P8.1-001 Long-Term Effectiveness of Cannabidiol Against Focal Seizures in Tuberous Sclerosis Complex: Results From the GWPCARE6 Open-Label Extension Trial

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Background

- Add-on cannabidiol (CBD) led to a significant reduction in seizures associated with tuberous sclerosis complex (TSC) in a randomized controlled trial (RCT; GWPCARE6), and most adverse events (AEs) were mild to moderate in severity.[1]
- In an open-label extension (OLE) of GWPCARE6, seizure frequency remained lower than the RCT baseline throughout 156 weeks of CBD treatment.[2]
- The specific effect of long-term treatment with CBD on focal seizures in patients with TSC is not well characterized.

Objective

- To present the effectiveness and safety results of CBD treatment in patients with focal-onset seizures in the GWPCARE6 OLE.

Methods

- Patients who had completed treatment in the 16-week randomized controlled phase of GWPCARE6 were enrolled in the OLE.
- Eligible patients were aged 1–65 years, had a clinical TSC diagnosis, were experiencing ≥8 TSC-associated seizures during the 4-week RCT baseline period, and were taking ≥1 antiseizure medication at baseline.
- TSC-associated seizures included all countable focal motor seizures without impairment of awareness (FAS), focal seizures with impairment of awareness (FIAS), focal seizures evolving to bilateral motor seizures (FBTCS), and generalized seizures (tonic-clonic, tonic, clonic, or atonic).
- Patients entering the OLE started a 2-week blinded transition period, during which the blinded medication (CBD 25 mg/kg/d, CBD 50 mg/kg/d, or placebo) from the RCT was tapered down to 0, while CBD was simultaneously titrated up to 25 mg/kg/d; the dose could then be decreased or increased up to maximum 50 mg/kg/d based on response and tolerability.
- In this post hoc analysis, the effectiveness of CBD was evaluated as the percentage change from baseline in the 28-day monthly average and responder rates (≥50%, ≥75%, and 100% reduction) of focal seizure frequency across 12-week intervals through 144 weeks of treatment.
- Safety endpoints included AEs, serious AEs, AEs leading to discontinuation, and deaths; safety results are reported for the full OLE treatment period.
- This trial was conducted with Epidiolex®, and results do not apply to other CBD-containing products.

Results

Patient disposition, baseline characteristics, and CBD exposure

- Of 224 randomized patients in GWPCARE6, 199 (89%) entered the OLE; of these,168 (84%) reported focal seizures, and 89 (45%) reported generalized seizures.

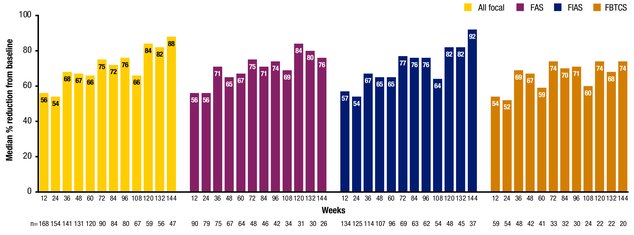
Table 1. Baseline characteristics and CBD exposure

	Patients with focal seizures (N=168)
Mean age, years (min, max)	12.8 (1, 56)
Sex, n (%)	
Female	69 (41)
No. of ASMs at baseline, median (min, max)	4 (0, 15)
Most common (>20%) ASMs at baseline, n (%)	
Valproate	68 (40)
Vigabatrin	58 (35)
Levetiracetam	45 (27)
Clobazam	42 (25)
Lamotrigine	37 (22)
Baseline median (Q1, Q3) monthly seizure frequency	
All focal seizures	59 (29, 118)
CBD exposure	
Median time on CBD, days (range)	596 (18–1462)
Mean modal dose, mg/kg/d (SD)	27 (9)

Patients received treatment in the OLE for a maximum of 1 year, except in the US and Poland, where patients could continue beyond 1 year. ASM, antiseizure medication; CBD, cannabidiol; OLE, open-label extension; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Efficacy results

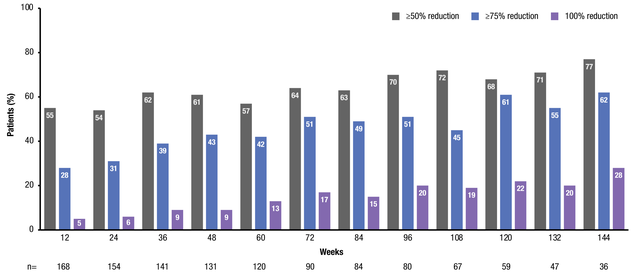
Figure 1. Median percentage reduction from baseline in focal seizures



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

- CBD treatment was associated with a median reduction of 54%–88% in all focal seizures across 12-week intervals through 144 weeks.
- There was a median reduction of 56%–84% in FAS, 54%–92% in FIAS, and 52%–74% in FBTCS with CBD treatment through 144 weeks.

Figure 2. Treatment responder rates for focal seizures



- Across 12-week visit intervals, responder rates (≥50%, ≥75%, and 100% reduction) for all focal seizures ranged from 54%–77%, 28%–62%, and 5%–28% of patients, respectively.
- The overall responder rates (≥50%, ≥ 75%, and 100%) were 54%, 30%, and 0% for FAS; 57%, 33%, and 2% for FIAS; and 53%, 32%, and 3% for FBTCS during the OLE.

Safety results

Table 2. Summary of AEs

Patients, n (%)	Patients with focal seizures (N=168)
TEAEs	
Any AEs	161 (96)
AEs leading to permanent discontinuation	9 (5)
Serious AEs	33 (20)
Deaths	1 (<1)
TEAEs reported in ≥10% of patients by MedDRA preferred term	
Diarrhea	79 (47)
Seizure	51 (30)
Decreased appetite	41 (24)
Pyrexia	38 (23)
Vomiting	36 (21)
Somnolence	31 (18)
Nasopharyngitis	28 (17)
Cough	25 (15)
Upper respiratory tract infection	24 (14)
Fall	18 (11)
Constipation	17 (10)
Influenza	17 (10)

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

- The most frequently reported serious AEs in ≥5% of patients were seizure (9%) and status epilepticus (5%).
- The most frequently reported AEs leading to treatment discontinuation in ≥1% of patients were seizure (2%), diarrhea (2%), liver function test increased (1%), and decreased appetite (1%).
- The one death during the study (due to cardiopulmonary failure) was deemed unrelated to treatment by the investigator
- Liver-related AEs in >1% of patients were increased alanine aminotransferase (n=12 [7%]) and increased aspartate aminotransferase (n=9 [5%]).

Conclusions

- In this post hoc, open-label analysis of patients with TSC in the GWPCARE6 OLE, CBD treatment was associated with a reduction in all focal seizure types through 144 weeks.
- At least 50% reduction was reported by the majority of patients across focal seizure types through 144 weeks.
- The safety profile was consistent with that observed in the overall CBD clinical development program.
- Reductions in focal seizures are consistent with the overall findings of the study.

References: 1. Thiele EA et al. *JAMA Neurol.* 2021;78(3):285-292. **2.** Thiele EA et al. Presented at the American Epilepsy Society (AES) Annual Meeting; Nashville, TN, USA; December 2–6, 2022.

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Clinical Trial ID: NCT02544763

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