Efficacy and Safety of Cannabidiol Dose Adjustment in Patients With Lennox-Gastaut Syndrome in a Phase 3 Trial and Open-Label Extension

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KEY POINTS

- In this post hoc analysis of patients with Lennox-Gastaut syndrome (LGS) who received add-on highly purified cannabidiol medicine (CBD; Epidyolex®) 10 mg/kg/day (CBD10) in the randomised controlled trial (RCT) GWPCARE3 and who after entering the open-label extension (OLE) GWPCARE5 maintained a modal dose of ≥12.5 mg/kg/day throughout the OLE treatment period:
  - Additional reductions in drop seizure frequency were observed among CBD10 patients after flexible dose titration in the OLE; the reductions were maintained throughout the OLE
  - Reduction in seizure frequency during the OLE was greater in previous CBD10 nonresponders (patients who did not have ≥50% reduction in drop seizures in the RCT) than in previous CBD10 responders (patients who had ≥50% reduction in the RCT)
  - More patients/caregivers reported improvement in the patient's overall condition at 24 weeks in the OLE than at the end of the RCT
  - The safety profile remained consistent with overall RCT and OLE trial populations
- This post hoc analysis emphasises the importance of titrating the dose of CBD based on individual patient response and tolerability, as dose adjustments may improve seizure reduction in some patients.
- The benefits of improved seizure reduction with dose adjustment should be balanced against the potential risk of AEs, emphasising the need for careful monitoring at each titration step.

INTRODUCTION

- Add-on CBD significantly reduced drop seizure frequency with an acceptable safety profile in patients with LGS in a phase 3 RCT (GWPCARE3).[1]
- Long-term safety and efficacy of CBD were established in an OLE trial (GWPCARE5) that enrolled patients who completed treatment in GWPCARE3.[2]
- We conducted this post hoc analysis of GWPCARE3 and GWPCARE5 to evaluate the effect of dose adjustments on the efficacy and safety of CBD in the subgroup of patients who were initially randomised to CBD10 in GWPCARE3 and then maintained a modal dose of ≥12.5 mg/kg/day during the OLE.

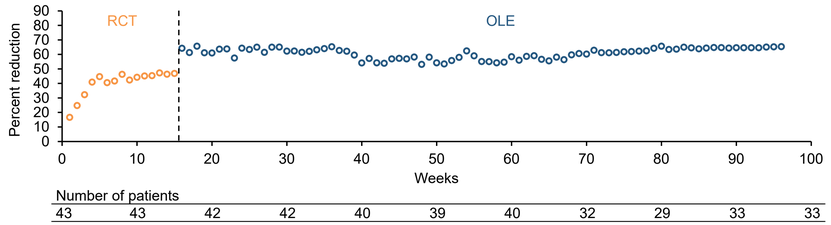
Demographics and characteristics at the RCT baseline

	CBD (n=43)[a]
Mean age, y (min, max)	14.0 (2.6, 38.2)
Age group, n (%)	
2–5 y	6 (14)
6–11 y	14 (33)
12–55 y	23 (53)
Sex, n (%)	
Female	20 (47)
Region, n (%)	
USA	35 (81)
Number of ASMs at RCT baseline, median (min, max)	
Previous	7 (2, 21)
Current	3 (1, 5)
Most common (>25%) concomitant ASMs, n (%)	
Clobazam	24 (56)
Valproate	14 (33)
Lamotrigine	11 (26)
Levetiracetam	11 (26)
Rufinamide	11 (26)
Seizure frequency per 28 days at RCT baseline, median (min, max)	
Drop	83 (14, 7494)

[a]Includes patients on CBD10 in the RCT who after entering the OLE maintained a modal dose of ≥12.5 mg/kg/day throughout the treatment period.
ASM, antiseizure medication; CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; OLE, open-label extension.

EFFICACY RESULTS

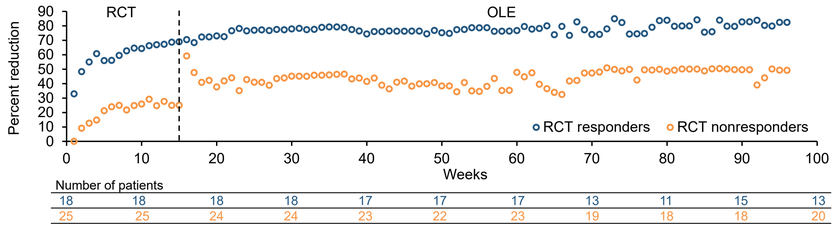
Cumulative weekly median percent reduction from RCT baseline in drop seizures



Each data point represents median percent reduction from baseline in drop seizures up to that week. OLE, open-label extension.

- At the end of the RCT, cumulative weekly median percent reduction from baseline was 47% in the CBD10 group. Reduction at the end of the OLE was 65%.
  - The mean modal dose for the 43 subjects was 25.8 mg/kg/day for the OLE treatment phase
- The improved reduction in seizure frequency was maintained throughout the OLE.
- In this subgroup, ≥50% responder rate was 42% (n=18) at the end of the RCT and 56% (n=24) at the end of the OLE; ≥75% responder rates were 12% (n=5) and 35% (n=15).

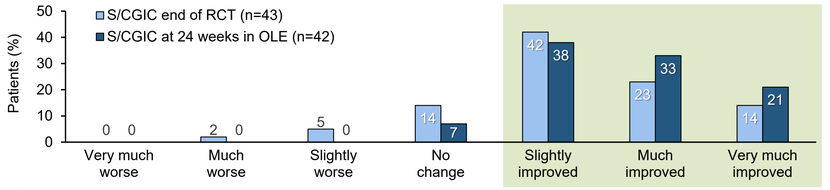
Cumulative weekly median percent reduction in CBD10 responders and nonresponders



Responders are the patients on CBD10 who had ≥50% reduction in drop seizures in the RCT; nonresponders did not have ≥50% reduction. CBD10, cannabidiol 10 mg/kg/day.

- In responders, median percent reduction from baseline at the end of the RCT was 69%; reduction at the end of the OLE was 82%.
- In nonresponders, median percent reduction from baseline at the end of the RCT was 25%; reduction at the end of the OLE was 49%.
- The improved reduction in seizure frequency was maintained throughout the OLE in both responders and nonresponders.

Overall Subject/Caregiver Global Impression of Change (S/CGIC)



OLE, open-label extension.

- Improvement in the patient's overall condition was reported by 79% of patients/caregivers at the end of the RCT and by 93% of patients/caregivers at 24 weeks in the OLE. Data for responders and nonresponders available via QR code.

SAFETY RESULTS

AE summary

Patients, n (%)	RCT (Weeks 1–15) [n=43]	OLE[a] (Weeks 16–96) [n=43]
AEs	36 (84)	42 (98)
AEs reported in ≥15% of patients by preferred term		
Decreased appetite	8 (19)	9 (21)
Convulsion	1 (2)	22 (51)
Somnolence	8 (19)	14 (33)
URTI	8 (19)	14 (33)
Pneumonia	2 (5)	10 (23)
Nasopharyngitis	2 (5)	7 (16)
Sinusitis	1 (2)	7 (16)
UTI	1 (2)	7 (16)
Diarrhoea	6 (14)	18 (42)
Vomiting	2 (5)	14 (33)
Pyrexia	4 (9)	16 (37)
Insomnia	4 (9)	10 (23)
Cough	1 (2)	10 (23)

[a]AE reported at any time during the OLE (up to 96 weeks). AE, treatment-emergent adverse event; OLE, open-label extension; URTI, upper respiratory tract infection; UTI, urinary tract infection.

- Serious AEs occurred in 22 patients during the RCT and the OLE; none were considered treatment related and all resolved by the end of the study.
- In the subgroup of patients on CBD10 during the RCT and who maintained a modal dose of ≥12.5 mg/kg/day during the OLE, no patient withdrew from the study because of an AE and there were no deaths.
- Alanine transaminase / aspartate transaminase elevations (≥3× upper limit of normal) occurred in 7 of 43 (16%) patients during the RCT and OLE; three of these patients (43%) were on concomitant valproate.
- No patient met the criteria for severe drug-induced liver injury (Hy's Law).

METHODS

- GWPCARE3 was a double-blind, placebo-controlled phase 3 trial that enrolled patients with LGS aged 2–55 years who had ≥2 drop seizures per week during the 4-week baseline period. Patients who completed the RCT were invited to enrol in the OLE trial GWPCARE5.
- During the RCT, patients received plant-derived highly purified CBD medicine (Epidyolex®; 100 mg/mL oral solution) at 10 mg/kg/day or 20 mg/kg/day or matched placebo for 14 weeks. During the OLE, the dose was titrated to an initial target of 20 mg/kg/day in all patients. Based on response and tolerability, CBD could then be decreased or increased up to a maximum of 30 mg/kg/day.
- These analyses included patients from the CBD10 group of GWPCARE3 whose dose was titrated up per OLE trial protocol and who maintained a modal dose of ≥12.5 mg/kg/day throughout the OLE treatment period.
- Efficacy was evaluated as the cumulative weekly median percent change from RCT baseline in drop seizure frequency through 96 weeks of treatment.
- This trial was conducted with Epidyolex® and results do not apply to other CBD-containing products.

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