3.291 Long-Term Effectiveness of Cannabidiol Against Focal-Onset Seizures in Treatment-Resistant Epilepsies

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Introduction

- Epidiolex® (cannabidiol [CBD]) is approved in the United States for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.[1]
- Patients with treatment-resistant epilepsy (TRE) received compassionate access to CBD through an Expanded Access Program (EAP) across 35 United States epilepsy centers from January 2014 to January 2019.
- Four-year results from the EAP demonstrated that CBD was associated with reduction in seizure frequency through 192 weeks of treatment[2]; furthermore, reduction was observed in the frequency of both convulsive and nonconvulsive seizures with CBD through 144 weeks of treatment.[3]
- The effect of CBD specifically in focal-onset seizure reduction in the real world is not well-defined.

Objective

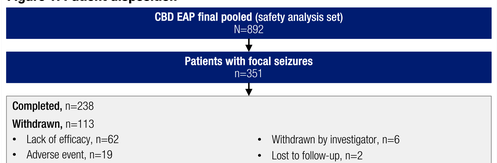
- To evaluate the effectiveness of CBD treatment for focal-onset seizures in patients with TRE treated in the CBD EAP.

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.
- Patients received plant-derived, highly purified 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.
- Effectiveness of CBD was evaluated as the percentage change from baseline in the median monthly frequency of focal-onset 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.
- This study was conducted with Epidiolex®, and results do not apply to other CBD-containing products.

Results

Figure 1. Patient disposition



CBD, cannabidiol; EAP, Expanded Access Program.

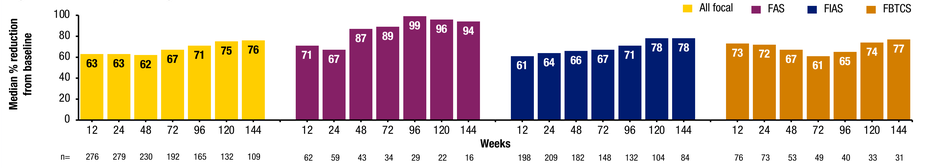
Table 1. Baseline characteristics and CBD exposure

	Efficacy population (n=348)
Mean age, years (min, max)	15.8 (0, 73)
Age category, years, n (%)	
≤5	53 (15)
6–11	101 (29)
12–17	90 (26)
≥18	102 (29)
Male sex, n (%)	179 (51)
No. of ASMs at baseline, median (min, max) [n]	3 (0, 10) [348]
Most common (>20%) ASMs at baseline, n (%)[a]	
Clobazam	150 (43)
Levetiracetam	124 (35)
Lacosamide	96 (27)
Lamotrigine	93 (26)
Valproate	75 (21)
Diagnosis at baseline, n (%)	
TSC	28 (8)
LGS	27 (8)
DS	24 (7)
Other	192 (55)
Unknown	77 (22)
Baseline median (Q1, Q3) monthly seizure frequency [n]	
FAS	28.0 (4, 87) [77]
FIAS	22.4 (7, 76) [259]
FBTCS	12.0 (4, 41) [93]
All focal seizures	25.8 (8, 88) [345]
CBD exposure	
Median time on CBD (range), days [n][b]	700 (281–1177) [347]
Median total daily dose (IQR), mg/kg/d [n][c]	22.0 (15–25) [347]

[a]Data from safety population (n=351). [b]Median time on CBD for safety population (range), days: 684 (281–1177) [n=350]. [c]Median total daily dose for safety population (IQR), mg/kg/d: 21.6 (15–25) [n=349].
ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; FAS, focal aware seizure; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; IQR, interquartile range; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

Efficacy results

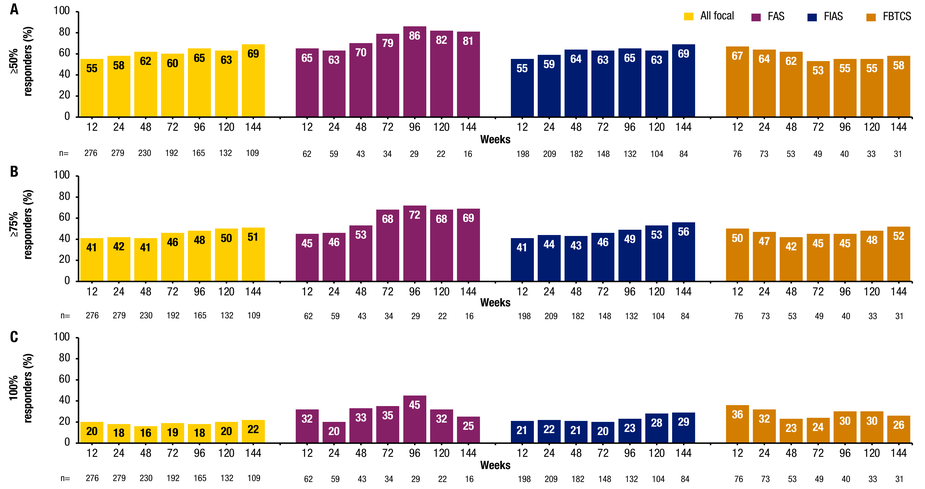
Figure 2. Median percentage reduction from baseline in focal seizures



FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

- Across 12-week visit intervals (data available via QR code), CBD treatment was associated with a median reduction of 63%–76% in all focal seizures, 67%–99% in FAS, 61%–78% in FIAS, and 50%–81% in FBTCS.

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



FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

- Across 12-week visit intervals (data available via QR code), responder rates (≥50%, ≥ 75%, and 100%) through 144 weeks were as follows:
  - **All focal seizures,** 55%–69%, 41%–51%, and 14%–23%; **FAS,** 61%–88%, 45%–72%, and 20%–46%; **FIAS,** 55%–69%, 41%–56%, and 18%–29%; **FBTCS,** 52%–69%, 41%–54%, and 23%–36%

Safety results

Table 2. Summary of AEs

Patients, n (%)	Safety population (n=351)
TEAEs	
Any AEs	315 (90)
Any TRAEs	241 (69)
AEs leading to permanent discontinuation	23 (7)
Serious AEs	132 (38)
Deaths	5 (1)
TRAEs in ≥5% of patients by MedDRA preferred term	
Diarrhea	105 (30)
Somnolence	62 (18)
Decreased appetite	35 (10)
Fatigue	32 (9)
Weight decreased	22 (6)
Dizziness	18 (5)
Sedation	18 (5)

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

- Most frequently reported serious AEs included convulsion (11%), status epilepticus (5%), pneumonia (5%), vomiting (3%), and dehydration (3%).
- Most frequently reported AEs leading to treatment discontinuation included convulsion, diarrhea, constipation, decreased weight, and lethargy (all 1%).
- Deaths were considered unrelated to treatment according to the investigators.

Laboratory investigations

- Liver-related AEs in >1% of patients were increased alanine aminotransferase (ALT) (n=15 [4%]), increased aspartate aminotransferase (AST) (n=15 [4%]), and abnormal liver function test (n=11 [3%]).
- The rate of treatment-emergent ALT >3 times the upper limit of normal (ULN) was 10% (n=34/347)
- The rate of treatment-emergent AST >3X ULN was 3% (n=3/101)

Conclusions

- In this analysis of patients with TREs in the CBD EAP, add-on CBD was associated with a reduction in focal-onset seizures through 144 weeks.
- At least 50% reduction was reported by the majority of patients across focal-onset seizure types through 144 weeks with FAS showing the greatest reduction in seizures.
- The CBD safety profile in this subgroup was similar to that observed in previously reported EAP analyses and clinical trials.
- Because the EAP was conducted in a real-world setting, it was not placebo-controlled and patients were not blinded. Other limitations include potential intersite variability in seizure classification and the potential impact of concomitant medications.
  - Despite these limitations, the results suggest that CBD may be effective against focal-onset seizures regardless of epilepsy diagnosis.
- These findings offer valuable insights into the long-term effectiveness of CBD for focal-onset seizures in a real-world clinical practice setting.

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.

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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. **YDP** and **RJF** have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.; **KR, TG,** and **FS** 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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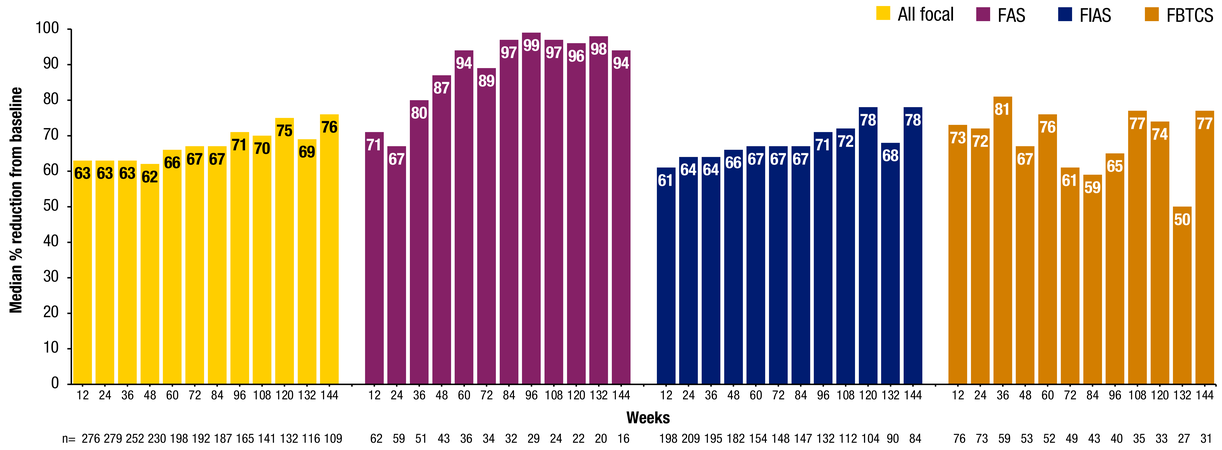
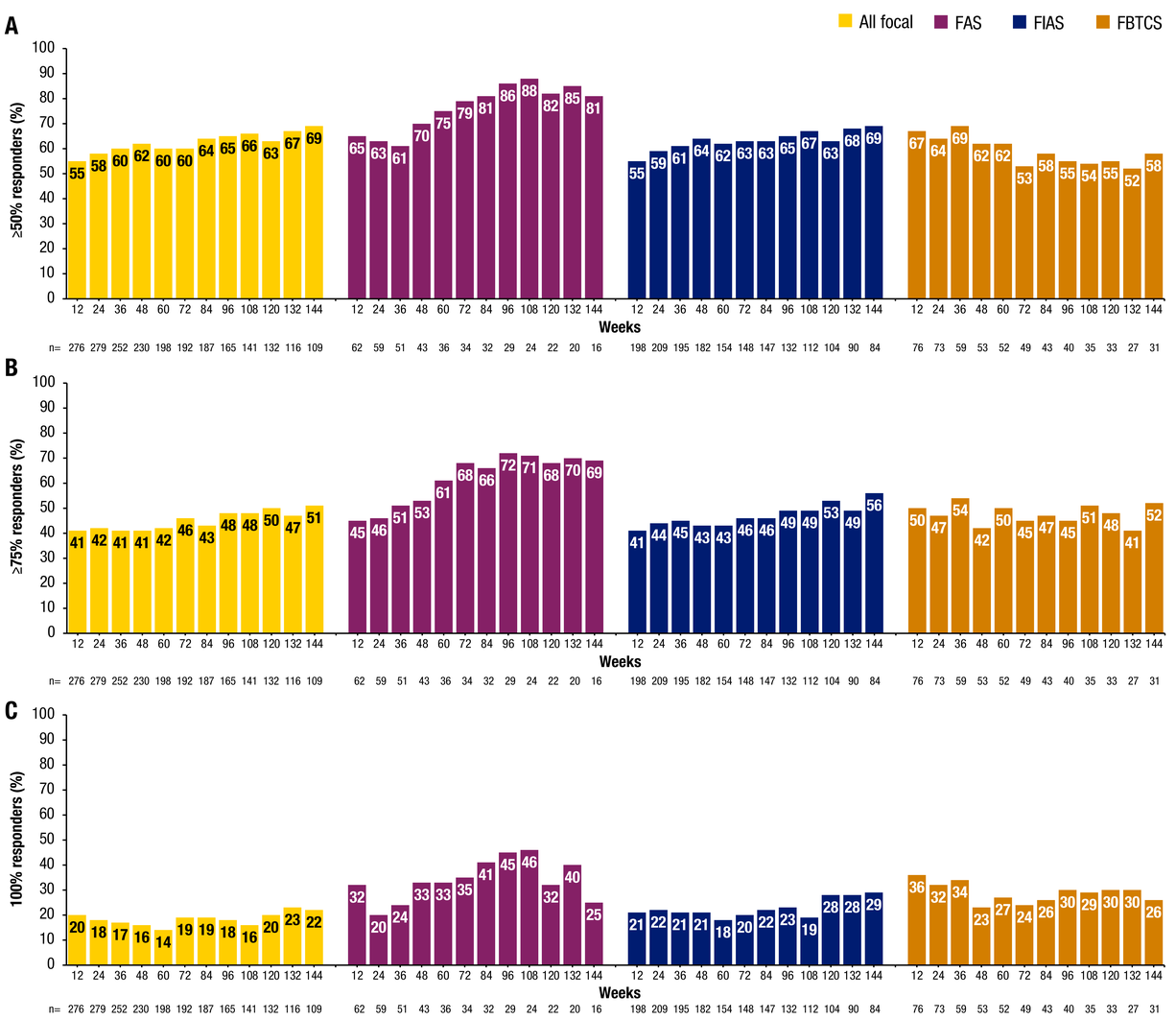
Supplementary Material

Figure S1. Median percentage reduction from baseline in focal seizures (12-week intervals)



FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Figure S2. Treatment response rates (12-week intervals): (A) ≥50% reduction, (B) ≥75% reduction, and (C) 100% reduction in focal seizures



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