Long-Term Safety and Efficacy of Cannabidiol (CBD) Treatment in Patients with Dravet Syndrome: 3-Year Interim Results of an Open-Label Extension Trial (GWPCARE5)

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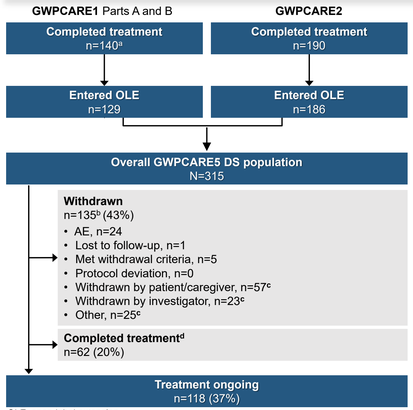
SUMMARY

- In this third analysis from the open-label extension (OLE) trial evaluating the long-term safety and efficacy of add-on highly purified CBD (Epidiolex®) in patients with Dravet syndrome (DS):
  - Patient retention rates at 1, 2, and 3 years were 72%, 53%, and 45%
  - CBD treatment had a similar safety profile to that observed in the completed parent RCTs
  - Sustained reductions in convulsive and total seizures were observed up to 156 weeks follow-up
- Results demonstrate the potential long-term benefits of CBD treatment for patients with DS.

INTRODUCTION

- DS is a developmental and epileptic encephalopathy that is often treatment-resistant.
- In 2 randomized, double-blind, placebo-controlled trials (GWPCARE1 and GWPCARE2), add-on CBD demonstrated a significant reduction in convulsive and total seizure frequency vs. placebo in patients with DS and had an acceptable safety profile.[1,2]
- Patients who completed GWPCARE1 or GWPCARE2 were invited to enroll in the ongoing OLE trial (GWPCARE5), in which all patients received CBD.[3]
- Here we present long-term safety and efficacy results from a third analysis of GWPCARE5, with safety data over the full duration of follow-up (up to 184 weeks) and efficacy data up to 156 weeks.

Patient disposition and demographics



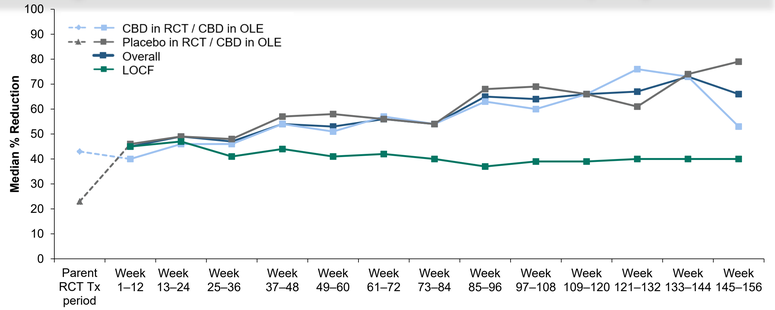
OLE, open-label extension
[a]Includes 32 patients from Part A. [b]Withdrawals are shown by the primary reason reported for each patient. [c]Of the 105 patients with primary reasons for withdrawal reported as withdrawn by patient/caregiver, withdrawn by investigator, or other, 87 patients had written-in comments suggesting withdrawal due to lack of efficacy. [d]Patients in the UK, the Netherlands, Australia, and Spain could receive treatment for a maximum of 1 year.

	Safety analysis set (N=315)
Age at entry to OLE, y	
Mean (min, max)	9.7 (2.5, 19.3)
Age group, n (%)	
2–5 y	82 (26)
6–11 y	134 (43)
12–17 y	90 (29)
18–55 y	9 (3)
Sex	
Male, n (%)	156 (50)
Most common (>20%) AEDs during OLE, n (%)	
Clobazam	214 (68)
Valproate	212 (67)
Stiripentol	120 (38)
Levetiracetam	92 (29)
Topiramate	83 (26)
Time on CBD treatment, d	
Median (min, max)	429 (18, 1291)
Modal CBD dose, mg/kg/d	
Mean (SD)	22 (5)
Baseline seizures per 28 days, median (min, max)	
Convulsive	12 (0, 770)
Total	36 (4, 4141)

- As the OLE was still ongoing at time of analysis, not all patients had reached the later time points; retention rate (i.e. number of patients who reached visit window÷number of patients who could have reached visit window based on their start date) at 3 years was 45% (full data available via QR code).

EFFICACY RESULTS

Percentage reduction from baseline in convulsive seizure frequency

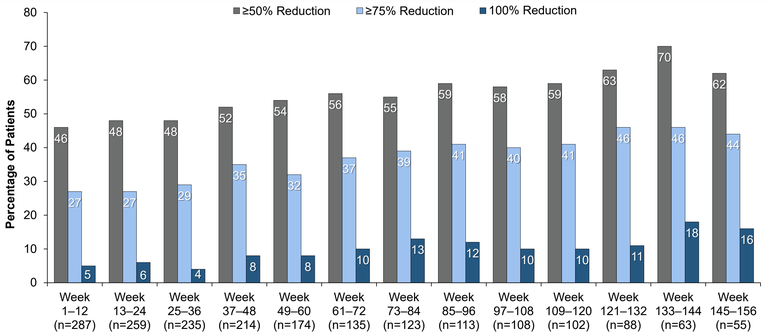


	Parent RCT Tx period	Week 1–12	Week 13–24	Week 25–36	Week 37–48	Week 49–60	Week 61–72	Week 73–84	Week 85–96	Week 97–108	Week 109–120	Week 121–132	Week 133–144	Week 145–156
Number of patients														
Overall		287	259	235	214	174	135	123	113	108	102	88	63	55
Overall (LOCF)		287	287	289	289	289	289	289	289	289	289	289	289	289
Parent RCT CBD	169	167	159	144	131	108	82	77	68	65	63	55	37	28
Parent RCT placebo	121	120	100	91	83	66	53	46	45	43	39	33	26	27

LOCF, last observation carried forward.
Note: Upper and lower quartiles for each data point are available via QR code.

- Patients who previously received placebo in the parent RCT showed marked reduction in seizure frequency with CBD in the OLE trial.

Convulsive seizure responder rates



Summary of other efficacy analyses

- Reductions in total seizure frequency were also observed, with median reductions from baseline of 49%–80% over the 156 weeks (full data available via QR code).
- At the timepoints assessed (24, 38, 48, 76, 104, 132, and 156 weeks), ≥83% of patients/caregivers reported improvement on the Subject/Caregiver Global Impression of Change (S/CGIC) scale (full data available via QR code).

SAFETY RESULTS

AE summary

Patients, n (%)	Safety analysis set (N=315)
AEs	306 (97)
AEs leading to withdrawal[a]	27 (9)
Serious AEs	129 (41)
Deaths	4 (1)[b]
AEs reported in >15% of patients	
Diarrhea	135 (43)
Pyrexia	122 (39)
Decreased appetite	99 (31)
Somnolence	87 (28)
Nasopharyngitis	78 (25)
Convulsion	78 (25)
Upper respiratory tract infection	76 (24)
Vomiting	63 (20)

AE, treatment-emergent adverse event reported any time during the full duration of follow-up (up to 184 weeks). [a]Includes all patients with an AE listed as one of the reasons for withdrawal. [b]Includes 3 deaths due to sudden unexpected death in epilepsy and 1 due to convulsion.

- Of the patients reporting any AE, 50% reported events as moderate severity.
- Of the patients reporting the 3 most common AEs, diarrhea resolved in 84% of patients, pyrexia in 98% of patients, and decreased appetite in 69% of patients during follow-up.
- Most frequently reported serious AEs: status epilepticus (15%), convulsion (10%), and pneumonia (6%).
- Most frequently reported AEs leading to discontinuation: convulsion (3%), AST increased (3%), ALT increased (2%), and liver function test abnormal (1%).
- No deaths were deemed related to CBD treatment by the investigator.

Laboratory investigations

- Increases in ALT or AST >3× ULN occurred in 67 patients (21%); of these patients, 62 (93%) were on concomitant valproate.
- No patient met the standard criteria for severe drug-induced liver injury (Hy's law).

METHODS

- Eligible patients, aged between 2–18 years, had a clinical diagnosis of DS inadequately controlled by ≥1 AED and had completed GWPCARE1 or GWPCARE2. Data cut-off date for analysis: 03 Feb 2019.
- All patients received plant-derived highly purified CBD (100 mg/mL oral solution). Dose was titrated over 2 weeks from 2.5 to 20 mg/kg/d, with 20 mg/kg/d as the target maintenance dose. Investigators could decrease or increase the dose of CBD up to a maximum of 30 mg/kg/d and could adjust the dose of concomitant AEDs after consultation with GW medical monitor; changes were recorded in the case report form.
- Efficacy outcomes were assessed through the Week 145–156 visit window, except the S/CGIC which was assessed at Weeks 24, 38, 48, 76, 104, 132, and 156. Convulsive seizures were defined as tonic-clonic, tonic, clonic, or atonic seizures. LOCF sensitivity analyses of change in seizure frequency data were performed to account for data from patients who withdrew.
- Safety outcomes were assessed through full extended follow-up (range: >2 to 184 weeks).
- This trial was conducted with Epidiolex® and results do not apply to other CBD-containing products.

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