2.493 Real-World Outcomes of Cannabidiol in Treatment-Resistant Focal Epilepsies: Experience From the Expanded Access Program

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Background

- Epidiolex® (cannabidiol [CBD]) is approved in the United States for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.[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 United States.
- Long-term results from the EAP showed that CBD treatment was associated with convulsive seizure reductions in the overall population, including in patients with severe genetic epilepsies.[2,3]
- The effect of CBD specifically in patients with focal epilepsies is not well-defined.

Objective

- To present the effectiveness and safety results of CBD treatment in patients with focal epilepsy in the EAP.

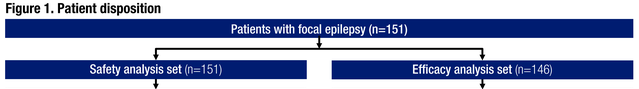
Methods

- Although some eligibility criteria varied by site, all patients in this study had TRE and were receiving stable doses of antiseizure medications for ≥4 weeks before enrollment.
- During the baseline period, patients/caregivers kept diaries of all countable seizure types.
- Patients received highly purified, plant-derived CBD (Epidiolex®; 100 mg/mL oral solution) starting at 2–10 mg/kg/d and further titrated based on clinical response and tolerance to a maximum dose of 25–50 mg/kg/d, at the discretion of the study site and institutional review board approval.
- Patients with a diagnosis and/or etiology indicating a focal epilepsy were identified and analyzed.
  - This analysis excluded individuals with a diagnosis of LGS, regardless of etiology.
- Effectiveness of CBD was evaluated as the percentage change from baseline in the median monthly frequency of focal and total seizures, and responder rates (≥50%, ≥75%, and 100% reduction) across 12-week intervals through 144 weeks of treatment.
- Safety endpoints included adverse events (AEs), serious AEs, AEs leading to discontinuation, and deaths; safety results are reported for the full follow-up (up to 240 weeks).
- This study was conducted with Epidiolex®, and results do not apply to other CBD-containing products.

Results

- From the total EAP population, 151 patients were identified as having either a confirmed focal etiology or diagnosis of focal epilepsy.

Figure 1. Patient disposition



Patients withdrawn, n (%)	54 (36)
Lack of efficacy	24 (16)
Adverse event	14 (9)
Other	6 (4)
Patient withdrawn by the investigator	4 (3)
Patient/caregiver withdrew consent	2 (1)
Patient met withdrawal criteria	2 (1)
Lost to follow-up	2 (1)

Patients withdrawn, n (%)	52 (36)
Lack of efficacy	24 (16)
Adverse event	13 (9)
Other	6 (4)
Patient withdrawn by the investigator	4 (3)
Patient/caregiver withdrew consent	2 (1)
Patient met withdrawal criteria	2 (1)
Lost to follow-up	1 (1)

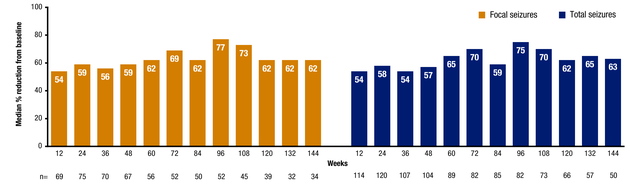
Table 1. Baseline characteristics and CBD exposure

	Safety population (n=151)	Efficacy population (n=146)
Mean age, years (min, max)	19.3 (1, 73)	19.1 (2, 73)
Sex, n (%)		
Female	79 (52)	77 (53)
No. of ASMs at baseline, median (min, max)	3 (0, 7)	3 (0, 7)
Most common (>15%) ASMs at baseline, n (%)		
Clobazam	55 (36)	55 (38)
Levetiracetam	51 (34)	48 (33)
Lamotrigine	50 (33)	48 (33)
Topiramate	25 (17)	24 (16)
Valproate	24 (16)	23 (16)
Diagnosis/etiology, n (%)		
TSC	34 (23)	34 (23)
Not specified[a]	32 (21)	31 (21)
Cortical dysplasia	20 (13)	20 (14)
Frontal lobe epilepsy	14 (9)	14 (10)
Malformation of cortical development	12 (8)	12 (8)
Temporal lobe epilepsy	12 (8)	10 (7)
Stroke-related	10 (7)	9 (6)
Sturge-Weber syndrome	6 (4)	5 (3)
Tumor-related	3 (2)	3 (2)
Other focal epilepsy[b]	8 (5)	8 (5)
Baseline median (Q1, Q3) monthly seizure frequency [n]		
Focal	—	27 (9, 96) [92]
Total (convulsive and nonconvulsive)	—	56 (15, 151) [143]
CBD exposure		
Median time on CBD (range), days	894 (15–1655)	901 (15–1655)
Median total daily dose (IQR), mg/kg/d	25 (17–30)	25 (15–30)

[a]These patients had diagnostic terms such as partial epilepsy, intractable localization related epilepsy, and multifocal epilepsy. [b]Includes the following etiologies for both safety and efficacy populations: 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.

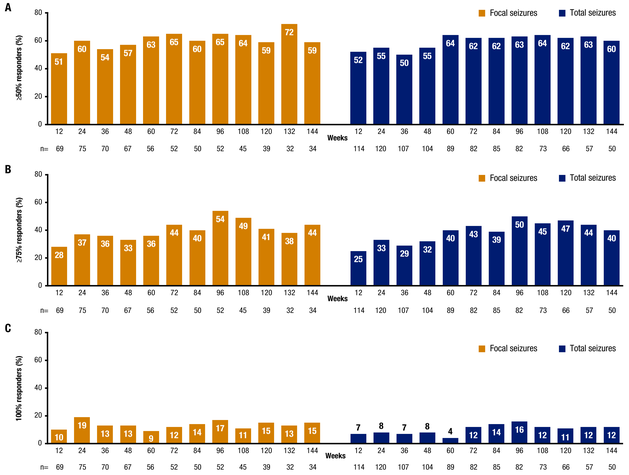
Efficacy results

Figure 2. Median percentage reduction from baseline in focal and total seizures



- CBD treatment was associated with a median 54%–77% reduction from baseline in focal seizures and 54%–75% reduction in total seizures during 12-week visit windows through 144 weeks of treatment.

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



- Across 12-week visit intervals, focal seizure responder rates (≥50%, ≥75%, and 100% reduction) ranged from 51%–72%, 28%–54%, and 9%–19% of patients, respectively.
- Total seizure responder rates ranged from 50%–64%, 25%–50%, and 4%–16% of patients, respectively.

Safety results

Table 2. Summary of AEs

Patients, n (%)	Safety population (n=151)
TEAEs	
Any AEs	140 (93)
Any TRAEs	112 (74)
AEs leading to permanent discontinuation	12 (8)
Serious AEs	58 (38)
Treatment-related serious AEs	3 (2)
Deaths	4 (3)
TRAEs reported in ≥5% of patients by MedDRA preferred term	
Diarrhea	62 (41)
Somnolence	29 (19)
Dizziness	10 (7)
Decreased appetite	10 (7)
Vomiting	9 (6)
Decreased weight	8 (5)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- The most frequently reported serious AEs in ≥5% of patients were convulsion (15%) and status epilepticus (5%).
- The most frequently reported AEs leading to treatment discontinuation (≥1% of patients) were diarrhea (2%), constipation (1%), and lethargy (1%).
- AEs led to death in 4 patients. Deaths were deemed unrelated to treatment according to the investigator.
- Liver-related AEs in >1% of patients were abnormal liver function test (n=7 [4.6%]), increased alanine aminotransferase (ALT) (n=4 [2.6%]), and increased aspartate aminotransferase (AST) (n=3 [2.0%]).

Conclusions

- In this analysis of patients with focal epilepsy in the CBD EAP, CBD treatment was associated with a reduction in focal and total seizures through 144 weeks.
- At least 50% reduction in focal and total seizures was reported by the majority of patients through 144 weeks.
- The CBD safety profile was similar to that observed in previously reported EAP analyses and clinical trials.[2, 4–8]
- This was an open-label study with varying enrollment criteria by site.
- These results provide evidence of real-world effectiveness of CBD in patients with treatment-resistant focal epilepsy and warrant further research.

References: 1. Jazz Pharmaceuticals. Epidiolex® (cannabidiol) oral solution [prescribing information]. 2023. https://www.epidiolex.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf. **2.** Szaflarski JP et al. *Epilepsia.* 2023;64(3):619-629. **3.** Flamini RJ et al. *Epilepsia.* 2023;64(8):e163. **4.** Devinsky O et al. *N Engl J Med.* 2018;378:1888-1897. **5.** Devinsky O et al. *N Engl J Med.* 2017;376:2011-2020. **6.** Thiele EA et al. *Lancet.* 2018;391:1085-1096. **7.** Miller I et al. *JAMA Neurol.* 2020;77:613-621. **8.** Thiele EA et al. *JAMA Neurol.* 2021;78:285-292.

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Disclosures: All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. **ADP, JPS, EAT,** and **PL** have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc; **MB, TG, TS, KR,** and **KS** are employees of Jazz Pharmaceuticals, Inc. Epidiolex® is approved in the U.S. for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 years of age.

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