg/kg/day. Patient visits were every 2–4 weeks. The percentage change from baseline in median monthly convulsive (ie, major motor) and total seizures was evaluated at 12-week intervals through 96 weeks. The percentages of patients who had  $\geq 50\%$ ,  $\geq 75\%$ , and 100% reduction in monthly seizures relative to the baseline period were also evaluated. Adverse events (AEs) were monitored and summarized for the safety analysis set (SAS) through 144 weeks.

**Results:** Of the 607 patients in the SAS, 58 had DS and 94 had LGS (N = 152); 455 patients had other TREs. Twenty-eight percent of LGS/DS patients withdrew, primarily owing to lack of efficacy (20%). LGS/DS patients were taking a median of 3 (0–10) concomitant AEDs. Median treatment duration was 78.3 (range, 4.1–146.4) weeks. Between weeks 12 and 96, median CBD dose ranged from 21 to 25 mg/kg/day. At 12 weeks, add-on CBD reduced median monthly major motor seizures by 50% and total seizures by 44%, with consistent reductions in both seizure types through 96 weeks. At 12 weeks, the proportions of patients with  $\geq 50\%$ ,  $\geq 75\%$ , and 100% reductions in major motor seizures were 53%, 23%, and 6%; the proportions with corresponding reductions in total seizures were 46%, 26%, and 5%. Responder rates for both seizure types were consistent through 96 weeks. CBD had an acceptable safety profile; the most common AEs were somnolence (30%) and diarrhea (24%).

**Conclusions:** Results from this interim analysis support add-on CBD as an effective long-term treatment option in LGS or DS.

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## 1. Introduction

In patients with severe, treatment-resistant epilepsies (TREs), anti-epileptic drugs (AEDs) provide only partial relief from seizures, often at the cost of severe adverse effects. The therapeutic potential of cannabidiol (CBD) as an AED has been of great interest, particularly for severe TREs. Previous studies in animal models (Jones et al., 2012, 2010) and open-label clinical studies (Devinsky et al., 2016; Gofshteyn et al., 2017; Hess et al., 2016) suggested that CBD has anti-seizure properties in a broad range of epilepsy syndromes and etiologies.

More recently, a randomized, double-blind, placebo-controlled trial (RCT) of add-on CBD (20 mg/kg/d) showed significantly greater reductions in convulsive seizure frequency in patients with Dravet syndrome (DS) who received 14 weeks of treatment with CBD versus placebo (Devinsky et al., 2017). Two additional RCTs of add-on CBD (10 and 20 mg/kg/d) in patients with Lennox-Gastaut syndrome (LGS) showed significantly greater reductions in drop-seizure frequency in patients who received CBD versus placebo for 14 weeks (Devinsky et al., 2018a; Thiele et al., 2018). In June 2018, on the basis of these three randomized trials, the U.S. Food and Drug Administration (FDA) approved CBD (Epidiolex®; Greenwich Biosciences, Inc.) for the treatment of seizures associated with LGS or DS in patients aged  $\geq 2$  years. CBD is the first FDA-approved plant-derived cannabinoid and the first FDA-approved drug for patients with DS (with stiripentol recently becoming the second FDA-approved drug for DS).

Although randomized placebo-controlled clinical trials are required for FDA approval of investigational drugs, the FDA can authorize expanded access programs (EAPs), also referred to as Compassionate Use Programs, to facilitate access to novel therapies before their approval. One advantage of EAPs is that they are more reflective of clinical practice. In January 2014, an EAP providing CBD (Epidiolex; GW Research Ltd) to patients with TRE was initiated. During its first year, the primary objective was to establish the safety and tolerability of CBD in patients with TREs. Multisite data from this EAP, including patients with multiple types of TRE were first reported through 12 weeks of follow-up (Devinsky et al., 2016) and recently updated for more than 600 patients through 96 weeks of follow-up (Szafarski et al., 2018). Here, we focus on the cohort of patients with the two indications for which CBD was recently FDA-approved, LGS and DS. While the RCTs were required for CBD to obtain FDA approval, the EAP provides longer-term efficacy and safety data that may better predict outcomes in real-world clinical practice.

## 2. Methods

### 2.1. Study design and patient population

The CBD EAP is an ongoing, open-label study being conducted at 25 US-based, independent epilepsy centers. Site-specific protocols varied in terms of eligibility criteria and endpoints; however, all patients had TREs and were receiving stable doses of AEDs for  $\geq 4$  weeks before enrollment. An Institutional Review Board at each site approved the study protocols, and patients or parents/caregivers provided written informed consent before any study-related assessments were performed. The study was conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice guidelines, and local standard operating procedures. We conducted an interim analysis of data relating to the long-term efficacy and tolerability of CBD in EAP patients with LGS/DS versus the EAP patients with other TRE.

### 2.2. Procedures

During the 4-week baseline period, parents/caregivers kept paper diaries of all countable seizure types. Data were collected on convulsive and total seizures. Convulsive seizures were defined as tonic, clonic, tonic-clonic, atonic, or focal seizures that evolved to generalized tonic,

clonic, or tonic-clonic components. Herein, these are referred to as “major motor seizures.” Based on this definition, major motor seizures would generally reflect tonic and atonic seizures for patients with LGS and tonic-clonic seizures for patients with DS. Total seizures included these major motor seizures as well as myoclonic, absence, myoclonic absence, and focal seizures with or without impaired consciousness. Concomitant AEDs were recorded at baseline; dose modifications were allowed and recorded. After the baseline observation period, patients received a plant-derived pharmaceutical formulation of highly purified CBD (100 mg/mL) in oral solution (Epidiolex® in the U.S.; GW Research Ltd) at a gradually increasing dose from 2 to 10 mg/kg/day until tolerability limit or a maximum dose of 25–50 mg/kg/day, depending on the site.

Patients were seen every 2–4 weeks through up to 144 weeks. For each visit, there was a prespecified target day and visit window. If more than one visit occurred within a visit window, data from the visit closest to the target day were used. If there were two visits that were equally close to the target day, data from these two visits were averaged. Some sites collected data at 2 and 4 weeks; therefore, it was assumed that the 4-weeks’ data were reported as weeks 2–4, which was expected to be the most conservative estimate.

### 2.3. Assessment of efficacy

During the 4-week baseline period, parents/caregivers kept daily paper diaries of all countable seizure types. Seizure frequency per week since the previous visit was collected at each site. For this report, all efficacy outcomes were assessed for the 12-, 24-, 48-, 72-, and 96-week visit windows based on data available since the previous visit. The 96-week visit window was deemed long enough to have sufficient patient numbers. For major motor and total seizures, weekly seizure frequency was converted to frequency per 28 days (weekly frequency  $\times 4$ ). Percentage change in seizure frequency for each patient was calculated as seizure frequency per 28 days, minus seizure frequency at baseline, divided by seizure frequency at baseline, multiplied by 100. These calculations have been used in a number of studies of CBD for epilepsy (Devinsky et al., 2017, 2016; Devinsky et al., 2018a; Szafarski et al., 2018; Thiele et al., 2018). Owing to wide inter-patient variability, median percentage changes in seizure frequency were calculated. The proportions of patients who had  $\geq 50\%$ ,  $\geq 75\%$ , and 100% reduction in monthly major motor and total seizure frequency since the previous visit compared to baseline (response rates) were calculated.

### 2.4. Assessment of dose

The use of concomitant AEDs was evaluated for eight of the most common agents (clobazam, felbamate, lamotrigine, levetiracetam, rufinamide, stiripentol, topiramate, and valproic acid). Total daily dose, summarized on a continuous scale, was recorded at baseline and during the treatment period. For each AED, results are presented for the number of patients whose dose was stable at each visit, the number of patients whose dose was reduced at any time and remained below baseline, the number of patients whose dose was increased at any time and remained above baseline, and the number of patients whose dose was both increased and decreased from baseline during the follow-up.

### 2.5. Assessment of safety

For this report, all safety outcomes were assessed through the full follow-up period (144 weeks). Treatment-emergent adverse events (AEs) were monitored and classified by the treating physician using the Medical Dictionary for Regulatory Activities (MedDRA, V17.1). Clinical laboratory parameters and vital signs were evaluated at regular time points during the study. Incidences of AEs, serious AEs, AEs leading to discontinuation, and AEs occurring in  $> 10\%$  of patients were assessed.

## 2.6. Analysis

Sample size was not pre-determined; it was based on patient enrollment at the study sites. The safety analysis set (SAS) included all patients who had  $\geq 1$  dose of CBD and  $\geq 1$  post-baseline evaluation. All patients in the SAS who had  $> 0$  seizures at baseline and seizure data for  $\geq 1$  post-baseline visit were included in the efficacy analysis set (EAS). For all efficacy endpoints, a last-observation-carried-forward (LOCF) analysis was performed using the data from the last available visit window for all patients with post-baseline efficacy data for major motor seizures (136/147) and total seizures (147/147). Findings reported herein are specific to GW Pharmaceuticals' CBD formulation and cannot be extrapolated to other CBD products.

## 3. Results

### 3.1. Patient disposition and characteristics

Between January 15, 2014 and December 16, 2016, 607 patients with TREs were enrolled in the EAP. Five patients were excluded from the EAS, and 28% withdrew, primarily owing to lack of efficacy (20%) or AEs (3%) (Fig. 1). Overall, withdrawals were spread across visit windows, with a greater incidence in the first 24 weeks (10%) versus the following 24 week intervals (1–6%) (Supplementary Table 1). Baseline demographic and clinical characteristics are summarized in Table 1. In the SAS, 152 patients had LGS/DS, and 455 had other or unknown epilepsy etiologies. Among LGS/DS patients, mean age (range) was 12.7 (1.7–51) years; nearly two-thirds of patients were male. The most common concomitant AEDs were clobazam (66%), valproic acid (43%), and levetiracetam (34%). A full listing of concomitant AEDs taken by  $\geq 3\%$  of all LGS/DS patients is provided in Supplementary Table 2. Baseline median monthly seizure frequencies, calculated on the EAS, were 41 and 63 for major motor and total seizures, respectively. In general, baseline demographic and clinical characteristics were comparable between patients with LGS/DS and other TREs.

### 3.2. Treatment effects in patients with LGS/DS

This interim analysis includes patients with a wide range of treatment duration (0.1–146.4 weeks). Median (25th percentile [Q1], 75th percentile [Q3]) treatment duration was 80.1 (20.7, 107.7) weeks. Not all patients had reached the later time points. After 12 weeks of CBD add-on therapy, median reductions of 50% in monthly major motor

**Table 1**  
Baseline demographics and characteristics.

	LGS/DS (SAS = 152)	Other TREs (SAS = 455)
Age, mean years (range)	12.8 (1.7–51)	13.3 (0.4–62.1)
Male gender, n (%)	93 (61%)	220 (48%)
Concomitant AEDs <sup>‡</sup> , median (range)	3 (0–10)	3 (0–8)
Epilepsy etiology, n (%)		
Dravet syndrome	58 (39%)	—
Lennox-Gastaut syndrome	94 (61%)	—
Tuberous sclerosis complex	—	26 (6%)
Aicardi syndrome	—	19 (4%)
CDKL5	—	19 (4%)
Doose, Dup15q, or febrile infection-related epilepsy syndromes	—	24 (6%)
Other <sup>†</sup>	—	243 (53%)
Unknown <sup>†</sup>	—	124 (27%)
Seizure frequency per 28 days <sup>‡</sup>		
Major motor, median (Q1, Q3)	41 (18, 98)	44 (11, 126)
Total, median (Q1, Q3)	63 (25, 140)	73 (20, 216)

AEDs: antiepileptic drugs; CBD: cannabidiol; CDKL5: cyclin-dependent kinase-like 5; DS: Dravet syndrome; Dup15q: chromosome 15q11.2–13.1 duplication syndrome; EAS: efficacy analysis set; LGS: Lennox-Gastaut syndrome; SAS: safety analysis set; TREs: treatment-resistant epilepsies. Median (range) or (Q1 [25th percentile], Q2 [75th percentile]).

\* 1 patient was not taking any concomitant AEDs at baseline.

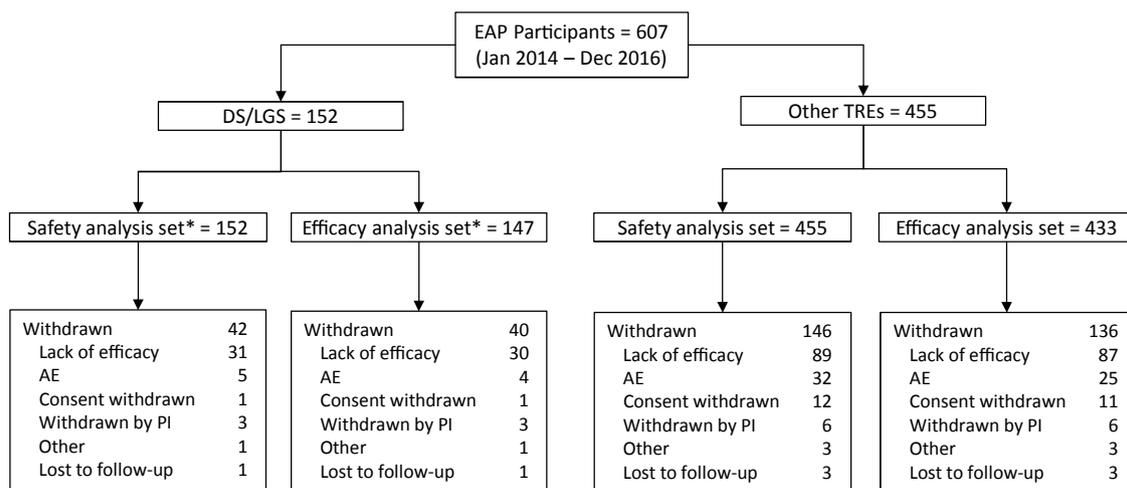
<sup>†</sup> Diagnoses recorded for patients in the “other” and “unknown” categories were mostly refractory epilepsy, idiopathic generalized epilepsy, seizures, and intractable epilepsy; specific etiologies recorded for several patients each included genetic abnormalities, focal epilepsy, Sturge-Weber syndrome, lissencephaly, cortical malformation/dysplasia, and myoclonic absence.

<sup>‡</sup> Seizure frequency is based on the EAS (LGS/DS = 147; other TREs = 433).

seizure frequency and 44% in monthly total seizure frequency were observed in both the EAS and LOCF. These reductions were maintained at each visit window through 96 weeks for both the EAS (Fig. 2A) and LOCF analyses (Fig. 2B). After 12 weeks of CBD add-on therapy, the percentage of LGS/DS patients with  $\geq 50\%$ ,  $\geq 75\%$ , and 100% seizure reductions compared to baseline were 53%, 23%, and 6% for major motor seizures (Fig. 3A) and 46%, 26%, and 5% for total seizures (Fig. 3B). Response rates remained stable between weeks 12 and 96.

### 3.3. Treatment effects in patients with other TRE

In the other TREs cohort, median percentage reductions in the



**Fig. 1.** Patient disposition. Between January 2014 and December 2016, 607 patients participated in the CBD EAP for TRE. Of this total, 152 patients had DS or LGS, and 455 had other epilepsy diagnoses. (AE: adverse event; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; PI: Principal Investigator; TREs: treatment-resistant epilepsies.).

frequency of major motor seizures and total seizures (Fig. 4) and in the  $\geq 50\%$ ,  $\geq 75\%$ , and  $100\%$  response rates for major motor (Fig. 5A) and total seizures (Fig. 5B) were similar to those observed for the LGS/DS cohort.

### 3.4. CBD and concomitant AED dose adjustments

For LGS/DS patients, the median (Q1, Q3) dose was 21 mg/kg/day (15–25) at 12 weeks and 25 mg/kg/day (21–25) at 96 weeks. Thirty-eight percent (58/152) of patients reduced their dose of CBD at any time during follow-up. The mean (SD) dose of concomitant clobazam at baseline was 29.1 (17.9) mg; the mean (SD) dose of valproic acid at baseline was 791 (423) mg. Forty-six percent of patients taking clobazam and 52% of those taking valproic acid reduced their dose during the study (Table 2). Among those taking concomitant levetiracetam, the majority remained on their mean (SD) baseline dose of 1964 (1215) mg.

### 3.5. Safety and tolerability of CBD

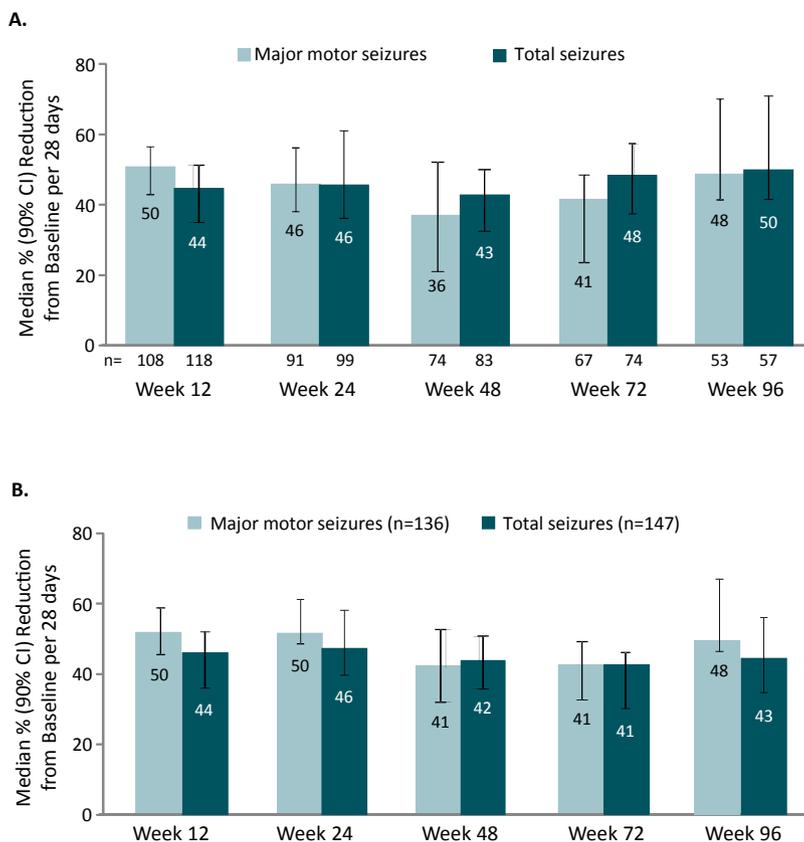
In the SAS, 91% of all LGS/DS patients experienced treatment-emergent AEs, and 41% experienced serious AEs (Table 3). The most commonly reported all-cause AEs were somnolence (30%), convulsion (24%), and diarrhea (24%). The most common all-cause serious AEs were convulsion (14%), status epilepticus (9%), pneumonia (5%), and pyrexia (4%). No cases of cannabinoid hyperemesis syndrome were reported. Abnormal liver AEs (i.e., alanine aminotransferase/aspartate aminotransferase  $> 3 \times$  upper limit of normal) were reported for 15% (22/152) of patients; of these, 82% (18/22) were on VPA. Fourteen percent (21/152) of patients had  $\geq 1$  of the MedDRA Preferred Terms for pneumonia. Of patients taking concomitant clobazam, 38% (38/101) experienced somnolence. By contrast, of those not taking concomitant clobazam, 18% (9/51) experienced somnolence. The safety profile was generally similar between the LGS/DS cohort and other TRE cohort (data not shown). There were 12 deaths during the study; all

were among patients with other TREs, and none was considered related to treatment by investigators. Two deaths were due to sudden unexplained death in epilepsy (SUDEP).

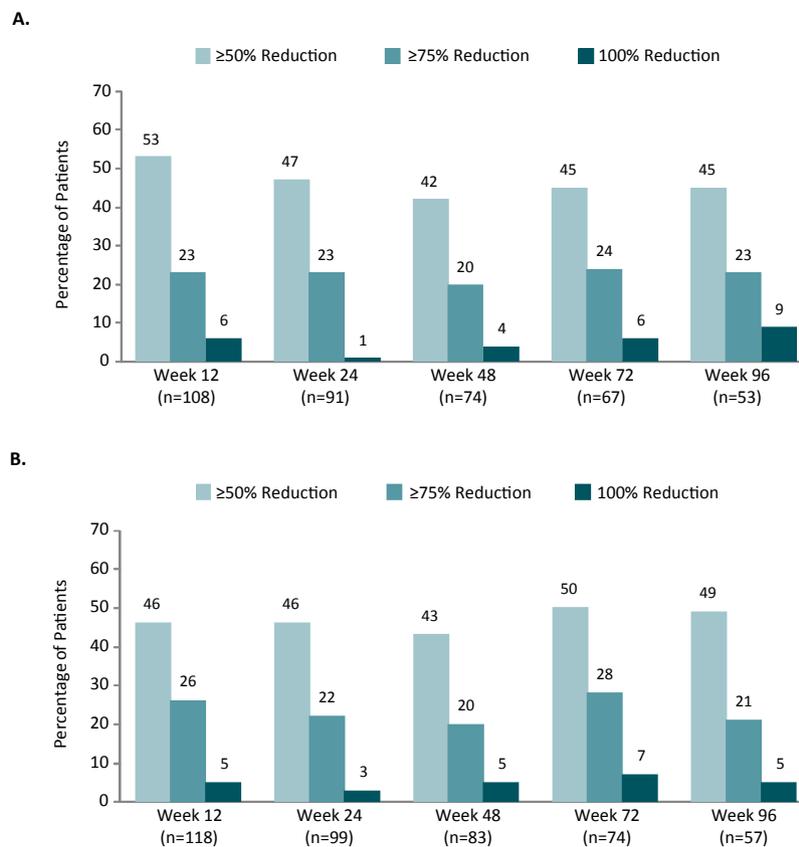
## 4. Discussion

The patient population in the ongoing, open-label CBD EAP includes highly treatment-resistant, severe epilepsies as reflected by number of concurrent and previously tried AEDs. In a previous report of the overall EAP population, CBD as add-on therapy provided clinically meaningful and sustained reductions in the median monthly frequency of major motor and total seizures through 96 weeks (Szaflarski et al., 2018). Here, we focused on the cohort of patients in the EAP with LGS/DS etiologies, the indications for which CBD (Epidiolex®) is now approved in the United States. Reductions in seizure frequency were similar to those reported in the LGS and DS RCTs, and persisted long-term (up to 96 weeks). Moreover, the proportions of patients achieving  $\geq 50\%$  and  $\geq 75\%$  reductions in seizure frequency were notable and consistent at each visit window through 96 weeks and even in this highly treatment-resistant population, some patients were seizure free between visit windows.

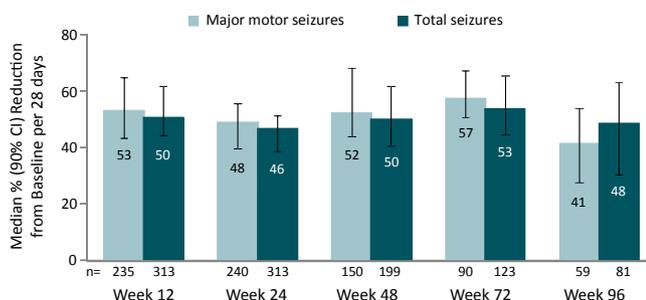
Although there have been no RCTs of CBD in patients with other TREs, the reductions in seizure frequency observed in the other TREs cohort in this EAP were similar to those observed in the LGS/DS patients, suggesting that CBD may have broad-spectrum effects on seizure frequency reduction. In a recent analysis of the patients from this EAP with CDKL5 deficiency disorder, Dup15q, Aicardi, and Doose syndromes, median reduction in seizure frequency was also in the same range, 51% at week 12 and 59% at week 48 (Devinsky et al., 2018b). A prior report on patients with tuberous sclerosis complex (TSC) from this EAP showed similar seizure reductions as well (Hess et al., 2016); a phase 3 randomized, controlled study of CBD in patients with TSC and seizures is due to complete in 2019 (NCT02544763). Data on other seizure subtypes, such as absence or focal seizures, are not available



**Fig. 2.** Percentage reduction from baseline in major motor and total\* seizures among patients with LGS/DS for the (A) EAS and (B) LOCF analysis. \*Total seizures included major motor seizures (ie, tonic, clonic, tonic-clonic, atonic, or focal seizures that evolved to generalized tonic, clonic, or tonic-clonic components) and non-convulsive seizures (ie, myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness). (CI: confidence interval; DS: Dravet syndrome; EAS: efficacy analysis set; LGS: Lennox-Gastaut syndrome; LOCF: last observation carried forward).



**Fig. 3.** Treatment response rates among patients with LGS/DS for (A) major motor and (B) total seizures (EAS). Response rates shown are based on data collected since the previous visit compared to the baseline period. (DS: Dravet syndrome; EAS: efficacy analysis set; LGS: Lennox-Gastaut syndrome.)



**Fig. 4.** Percentage reduction from baseline in convulsive and total\* seizures for patients with other TREs (EAS). \* Total seizures included major motor seizures (ie, tonic, clonic, tonic-clonic, atonic, or focal seizures that evolved to generalized tonic, clonic, or tonic-clonic components) and non-convulsive seizures (ie, myoclonic, absence, myoclonic-absence, focal with and without impaired consciousness). (CI: confidence interval; EAS: efficacy analysis set; TREs: treatment-resistant epilepsies.)

from this EAP cohort. Data from GW’s randomized, controlled study of CBD in Dravet syndrome have been published, but these seizure subtypes occurred in only a subset of patients, which limits any conclusions that can be drawn (Devinsky et al., 2017).

During the full safety follow-up period (up to 144 weeks), the pattern and incidence of AEs were similar to those reported in the both the initial analysis of the EAP (Devinsky et al., 2016) and in the randomized controlled trials (Devinsky et al., 2017, 2018a; Thiele et al., 2018), with the most common being somnolence and diarrhea. The most common serious AEs in the EAP LGS/DS population were convulsion (14%), status epilepticus (9%), pneumonia (5%), and pyrexia (4%), also consistent with previous reports of open-label studies (Devinsky et al.,

2016; Szaflarski et al., 2018) and randomized controlled trials (Devinsky et al., 2017, 2018a; Thiele et al., 2018) of patients treated with CBD for serious TREs.

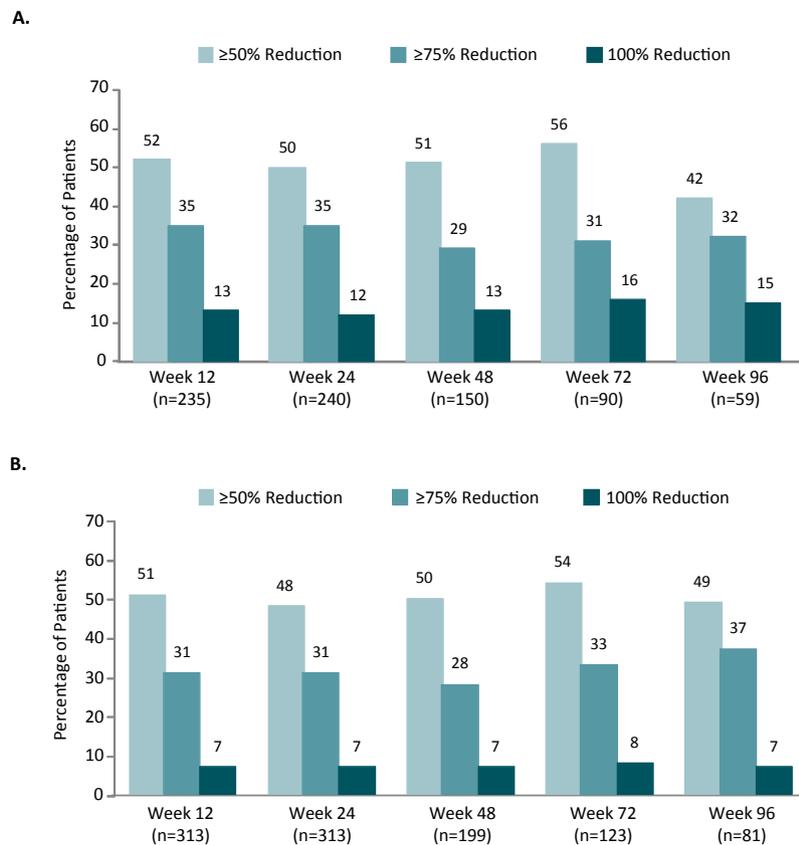
Completion rates in the three, 14-week CBD RCTs were high at 90% (Devinsky et al., 2017), 91% (Thiele et al., 2018), and 94% (Devinsky et al., 2018a). Considering the greatly extended follow-up time of this EAP analysis (up to two years, median treatment duration 338 days), the retention rate of 76% for the LGS/DS cohort is encouraging. This retention rate also compares favorably to that of another long-term trial of AEDs in less severe epilepsies (63–72%) (Toledo et al., 2017), suggesting better tolerability, efficacy, or both. Indeed, AEs were generally mild when the effect of withdrawals was assessed in the LOCF sensitivity analysis, consistent reductions in the frequency of major motor and total seizures were still observed through 96 weeks.

CBD dosing varied throughout the study period, and > 50% of patients reduced their dose at some point. Nevertheless, the median dose of CBD remained stable (25 mg/kg/day) at all visit windows. Thus, the efficacy findings were not associated with CBD “dosage creep” (i.e., the need to increase drug dosage to maintain the same level of efficacy).

The study is not without limitations. By design, the EAP is not controlled and there was inter-site variability in reporting methods. However, the design of the EAP more closely resembles clinical practice, and the results support the external validity and generalizability of the findings from the CBD RCTs.

### 5. Conclusions

In this ongoing, US-based EAP enrolling children and adults with TREs, add-on CBD effectively reduced the median monthly frequency of major motor and total seizures after 12 weeks of treatment in the subgroup of patients with LGS/DS. These reductions remained stable during a 2-year period, without increases in CBD dosage. On average,



**Fig. 5.** Treatment response rates among other TREs patients for (A) major motor and (B) total seizures (EAS). Response rates shown are based on data collected since the previous visit compared to the baseline period. (EAS: efficacy analysis set; TREs: treatment-resistant epilepsies.).

**Table 2**  
Most common Concomitant AED dose adjustments in LGS/DS cohort\* (SAS).

	Clobazam (n = 99)	Valproic Acid (n = 64)	Levetiracetam (n = 50)
Baseline dose stable at all visits	38 (38%)	23 (36%)	35 (70%)
Baseline dose increased	11 (11%)	4 (6%)	4 (8%)
Baseline dose decreased	46 (46%)	33 (52%)	8 (16%)
Dose changed above and below baseline	4 (4%)	4 (6%)	3 (6%)

AEDs: antiepileptic drugs; SAS: safety analysis set.  
\* After initiating CBD treatment.

**Table 3**  
Summary of TEAEs (SAS) in LGS/DS cohort.

	CBD dose (mg/kg/day)					All (N = 152)
	0–10 (n = 5)	> 10–20 (n = 31)	> 20–30 (n = 93)	> 30–40 (n = 16)	> 40 (n = 7)	
Overall TEAE rate, n (%)	4 (80%)	27 (87%)	86 (93%)	15 (94%)	6 (86%)	138 (91%)
Overall serious TEAE rate, n (%)	1 (20%)	9 (29%)	45 (48%)	4 (25%)	4 (57%)	63 (41%)
TEAEs leading to discontinuation of study medication, n (%)	1 (20%)	0 (0%)	9 (10%)	2 (13%)	0 (0%)	12 (8%)
TEAE, n (%)						
Somnolence	1 (20%)	4 (13%)	32 (34%)	5 (31%)	3 (43%)	45 (30%)
Convulsion	1 (20%)	5 (16%)	27 (29%)	2 (13%)	1 (14%)	36 (24%)
Diarrhea	0 (0%)	5 (16%)	25 (27%)	6 (38%)	0 (0%)	36 (24%)
URTI	0 (0%)	6 (19%)	21 (23%)	2 (13%)	1 (14%)	30 (20%)
Decreased appetite	1 (20%)	1 (3%)	19 (20%)	3 (19%)	0 (0%)	24 (16%)
Fatigue	0 (0%)	3 (10%)	16 (17%)	3 (19%)	2 (29%)	24 (16%)
Pyrexia	0 (0%)	3 (10%)	19 (20%)	2 (13%)	0 (0%)	24 (16%)
Vomiting	0 (0%)	2 (7%)	17 (18%)	1 (6%)	0 (0%)	20 (13%)

CBD: cannabidiol; SAS: safety analysis set; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection.

## Conflicts of interest

In the past two years, L.C. Laux is a Principal Investigator for GW Pharma Ltd and Zogenix. E. Martina Bebin has served on an advisory panel for GW Pharmaceuticals and is a clinical investigator on the GW1521 clinical trial. Dr. Bebin is Director of the EAP pediatric program at the University of Alabama Birmingham, which is supported by the State of Alabama. D. Checketts is an employee of GW Research Ltd. M. Chez has been a clinical investigator for the EAP study and the GWEP1332 trial, receiving support from GW Research. He has been a consultant to GW Pharmaceuticals and served as speaker for Greenwich Biosciences. R. Flamini received funding from GW Research Ltd for activities associated with his site's individual EAP (the State of Georgia funds part of the Georgia State EAP) and is a principle investigator for GW Research studies. E.D. Marsh has been a PI on GW Pharma and Zogenix studies. Dr. Marsh has received grant funding from Zogenix Pharma, GW Pharma, National Institutes of Health, Rett Syndrome Research Trust, RettSyndrome.org, and the Commonwealth of Pennsylvania. He also has served as consultant for Stoke Therapeutics. I. Miller has received research support, travel funds, or consulting fees from: Biomarin, Dravet Syndrome Foundation, Greenwich Biosciences, Hope for HH Foundation, Insys Therapeutics, Insightec, Inc., NeuroPace, Inc., Neurelis, Inc., Tuberous Sclerosis Alliance, Ultragenyx, Upsher-Smith, and Zogenix. K. Nichol is employed by Greenwich Biosciences, Inc. Y. Park served as Principal Investigator on the GWEP 1414 and 1415 clinical trials and leads the pediatric EAP program at Augusta University, which is funded by the State of Georgia. E. Segal has served as a speaker for GW Pharmaceuticals, Eisai Pharmaceuticals, Nutricia, Novartis, Lundbeck, and Lineagen. Dr. Segal has served as a consultant for GW Pharmaceuticals, Celgene, Encoded Therapeutics, qBiomed, and Epitel. He has served on Advisory Boards for GW Pharmaceuticals, Zogenix, and Aquestive. L. Seltzer is the site Principal Investigator for the EAP at the University of Rochester, supported by GW Pharmaceuticals and New York State. She is also the site Principal Investigator for GW Pharmaceuticals GW1521 and Shire Pharmaceuticals SPD489 clinical trials. J.P. Szaflarski has received funding from the National Institutes of Health, the National Science Foundation, Shor Foundation for Epilepsy Research, EFA, U.S. Department of Defense, UCB Biosciences, NeuroPace Inc., SAGE Therapeutics Inc., Greenwich Biosciences Inc., Serina Therapeutics Inc., and Eisai, Inc. Dr. Szaflarski has served as a consultant for SAGE Therapeutics Inc., Greenwich Biosciences Inc., NeuroPace, Inc., Upsher-Smith Laboratories, Inc., Medical Association of the State of Alabama, Serina Therapeutics Inc., LivaNova Inc., Lundbeck, and Elite Medical Experts LLC. He currently serves as an editorial board member for *Epilepsy & Behavior*, *Journal of Epileptology* (Associate Editor), *Restorative Neurology and Neuroscience* (Associate Editor), *Journal of Medical Science*, *Epilepsy Currents* (Contributing Editor), and *Folia Medica Copernicana*. E.A. Thiele serves as consultant to GW Pharmaceuticals companies, Aquestive, Ovid, Upsher Smith, West Therapeutics, and Zogenix. She has served as an investigator in the DS, LGS and TSC clinical trials, and received funding from GW Pharma for the expanded access program. A. Weinstock is the Director of the EAP program at the University at Buffalo, NY, which is supported by the New York State Department of Health and serves as a paid speaker for Greenwich Biosciences Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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with funds to undertake the study. No funds were provided for salary support. GW Pharmaceuticals collected the data from the sites and collected the statistical analyses. The authors would like to thank the patients, their families, and the sites that provided data for this analysis.

## Appendix A

### CBD EAP Study Group

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## Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.epilepsyres.2019.03.015>.

## References

- Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., Miller, I., Flamini, R., Wilfong, A., Filloux, F., Wong, M., Tilton, N., Bruno, P., Bluvstein, J., Hedlund, J., Kamens, R., Maclean, J., Nangia, S., Singhal, N.S., Wilson, C.A., Patel, A., Cilio, M.R., 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 15, 270–278.
- Devinsky, O., Cross, J.H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I.E., Thiele, E.A., Wright, S., Cannabidiol in Dravet Syndrome Study, G, 2017. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. *N. Engl. J. Med.* 376, 2011–2020.
- Devinsky, O., Patel, A.D., Cross, J.H., Villanueva, V., Wirrell, E.C., Privitera, M., Greenwood, S.M., Roberts, C., Checketts, D., VanLandingham, K.E., Zuberi, S.M., Group, G.S., 2018a. Effect of Cannabidiol on drop seizures in the lennox-gastaut syndrome. *N. Engl. J. Med.* 378, 1888–1897.
- Devinsky, O., Verducci, C., Thiele, E.A., Laux, L.C., Patel, A.D., Filloux, F., Szaflarski, J.P., Wilfong, A., Clark, G.D., Park, Y.D., Seltzer, L.E., Bebin, E.M., Flamini, R., Wechsler, R.T., Friedman, D., 2018b. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav.* 86, 131–137.
- Gofshteyn, J.S., Wilfong, A., Devinsky, O., Bluvstein, J., Charuta, J., Ciliberto, M.A., Laux, L., Marsh, E.D., 2017. Cannabidiol as a potential treatment for febrile infection-related epilepsy syndrome (FIRES) in the acute and chronic phases. *J. Child Neurol.* 32, 35–40.
- Hess, E.J., Moody, K.A., Geoffrey, A.L., Pollack, S.F., Skirvin, L.A., Bruno, P.L., Paolini, J.L., Thiele, E.A., 2016. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia* 57, 1617–1624.
- Jones, N.A., Hill, A.J., Smith, I., Bevan, S.A., Williams, C.M., Whalley, B.J., Stephens, G.J., 2010. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J. Pharmacol. Exp. Ther.* 332, 569–577.
- Jones, N.A., Glyn, S.E., Akiyama, S., Hill, T.D., Hill, A.J., Weston, S.E., Burnett, M.D., Yamasaki, Y., Stephens, G.J., Whalley, B.J., Williams, C.M., 2012. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure* 21, 344–352.
- Szaflarski, J.P., Bebin, E.M., Comi, A.M., Patel, A.D., Joshi, C., Checketts, D., Beal, J.C.,

Laux, L.C., De Boer, L.M., Wong, M.H., Lopez, M., Devinsky, O., Lyons, P.D., Pichon Zentil, P., Wechsler, R., on behalf of the CBD EAP Study Group, 2018. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. *Epilepsia* 59, 1540–1548.

Thiele, E.A., Marsh, E.D., French, J.A., Mazurkiewicz-Beldzinska, M., Benbadis, S.R.,

Joshi, C., Lyons, P.D., Taylor, A., Roberts, C., Sommerville, K., Group, G.S., 2018. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 391, 1085–1096.