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Real-World Outcomes of Cannabidiol (CBD) in Tuberous Sclerosis Complex (TSC) and Other Focal Epilepsies: Experience From the Expanded Access Program (EAP)

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Introduction

- Epidiolex® (cannabidiol [CBD]) is approved in the United States (US) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome, or tuberous sclerosis complex (TSC) in patients aged ≥1 year[1]
- Prior to initial FDA approval in 2018, the CBD Expanded Access Program (EAP) was initiated in 2014 to provide CBD to patients with a diverse range of treatment-resistant epilepsies (TREs) across 35 centers in the US[2]
- Efficacy of CBD in seizures associated with TSC, a condition with mainly focal seizures, was demonstrated in a phase 3 trial (NCT02544763)[2–4]
- CBD treatment in the EAP demonstrated sustained seizure reductions in patients with various TREs, including genetic and syndromic epilepsies[2,5]
- Here we present CBD treatment outcomes in EAP participants with focal epilepsies including TSC (TSC group) vs those with other types of focal epilepsy (non-TSC group)

Objective

- To report the long-term effectiveness and safety results of adjunctive CBD treatment in patients with TSC and other non-TSC focal epilepsies in the EAP

Methods

- All patients enrolled in the study had TREs and were receiving stable doses of antiseizure medications (commonly referred to as antiepileptic drugs) for ≥4 weeks before enrollment
- Patients received highly purified plant-derived CBD (Epidiolex®; 100 mg/mL oral solution), doses starting at 2–10 mg/kg/day and titrated up to each patient's limit or to a maximum of 25–50 mg/kg/day, at the discretion of the study site investigators and institutional review board approval
- Patients with a diagnosis and/or etiology indicating focal epilepsy were identified and analyzed
  - This analysis excluded individuals with a diagnosis of LGS, regardless of etiology
- Effectiveness of CBD was evaluated as percent change from baseline in median monthly focal and total seizure frequencies and responder rates (≥50%, ≥75%, 100% reduction) across 12-week windows through 144 weeks of treatment
- Safety results were reported for the full follow-up of up to 240 weeks

Results

Table 1. Baseline characteristics and CBD exposure

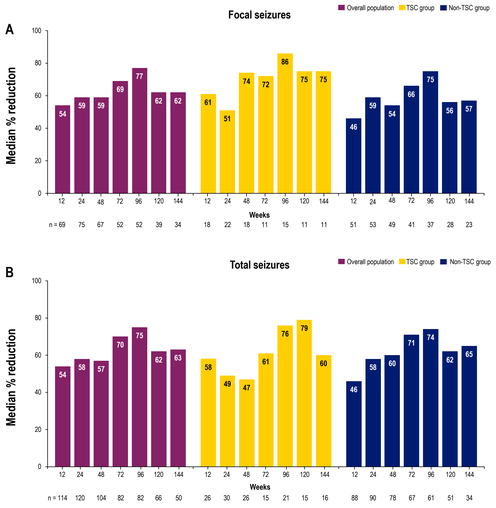
	All focal epilepsies (N=146)	TSC group (n=34)	Non-TSC group (n=112)
Age, years			
Mean (SD)	19.1 (14.5)	12.5 (8.2)	21.1 (15.4)
Median (range)	15.7 (2–73)	12.1 (2–31)	17.1 (2–73)
Sex, female, n (%)	77 (53)	16 (47)	61 (55)
Concomitant ASMs at baseline, median (range)	3 (0–7)	3 (1–7)	3 (0–5)
Baseline ASMs, ≥10% of patients in any group, n (%)			
Clobazam	55 (38)	18 (53)	37 (33)
Lamotrigine	48 (33)	15 (44)	33 (30)
Levetiracetam	48 (33)	10 (29)	38 (34)
Lacosamide	45 (31)	17 (50)	28 (25)
Topiramate	24 (16)	1 (3)	23 (21)
Valproate	23 (16)	7 (21)	16 (14)
Oxcarbazepine	22 (15)	6 (18)	16 (14)
Zonisamide	22 (15)	2 (6)	20 (18)
Rufinamide	15 (10)	4 (12)	11 (10)
Phenobarbital	12 (8)	–	12 (11)
Vigabatrin	13 (9)	7 (21)	6 (5)
Diazepam	7 (5)	4 (12)	3 (3)
Epilepsy diagnosis, n (%)			
TSC	34 (23)	34 (100)	–
Non-TSC	112 (77)	–	112 (100)
Not specified[a]	31 (21)	–	31 (28)
Cortical dysplasia	20 (14)	–	20 (18)
Frontal lobe epilepsy	14 (10)	–	14 (13)
Malformation of cortical development	13 (9)	–	13 (12)
Temporal lobe epilepsy	10 (7)	–	10 (9)
Stroke related	9 (6)	–	9 (8)
Other focal epilepsy[b]	7 (5)	–	7 (6)
Sturge-Weber syndrome	5 (3)	–	5 (4)
Tumor related	3 (2)	–	3 (3)
Seizure frequency per 28 days, median (Q1, Q3) [n]			
Focal	27 (9, 96) [92]	41 (25, 86) [24]	20 (8, 104) [68]
Total	56 (15, 151) [143]	66 (36, 164) [32]	51 (10, 151) [111]
CBD exposure			
Median time on CBD, days (range)	901 (15–1655)	1102 (85–1631)	880 (15–1655)
Median total dose, mg/kg/day (Q1, Q3)	25 (15, 30)	25 (17, 35)	24 (15, 26)

[a]These patients had diagnostic terms such as partial epilepsy, intractable localization-related epilepsy, and multifocal epilepsy. [b]Includes the following etiologies: n=2 (1%) each for hypoxic ischemic encephalopathy, encephalitis, and congenital malformation, and n=1 (<1%) each for occipital lobe epilepsy and malignant migrating partial epilepsy of infancy.
ASM, antiseizure medication; CBD, cannabidiol; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

Efficacy results

Seizure frequency

Figure 1. Median percent reduction from baseline in seizure frequencies in (A) focal seizures and (B) total seizures

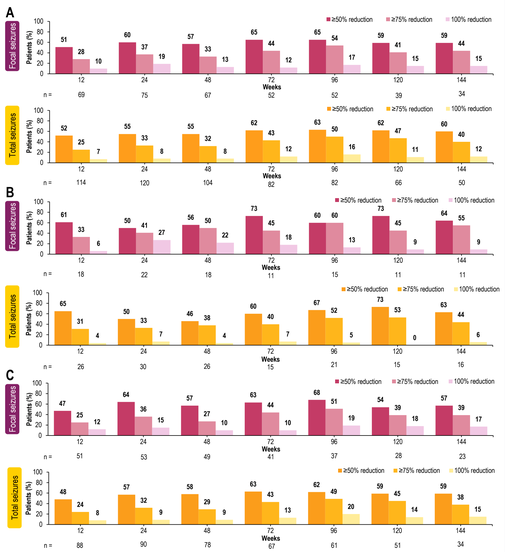


TSC, tuberous sclerosis complex.

- Across 12-week visit windows, CBD treatment was associated with a median percentage reduction in focal seizures of 54–77% in the overall population, 51–87% in patients with TSC (TSC group), and 46–75% in patients with other focal epilepsies (non-TSC group) (**Figures 1 and S1**)
- Across 12-week visit windows, CBD treatment was associated with a median percentage reduction in total seizures of 54–75% in the overall population, 44–87% in patients with TSC (TSC group), and 46–74% in patients with other focal epilepsies (non-TSC group) (**Figures 1 and S1**)

Response rates

Figure 2. Treatment response rates in (A) the overall population of patients with focal and total seizures, (B) patients with TSC (TSC group), and (C) patients with other focal epilepsies (non-TSC group)



TSC, tuberous sclerosis complex.

- Across 12-week visit windows, responder rates (≥50%, ≥75%, and 100%) from week 12 through week 144 were as follows:
  - **Focal seizures: overall population,** 51–72%, 28–54%, 9–19%; **TSC group,** 50–75%, 33–60%, 6–28%; **non-TSC group,** 47–72%, 25–51%, 7–19% (**Figures 2 and S2**)
  - **Total seizures: overall population,** 50–64%, 25–50%, 4–16%; **TSC group,** 43–76%, 31–65%, 0–8%; **non-TSC group,** 48–69%, 24–49%, 6–20% (**Figures 2 and S2**)

Safety results

Table 2. Summary of adverse events

	All focal epilepsies (N=151)	TSC group (n=34)	Non-TSC group (n=117)
Patients, n (%)			
Any TEAEs	140 (93)	30 (88)	110 (94)
Any TRAEs	112 (74)	22 (65)	90 (77)
TEAEs leading to CBD discontinuation	12 (8)	2 (6)	10 (9)
Serious TEAEs	58 (38)	14 (41)	44 (38)
Treatment-related serious AEs	3 (2)	0	3 (3)
Deaths[a]	4 (3)	0	4 (3)
TEAEs reported in ≥10% of patients in any group by preferred term, n (%)			
Diarrhea	71 (47)	10 (29)	61 (52)
Convulsion	37 (25)	5 (15)	32 (27)
Somnolence	32 (21)	11 (32)	21 (18)
Vomiting	27 (18)	6 (18)	21 (18)
URTI	24 (16)	4 (12)	20 (17)
Headache	20 (13)	4 (12)	16 (14)
Decreased appetite	18 (12)	5 (15)	13 (11)
Gastroenteritis viral	17 (11)	5 (15)	12 (10)
Nasopharyngitis	15 (10)	3 (9)	12 (10)
Dizziness	13 (9)	1 (3)	12 (10)
Fall	13 (9)	0	13 (11)
Influenza	14 (9)	2 (6)	12 (10)
UTI	14 (9)	2 (6)	12 (10)
Nausea	12 (8)	0	12 (10)
Pyrexia	12 (8)	4 (12)	8 (7)
Abnormal behavior	10 (7)	4 (12)	6 (5)
Ataxia	7 (5)	5 (15)	2 (2)
Sleep disorder	8 (5)	5 (15)	3 (3)

[a]All deaths were considered unrelated to CBD treatment by the respective investigators.
AE, adverse event; CBD, cannabidiol; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TSC, tuberous sclerosis complex; URTI, upper respiratory tract infection; UTI, urinary tract infection.

- Treatment-emergent adverse events (TEAEs) were reported by 93%, which included 30/34 patients in the TSC group and 110/117 patients in the non-TSC group; serious TEAEs occurred in 41% and 38% of patients, respectively (**Table 2**)
- The most common TEAEs that occurred in ≥20% of patients with all focal epilepsies were diarrhea (47%), convulsion (25%), and somnolence (21%)
  - The most common TEAEs were somnolence (32%) in the TSC group and diarrhea (52%) in the non-TSC group
- TEAEs leading to CBD discontinuation occurred in 8% overall, including 2 patients in the TSC group and 10 in the non-TSC group
  - The most frequently reported TEAEs leading to treatment discontinuation in patients with all focal epilepsies were diarrhea (2%), constipation (1%), and lethargy (1%)

Conclusions

- CBD treatment was associated with similar reductions in focal and total seizure frequencies in both the TSC and other focal epilepsy groups through 144 weeks
- The response rates of ≥50%, ≥75%, or 100% reduction in seizure frequency were maintained across the 12-week visit windows through 144 weeks
- These results suggest that CBD has similar effectiveness in TSC and other focal epilepsies

References: **1.** Epidiolex® (cannabidiol) oral solution. Prescribing information. Jazz Pharmaceuticals, Inc.; 2024. **2.** Szaflarski JP, et al. *Epilepsia*. 2023;64(3):619–629. **3.** Thiele EA, et al. *JAMA Neurol*. 2021;78(3):285–292. **4.** Thiele EA, et al. *Epilepsia*. 2022;63(2):426–439. **5.** Flamini RJ, et al. *Epilepsia*. 2023;64(8):e163.

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Supplementary Material

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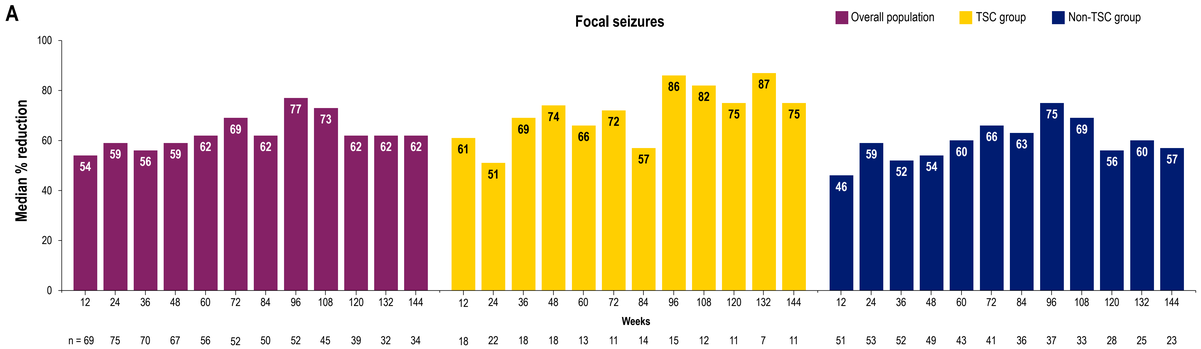
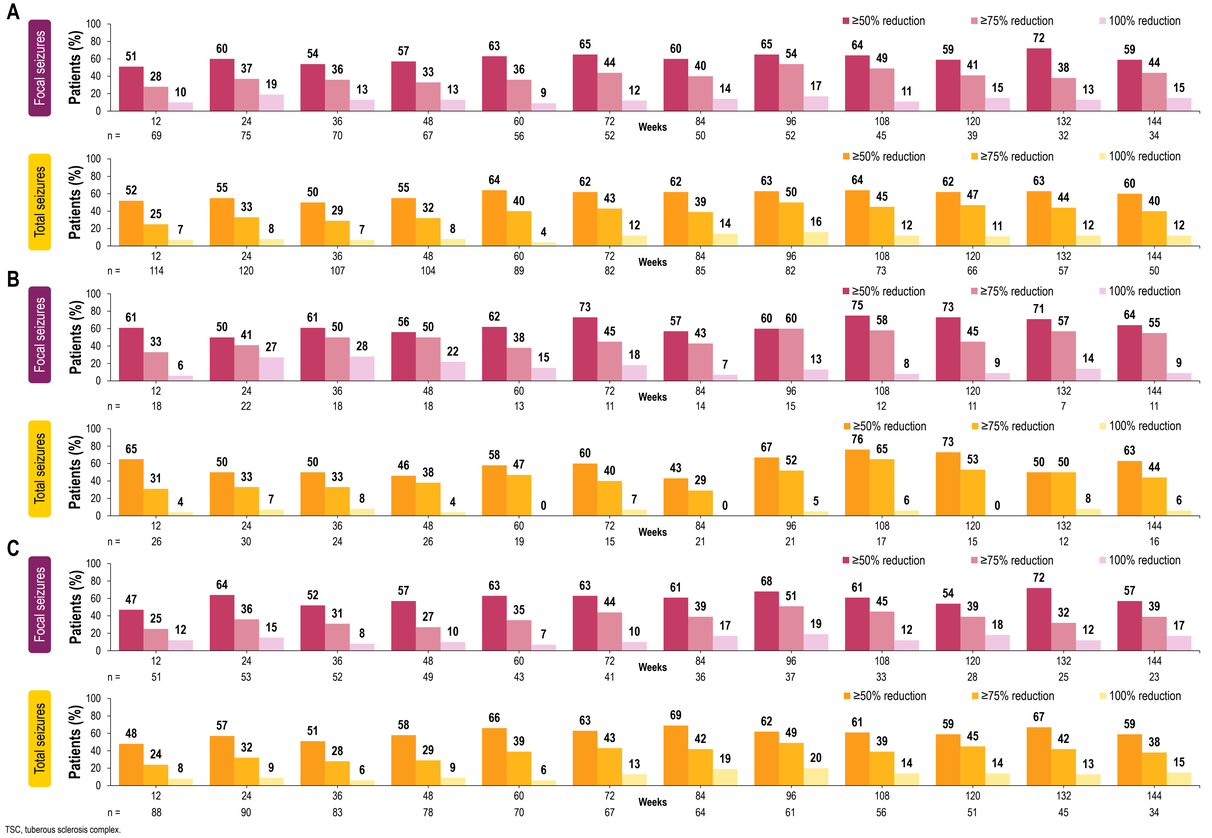
Seizure frequency

Figure S1. Median percent reduction from baseline in seizure frequencies in (A) focal seizures and (B) total seizures



TSC, tuberous sclerosis complex.

Figure S2. Treatment response rates in (A) the overall population of patients with focal and total seizures, (B) patients with TSC (TSC group), and (C) patients with other focal epilepsies (non-TSC group)



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