2.337 Effectiveness of Cannabidiol in Patients With Rare Epilepsies Compared to External Placebo Control: A Post Hoc Analysis From the Expanded Access Program

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Introduction

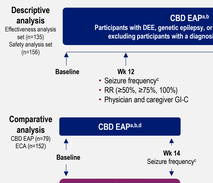
- Developmental and epileptic encephalopathies (DEEs) are a group of rare and severe childhood-onset epilepsies, marked by high seizure burden, pharmacoresistance, and disabling comorbidities, presenting several unmet clinical needs[1]
- Plant-derived, highly purified cannabidiol (CBD; Epidiolex®, 100 mg/mL oral solution) is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients ≥1 year of age[2]
- Real-world evidence suggests that CBD may have utility in other DEEs, such as Aicardi syndrome, *CDKL5* deficiency disorder, Dup15q syndrome, and epilepsy with myoclonic-atonic seizures (EMAS)[3]
- The CBD Expanded Access Program (EAP) provided compassionate access to CBD for patients with diverse treatment-resistant epilepsies, including DEEs
- This post hoc analysis of the US CBD EAP evaluates seizure and safety outcomes in participants with rare and severe childhood-onset epilepsies, compared with an external placebo control arm (ECA)[2–4]

Objectives

- To describe the baseline demographics and clinical characteristics, effectiveness, and safety of CBD among EAP participants with rare epilepsy syndromes including DEEs other than LGS, DS, and TSC
- To compare the effectiveness of CBD treatment in participants with rare epilepsy syndromes to an ECA

Methods

Figure 1. Study design: Descriptive analysis of CBD EAP and comparative analysis of CBD EAP vs ECA



[a]Participants received CBD (Epidiolex®) doses starting at 2–10 mg/kg/day and titrated up as tolerated or to a maximum of 25–50 mg/kg/day at the discretion of the investigator and institutional review board at each EAP site.
[b]All participants enrolled in both CBD EAP and ECA had treatment-resistant epilepsy and were receiving stable doses of antiseizure medications for ≥4 weeks before enrollment.
[c]Convulsive and total seizures.
[d]Participants with a minimum frequency of 8 convulsive seizures per 28 days during baseline were included in the analysis.
CBD, cannabidiol; DEEs, developmental and epileptic encephalopathies; DS, Dravet syndrome; EAP, Expanded Access Program; ECA, external placebo control arm; GI-C, Global Impression of Change; LGS, Lennox-Gastaut syndrome; PBO, placebo; RCTs, randomized controlled trials; RR, responder rate; TSC, tuberous sclerosis complex.

Descriptive analysis: CBD EAP cohort

- Participants with rare and severe childhood-onset epilepsies—including those diagnosed with DEE, genetic epilepsy, or a rare epilepsy syndrome—were included in the CBD EAP analysis cohort (**Figure 1**). Participants with a diagnosis or co-diagnosis of LGS, DS, or TSC were excluded from this cohort
  - Rare epilepsy subgroups including Aicardi syndrome, *CDKL5* deficiency disorder, Dup15q syndrome, early infantile epileptic encephalopathy (EIEE), EMAIS, febrile infection–related epilepsy syndrome (FIRES), myoclonic absence epilepsy, *SCN2A*-DEE, Sturge-Weber syndrome (SWS), and other genetic epilepsies were analyzed
    - Rare epilepsies with <5 participants were pooled into an "other genetic epilepsies" subgroup
- Effectiveness of CBD was assessed as percentage reduction from baseline in median 28-day convulsive and total seizure frequencies at Weeks 12 and 48
- Responder rates (RRs; ≥50%, ≥75%, and 100% seizure reduction) were reported at Weeks 12 and 48
- Physician and Caregiver Global Impression of Change (GI-C) data were reported at Weeks 12 and 48
- Safety results were reported for the entire treatment period (median duration, 617 days)

Comparative analysis: CBD EAP vs ECA

- A comparative effectiveness analysis was conducted using an ECA to evaluate the effectiveness of CBD in reducing the 28-day average number of convulsive or total seizure frequencies during the first 14 weeks of treatment (**Figure 1**)
  - Participants with a seizure frequency of <8 convulsive seizures per 28 days during the baseline period were excluded
  - The ECA was composed of participants with LGS who were randomized to placebo in the GWPCARE3 and GWPCARE4 randomized controlled trials
  - To minimize information bias, comparability was verified in terms of eligibility criteria, treatment strategy, assignment procedure, follow-up period, measures at baseline, and endpoints[5]
- Inverse probability weighting based on propensity scores[6,7] was applied to minimize the association between treatment exposure and study participation and balance key baseline covariates, including age, sex, convulsive seizure frequency at baseline, number of concomitant antiseizure medications (ASMs), and current clobazam use
  - Assuming that no other confounding variables were associated with both the response variable and the treatment, the average treatment effect of CBD compared with placebo was estimated by performing a weighted log-transformed analysis of covariance model
  - Balancing performance was investigated using a standardized weighted mean differences plot
  - Absence of hidden bias was confirmed through the Rosenbaum sensitivity analysis
- This study used data on Epidiolex®, and the results of this post hoc analysis do not apply to other CBD-containing products

Results

Baseline demographics and clinical characteristics of CBD EAP participants with rare epilepsies

Table 1. Participant demographics and baseline antiseizure medications (CBD EAP effectiveness analysis set)

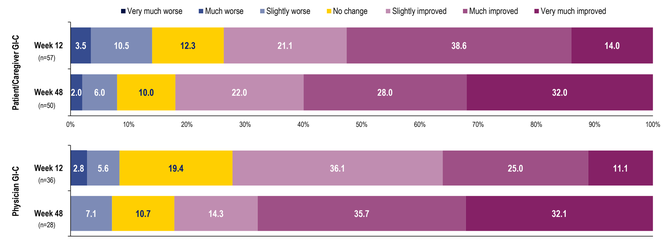
	Overall	Aicardi syndrome	*CDKL5*	Dup15q syndrome	EIEE	EMAtS	FIRES	Myoclonic absence	*SCN2A*	SWS	Other genetic epilepsies[a]
N (%)	135	17 (12.6)	20 (14.8)	11 (8.1)	6 (4.4)	11 (8.1)	13 (9.6)	5 (3.7)	5 (3.7)	5 (3.7)	42 (31.1)
Age, years, Mean (SD)	9.7 (6.0)	10.2 (5.8)	6.8 (4.2)	12.4 (4.9)	6.0 (6.1)	9.5 (3.4)	9.4 (5.6)	14.4 (4.4)	5.0 (2.6)	8.9 (6.1)	11.2 (7.1)
Sex, female, n (%)	87 (64.4)	17 (100)	19 (95.0)	5 (45.5)	6 (100)	3 (27.3)	7 (53.8)	2 (40.0)	3 (60.0)	4 (80.0)	21 (50.0)
Number of ASMs, mean (SD)	2.8 (1.2)	2.5 (1.0)	2.5 (0.8)	3.0 (0.5)	3.5 (1.1)	2.8 (0.9)	4.5 (1.7)	–	2.8 (0.8)	2.6 (1.3)	2.5 (1.2)
ASMs, n (%)											
Clobazam	54 (40)	9 (53)	6 (30)	5 (46)	2 (33)	5 (45)	7 (54)	–	1 (20)	1 (20)	18 (43)
Levetiracetam	45 (33)	5 (29)	6 (30)	4 (36)	3 (50)	2 (18)	10 (77)	–	2 (40)	2 (40)	11 (26)
Valproic acid	40 (30)	5 (29)	10 (50)	5 (46)	0	2 (18)	3 (23)	–	0	3 (60)	12 (29)
Topiramate	13 (10)	0	4 (20)	1 (9)	1 (17)	0	3 (23)	–	1(20)	1 (20)	2 (5)
Lamotrigine	28 (21)	7 (41)	5 (25)	4 (36)	0	3 (27)	1 (8)	–	1 (20)	0	7 (17)
Rufinamide	24 (18)	4 (24)	2 (10)	6 (55)	1 (17)	4 (36)	2 (15)	–	1 (20)	1 (20)	3 (7)
Felbamate	9 (7)	0	0	0	0	3 (27)	3 (23)	–	0	1 (20)	2 (5)
Seizure frequency, median (Q1, Q3), [n]											
Convulsive seizures	42 (16, 104) [100]	47 (18, 74) [14]	52 (25, 100) [18]	58 (5, 209) [11]	170 (29, 2950) [4]	61 (32, 116) [9]	60 (24, 2840) [5]	4 (4, 4) [1]	25 (13, 112) [5]	1 (1, 1) [1]	40 (4, 98) [32]
Total seizures	80 (28, 294) [135]	57 (34, 109) [17]	95 (42, 231) [20]	89 (55, 272) [11]	205 (18, 384) [6]	86 (32, 404) [11]	216 (60, 4000) [13]	2800 (1750, 2800) [5]	112 (74, 138) [5]	2 (1, 6) [5]	72 (20, 217) [42]

[a]Included rare epilepsies affecting <5 participants, had diagnostic terms: 16p11.2 deletion, 1p36 deletion, 22q11 duplication, *ADNFLE-DEPDC5* mutation, Angelman syndrome, *BRAF* mutation, *CACNA1E* mutation, *CLCN4* mutation, *COL4A1* mutation, deletion 16 p13.11q13.1), Disorny X, *Dup3p* mutation, *DYRK1A* mutation, EIMFS, EOEE, GLUT1 deletion, *GPHN* mutation, *GRIN2A* mutation, *HCN2* mutation, infantile spasms, Jeavons syndrome, *KCNA1* mutation, *KCNQ2* mutation, LYPB2 haplotype deficiency, MECP2 duplication, Rasmussen syndrome, Rett syndrome, *SCN1A* mutation, *SCN8A* mutation, *SNAP25* mutation, sodium channelopathy, *SYNGAP1* mutation, Trisomy 21, and *ZDHHC9* mutation.
—, not applicable; ASMs, antiseizure medications; CBD, cannabidiol; *CDKL5*, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAtS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; Q1, first quartile; Q3, third quartile; SWS, Sturge-Weber syndrome.

- The overall analysis set included 135 participants in the CBD EAP effectiveness analysis set with rare epilepsies (**Table 1**)
- The mean age across subgroups ranged from 5.0 to 14.4 years, and in the overall population the most commonly used ASMs at baseline were clobazam (40%), levetiracetam (33%), and valproic acid (30%)
- Median (Q1, Q3) total daily CBD dose was 25 mg/kg/day (15.0, 25.0) at Week 12 and 25 mg/kg/day (20.0, 27.2) at Week 48

Global Impression of Change (CBD EAP safety analysis set)

Figure 4. GI-C ratings by patients/caregivers and physicians in the overall CBD EAP group



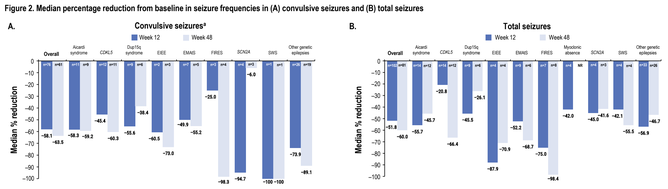
CBD, cannabidiol; EAP, Expanded Access Program; GI-C, Global Impression of Change.

- In the overall CBD EAP group, at Weeks 12 and 48, patient/caregiver-reported GI-C improvement (slightly improved, much improved, very much improved) was reported in 73.7% and 82.0% of participants, respectively, and physician-reported GI-C improvement (slightly improved, much improved, very much improved) was 72.2% and 82.1%, respectively (**Figure 4**)

Effectiveness results

Seizure frequency (CBD EAP effectiveness analysis set)

Figure 2. Median percentage reduction from baseline in seizure frequencies in (A) convulsive seizures and (B) total seizures

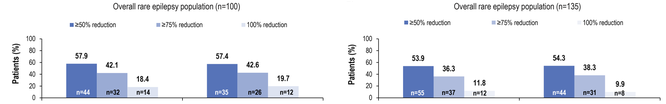


[a]In 1 participant with myoclonic absence epilepsy, no change in convulsive seizure frequency was observed at Week 12. Week 48 data were not reported.
CBD, cannabidiol; *CDKL5*, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAtS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; NR, not reported; SWS, Sturge-Weber syndrome.

- At Week 12, participants experienced a median percent reduction in seizure frequency of 58.1% and 51.8% in convulsive and total seizures, respectively; this median reduction from baseline was maintained through Week 48 for convulsive seizures (63.5%) and total seizures (60.0%) (**Figure 2A** and **2B**)

Responder rates (CBD EAP effectiveness analysis set)

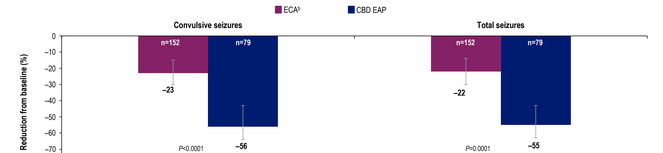
Figure 3. Treatment response rates (≥50%, ≥75%, 100%) in (A) convulsive seizures and (B) total seizures



- At Week 12 and Week 48, responder rates (≥50%, ≥75%, and 100%) were:
  - **Convulsive seizures: overall population**, 57.9% and 57.4%; 42.1% and 42.6%; and 18.4% and 19.7%, respectively (**Figure 3A**); **rare epilepsy subgroups:** responder rates for individual subgroups are shown in **Figure S1A**
  - **Total seizures: overall population**, 53.9% and 54.3%; 36.3% and 38.3%; and 11.8% and 9.9%, respectively (**Figure 3B**); **rare epilepsy subgroups:** responder rates for individual subgroups are shown in **Figure S1B**

Comparative effectiveness analysis of CBD EAP vs ECA

Figure 5. Comparative analysis of percent reduction from baseline to Week 14 in convulsive and total seizures in the CBD EAP vs ECA groups[a]



[a]To avoid large standard error for causal effect estimates, the analysis used a support region of all observations having a percentile from 2 to 98 of the propensity score distribution. The support region included 79 CBD EAP and 152 ECA participants with balanced baseline characteristics.
[b]Assessment at RCT and of treatment represents the 28-day average number of seizures during the first 14 weeks. The ECA was composed of participants with LGS who were randomized to placebo in the GWPCARE3 and GWPCARE4 RCTs.
CBD, cannabidiol; EAP, Expanded Access Program; ECA, external placebo control arm; LGS, Lennox-Gastaut syndrome; RCT, randomized controlled trial.

- Comparative effectiveness analysis included 79 of 135 CBD EAP participants and 152 of 161 ECA participants; baseline characteristics and demographics were balanced based on the standardized weight mean difference (**Table S1 and Figure S1**)
- CBD groups demonstrated greater reductions in convulsive and total seizure frequency compared with the ECA group (**Figure 5**)

Table 2. Comparative analysis of percentage reductions from baseline and treatment ratios

	Reduction from baseline (95% CI)	Treatment ratio % (95% CI)	*P* value
Convulsive seizures			
ECA	23% (15%–30%)	43% (25%–57%)	<0.0001
CBD EAP	56% (43%–66%)		
Total seizures			
ECA	22% (14%–30%)	43% (24%–56%)	0.0001
CBD EAP	55% (43%–65%)		

Percentage reductions from baseline and treatment ratios were calculated as (1-estimate) x 100.
CBD, cannabidiol; EAP, Expanded Access Program; ECA, external placebo control arm.

- CBD was associated with a 43% greater seizure reduction compared with ECA (*P*≤0.0001; **Table 2**)

Safety results (CBD EAP safety analysis set)

Table 3. Summary of adverse events

	Overall[a]	Aicardi syndrome	*CDKL5*	Dup15q syndrome	EIEE	EMAtS	FIRES	*SCN2A*	SWS	Other genetic epilepsies
Participants, n (%)	156 (100)	19 (12.2)	23 (14.7)	9 (5.8)	6 (3.8)	11 (7.1)	20 (12.8)	5 (3.2)	6 (3.8)	50 (32.1)
Any TEAEs	134 (85.9)	19 (100)	21 (91.3)	9 (81.8)	6 (100)	9 (81.8)	18 (90.0)	4 (80.0)	6 (100)	42 (84.0)
Any TRAEs	81 (51.9)	14 (73.7)	11 (47.8)	9 (81.8)	3 (50.0)	7 (63.6)	3 (15.0)	2 (40.0)	6 (100)	26 (52.0)
TEAEs leading to CBD discontinuation	21 (13.5)	2 (10.5)	3 (13.0)	2 (18.2)	2 (33.3)	1 (9.1)	2 (10.0)	1 (20.0)	1 (16.7)	7 (14.0)
Serious TEAEs	79 (50.6)	12 (63.2)	12 (52.2)	6 (54.5)	3 (50.0)	4 (36.4)	12 (60.0)	3 (60.0)	4 (66.7)	23 (46.0)
Treatment-related serious AEs	5 (3.2)	0	2 (8.7)	1 (9.1)	0	0	1 (5.0)	0	0	1 (2.0)
Deaths[b]	11 (7.1)	1 (5.3)	0	0	2 (33.3)	0	2 (10.0)	1 (20.0)	0	5 (10.0)
TRAEs reported in ≥10% of participants in any group by preferred term, n (%)										
Diarrhea	29 (18.6)	5 (26.3)	4 (17.4)	2 (18.2)	1 (16.7)	1 (9.1)	2 (10.0)	0	1 (16.7)	13 (26.0)
Fatigue	20 (12.8)	4 (21.1)	5 (21.7)	3 (27.3)	1 (16.7)	2 (18.2)	1 (5.0)	0	1 (16.7)	3 (6.0)
Somnolence	19 (12.2)	2 (10.5)	3 (13.0)	3 (27.3)	1 (16.7)	4 (36.4)	0	0	0	6 (12.0)
Decreased appetite	11 (7.1)	1 (5.3)	3 (13.0)	3 (27.3)	0	1 (9.1)	1 (5.0)	0	0	2 (4.0)
Sedation	8 (5.1)	2 (10.5)	0	0	1 (16.7)	0	0	1 (20.0)	0	4 (8.0)
Abnormal behavior	7 (4.5)	2 (10.5)	1 (4.3)	1 (9.1)	0	1 (9.1)	0	0	2 (33.3)	0
Convulsion	6 (3.8)	1 (5.3)	1 (4.3)	0	0	1 (9.1)	1 (5.0)	0	2 (33.3)	0
Liver function test abnormal	6 (3.8)	0	1 (4.3)	2 (18.2)	0	0	0	0	1 (16.7)	2 (4.0)
Vomiting	5 (3.2)	2 (10.5)	1 (4.3)	1 (9.1)	0	0	0	0	0	1 (2.0)
Aggression	4 (2.6)	2 (10.5)	0	0	0	0	0	0	0	2 (4.0)
Ataxia	4 (2.6)	0	0	3 (27.3)	0	0	0	0	0	1 (2.0)
Weight decreased	4 (2.6)	2 (10.5)	1 (4.3)	1 (9.1)	0	0	0	0	0	0
Weight increased	2 (1.3)	1 (5.3)	0	0	0	0	0	0	1 (16.7)	0
Secretion discharge	2 (1.3)	1 (5.3)	0	0	1 (16.7)	0	0	0	0	0
Seizure cluster	1 (0.6)	0	0	0	0	0	0	0	1 (16.7)	0
Lethargy	1 (0.6)	0	0	0	1 (16.7)	0	0	0	0	0
Hematemesis	1 (0.6)	0	0	0	1 (16.7)	0	0	0	0	0
Blood alkaline phosphatase increased	1 (0.6)	0	0	0	1 (16.7)	0	0	0	0	0
Throat irritation	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Ocular hyperemia	1 (0.6)	0	0	0	0	0	0	0	1 (16.7)	0
Strabismus	1 (0.6)	0	0	0	0	0	0	0	1 (16.7)	0

[a]Adverse event data was not available for the participants with myoclonic absence epilepsy (n=5; 3.2%).
[b]All deaths were considered unrelated to CBD treatment by the respective investigators. The 11 AEs that were reported among participants who died were respiratory failure (n=2), pulmonary hemorrhage (n=1), asphyxia (n=1), respiratory arrest (n=1), acute sinusitis (n=1), convulsion (n=1), ear infection (n=1), foot deformity (n=1), disease progression (n=1), and death (n=1).
AEs, adverse events; CBD, cannabidiol; *CDKL5*, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAtS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; SWS, Sturge-Weber syndrome; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

- Treatment-emergent adverse events (TEAEs) were reported by 85.9% (134/156 [CBD EAP safety analysis set]) of participants in the overall population (**Table 3**)
  - Serious TEAEs occurred in 50.6% of participants; 3.2% of participants experienced treatment-related serious TEAEs
  - Deaths (n=11, 7.1%) were investigator-assessed as unrelated to CBD treatment
- The most common treatment-related AEs that occurred in ≥10% of participants in the overall population were diarrhea (18.6%), fatigue (12.8%), and somnolence (12.2%)
- The most common TEAEs that occurred in ≥20% of participants in the overall population were convulsion (26.9%) and diarrhea (28.2%) (**Table S2**)
- TEAEs leading to CBD discontinuation occurred in 13.5% of participants in the overall population
  - The most frequently reported TEAEs leading to treatment discontinuation in the overall population were convulsion and diarrhea (both 2.6%)

Limitations

- A key limitation is the potential for design-related bias from comparing populations in separate studies. The ECA included only LGS participants, whereas the EAP had diverse etiologies, limiting direct comparability. Limitations of the EAP data reporting may also have an impact on the descriptive results

Conclusions

- CBD treatment is associated with reductions in convulsive and total seizure frequencies in participants with DEEs and rare epilepsies beyond LGS, DS, and TSC
- The comparative effectiveness analysis confirms superiority of CBD compared with an ECA (placebo) in reducing seizure frequency from baseline
- This analysis supports further investigation of CBD effectiveness for a broad range of DEEs and other rare epilepsies

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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

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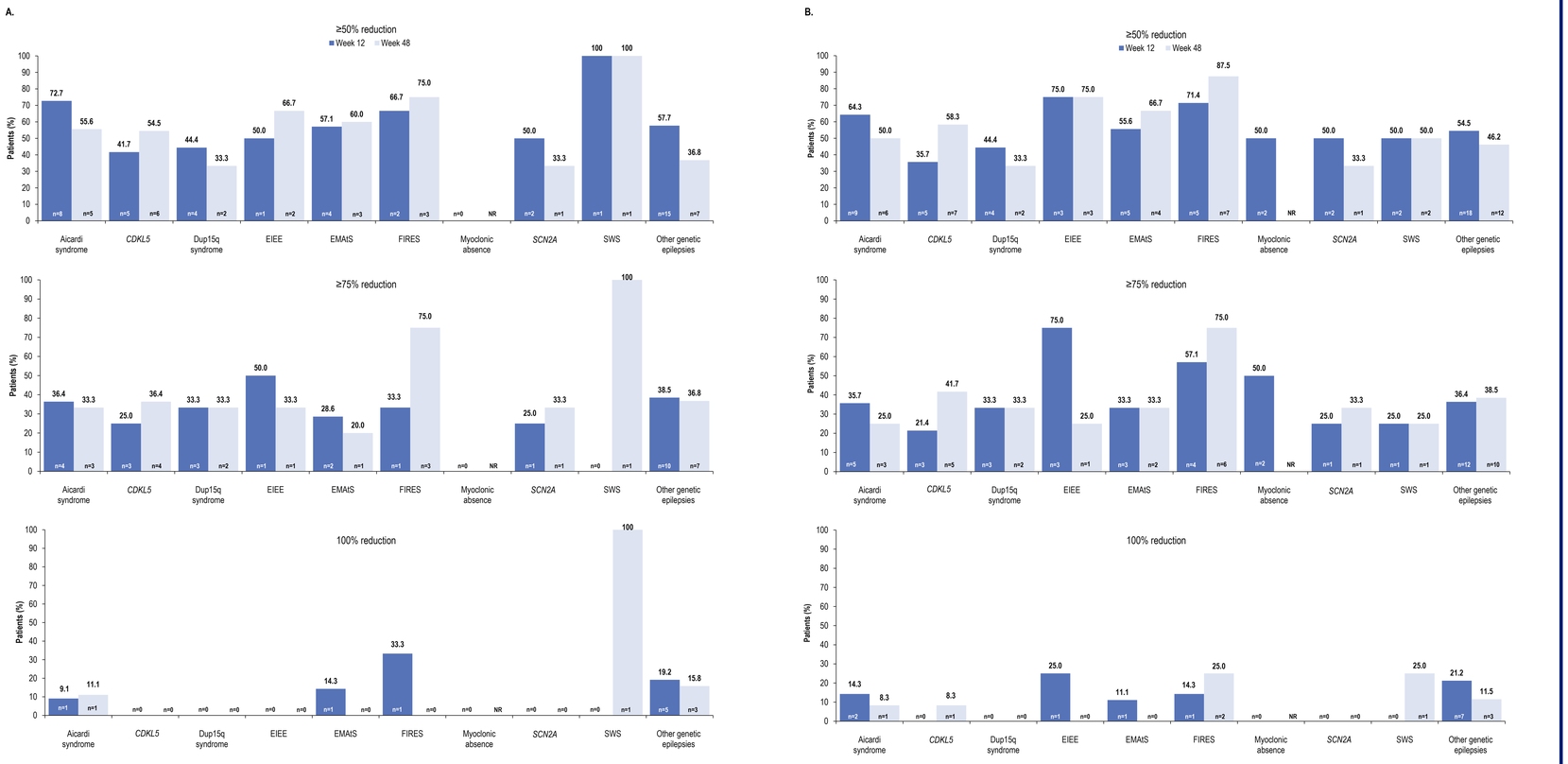
Supplementary Material

Descriptive analysis: CBD EAP effectiveness analysis set

Figure S1. Subgroup treatment response rates for convulsive seizures and total seizures: (A) convulsive and (B) total seizures at ≥50%, ≥75%, and 100%



CBD, cannabidiol; *CDKL5*, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAtS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; NR, not reported; SWS, Sturge-Weber syndrome.

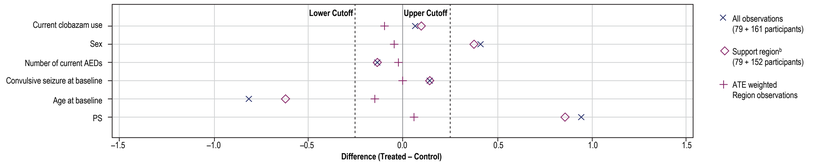
Comparative effectiveness analysis of CBD EAP vs ECA

Table S1. Baseline characteristics: Comparative effectiveness analysis set

	Unweighted		Weighted[a,b]	
	CBD EAP	ECA	CBD EAP	ECA
N, Effectiveness analysis set	79	161	79	152
Age, years, Mean (SD)	9.2 (4.7)	15.3 (9.5)	11.1 (8.3)	12.2 (8.9)
Sex, female, n (%)	52 (65.8)	74 (46.0)	52 (51.2)	72 (53.3)
Number of ASMs, mean (SD)	2.8 (1.2)	2.9 (0.9)	2.9 (2.0)	2.9 (1.2)
ASMs, n (%)				
Clobazam	36 (45.6)	79 (49.1)	36 (55.0)	77 (50.3)
Levetiracetam	27 (34.2)	58 (36.0)	27 (30.1)	56 (37.2)
Valproic acid	23 (29.1)	63 (39.1)	23 (32.7)	60 (38.3)
Lamotrigine	18 (22.8)	56 (34.8)	18 (28.1)	53 (33.8)
Rufinamide	18 (22.8)	41 (25.5)	18 (27.9)	38 (23.5)
Convulsive seizure frequency, mean (SD)	328.1 (1002.1)	219.7 (409.4)	260.2 (1417.5)	260.3 (613.6)
Total seizure frequency, mean (SD)	626.9 (2187.7)	437.4 (713.5)	522.7 (3206.2)	519.1 (1003.8)

[a]Summary statistics are weighted for propensity score derived by balancing the average distribution of age, sex, convulsive seizure frequency at baseline, number of concomitant ASMs, and current use of clobazam.
[b]To avoid large standard error for causal effect estimates, the analysis used a support region of all observations having a percentile from 2 to 98 of the propensity score distribution. The support region included 79 CBD EAP and 152 ECA participants with balanced baseline characteristics.
ASM, antiseizure medication; CBD, cannabidiol; EAP, Expanded Access Program; ECA, external placebo control arm.

Figure S2. Standardized weighted mean difference for covariate balance assessment[a]



[a]Summary statistics are weighted for PS derived by balancing the average distribution of age, sex, convulsive seizure frequency at baseline, number of concomitant ASMs, and current use of clobazam. Differences (SWMD) were calculated to show the difference in means of covariates between treated and control groups, standardized by the pooled SD, for each balancing covariate. A value SWMD <0.1 is acceptable; SWMD between 0.1 and 0.25 is not alarming; SWMD >0.25 denotes a serious imbalance.
[b]To avoid large standard error for causal effect estimates, the analysis used a support region of all observations having a percentile from 2 to 98 of the propensity score distribution. The support region included 79 CBD EAP and 152 ECA participants with balanced baseline characteristics.
AEDs, antiepileptic drugs; ATE, average treatment difference; PS, propensity score; SWMD, standardized weight mean difference.

Safety results (CBD EAP safety analysis set)

Table S2. Summary of TEAEs reported in ≥20% of participants (CBD EAP safety analysis set)

	Overall[a]	Aicardi syndrome	*CDKL5*	Dup15q syndrome	EIEE	EMAtS	FIRES	*SCN2A*	SWS	Other genetic epilepsies
TEAEs reported in ≥20% of participants in any group by preferred term, n (%)										
Diarrhea, n (%)	44 (28.2)	7 (36.8)	7 (30.4)	2 (18.2)	3 (50.0)	3 (27.3)	5 (25.0)	0	1 (16.7)	16 (32.0)
Convulsion, n (%)	42 (26.9)	5 (26.3)	7 (30.4)	4 (36.4)	3 (50.0)	2 (18.2)	5 (25.0)	0	5 (83.3)	11 (22.0)
URTI, n (%)	29 (18.6)	3 (15.8)	6 (26.1)	0	2 (33.3)	3 (27.3)	0	0	5 (83.3)	10 (20.0)
Vomiting, n (%)	25 (16.0)	3 (15.8)	8 (34.8)	1 (9.1)	2 (33.3)	2 (18.2)	4 (20.0)	0	2 (33.3)	3 (6.0)
Pyrexia, n (%)	24 (15.4)	3 (15.8)	7 (30.4)	0	3 (50.0)	1 (9.1)	2 (10.0)	1 (20.0)	1 (16.7)	6 (12.0)
Fatigue, n (%)	22 (14.1)	4 (21.1)	6 (26.1)	3 (27.3)	1 (16.7)	2 (18.2)	1 (5.0)	0	1 (16.7)	4 (8.0)
Somnolence, n (%)	20 (12.8)	3 (15.8)	3 (13.0)	3 (27.3)	1 (16.7)	4 (36.4)	0	0	0	6 (12.0)
Pneumonia, n (%)	19 (12.2)	4 (21.1)	2 (8.7)	1 (9.1)	3 (50.0)	0	4 (20.0)	0	1 (16.7)	4 (8.0)
Status epilepticus, n (%)	17 (10.9)	3 (15.8)	1 (4.3)	1 (9.1)	1 (16.7)	1 (9.1)	1 (5.0)	1 (20.0)	1 (16.7)	7 (14.0)
Decreased appetite, n (%)	16 (10.3)	1 (5.3)	5 (21.7)	4 (36.4)	0	1 (9.1)	1 (5.0)	0	1 (16.7)	3 (6.0)
Gastroenteritis viral, n (%)	12 (7.7)	1 (5.3)	0	0	0	0	1 (5.0)	3 (60.0)	2 (33.3)	5 (10.0)
Abnormal behavior, n (%)	12 (7.7)	2 (10.5)	2 (8.7)	1 (9.1)	0	1 (9.1)	0	1 (20.0)	4 (66.7)	1 (2.0)
Sedation, n (%)	12 (7.7)	3 (15.8)	0	0	1 (16.7)	0	0	1 (20.0)	0	7 (14.0)
Rash, n (%)	12 (7.7)	0	4 (17.4)	2 (18.2)	0	1 (9.1)	0	0	2 (33.3)	3 (6.0)
Weight decreased, n (%)	9 (5.8)	3 (15.8)	2 (8.7)	1 (9.1)	0	0	1 (5.0)	1 (20.0)	0	1 (2.0)
Hypoxia, n (%)	6 (3.8)	0	1 (4.3)	0	1 (16.7)	0	1 (5.0)	1 (20.0)	0	2 (4.0)
Weight increased, n (%)	5 (3.2)	2 (10.5)	0	0	0	0	0	1 (20.0)	1 (16.7)	1 (2.0)
Ataxia, n (%)	4 (2.6)	0	0	3 (27.3)	0	0	0	0	0	1 (2.0)
Secretion discharge, n (%)	4 (2.6)	1 (5.3)	0	0	2 (33.3)	0	1 (5.0)	0	0	0
Headache, n (%)	4 (2.6)	0	0	0	0	0	0	0	2 (33.3)	2 (4.0)
Leukocytosis, n (%)	2 (1.3)	0	0	0	0	0	0	1 (20.0)	0	1 (2.0)
Pneumonia streptococcal, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Infectious mononucleosis, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Dermatitis allergic, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Pneumothorax spontaneous, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0
Throat irritation, n (%)	1 (0.6)	0	0	0	0	0	0	1 (20.0)	0	0

[a]Adverse event data was not available for the participants with myoclonic absence epilepsy (n=5; 3.2%).
CBD, cannabidiol; *CDKL5*, cyclin-dependent kinase-like 5; EAP, Expanded Access Program; EIEE, early infantile epileptic encephalopathy; EMAtS, epilepsy with myoclonic-atonic seizures; FIRES, febrile infection-related epilepsy syndrome; SWS, Sturge-Weber syndrome; TEAEs, treatment-emergent adverse events; URTI, upper respiratory tract infection.

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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

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