3.266 Efficacy and Safety of Cannabidiol for Seizures Associated With Tuberous Sclerosis Complex in Pediatric and Adult Patients From GWPCARE6: A Phase 3 Trial With an Open-Label Extension

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Background

- Add-on treatment with a plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD) reduced seizures associated with tuberous sclerosis complex (TSC) with an acceptable safety profile in a randomized, placebo-controlled phase 3 trial (GWPCARE6).[1]
  - While GWPCARE6 evaluated CBD doses of 25 and 50 mg/kg/d, similar efficacy was observed with a higher rate of adverse events in the 50 mg/kg/d group. The FDA-approved recommended maintenance dosage of CBD for the treatment of seizures associated with TSC is 25 mg/kg/d.
- In the open-label extension (OLE) of GWPCARE6, long-term treatment with CBD demonstrated a safety profile that was consistent with the randomized controlled phase of the trial and a reduction in the frequency of TSC-associated seizures through 156 weeks of treatment.[2]
- This post hoc analysis evaluated the efficacy and safety of add-on CBD treatment in pediatric (<18 y) and adult (≥18 y) patients of GWPCARE6.

Objective

- To present efficacy and safety outcomes of CBD treatment in pediatric and adult patients treated in the randomized controlled phase and the OLE of GWPCARE6.

Methods

- Patients eligible for GWPCARE6 were aged 1–65 years with a clinical diagnosis of TSC, were experiencing ≥8 TSC-associated seizures during the 4-week baseline period of the randomized phase with ≥1 seizure in ≥3 out of 4 weeks, and were currently taking ≥1 antiseizure medication at baseline.
- In this trial, TSC-associated seizures included all countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral motor seizures, and generalized seizures (tonic-clonic, tonic, clonic, or atonic).
- Patients received placebo or CBD (Epidiolex®; 100 mg/mL, oral solution) at 25 mg/kg/d (CBD25) or 50 mg/kg/d (CBD50) in the randomized phase, which consisted of a 4-week titration period followed by a 12-week maintenance period.
- Patients who completed treatment in the 16-week randomized controlled phase could enroll in the OLE.
  - Treatment in the OLE could continue for up to 1 year, except in the United States and Poland, where patients could continue treatment beyond 1 year.
- All patients entering the OLE started a 2-week blinded transition period, during which the blinded medication from the randomized phase was tapered down to 0 while simultaneously CBD was titrated up to 25 mg/kg/d; the dose could then be decreased or increased up to the maximum dose of 50 mg/kg/d based on response and tolerability.
- In this post hoc analysis, the efficacy of CBD treatment was assessed in pediatric and adult patients by calculating the ≥50%, ≥75%, and 100% reductions from baseline in TSC-associated seizures during the randomized phase maintenance period and the OLE. Change from baseline in patients' condition was measured using the Subject/Caregiver Global Impression of Change (S/CGIC) scale.
- The trial was conducted with Epidiolex®, and the results do not apply to other CBD-containing products.

Results

Figure 1. Patient disposition

CBD, cannabidiol; CBD25, CBD 25 mg/kg/d; CBD50, CBD 50 mg/kg/d; OLE, open-label extension.

- Among patients who withdrew from the OLE, the main reason for withdrawal was transition to commercial product in both pediatric (59%) and adult (50%) patients (additional details for patient disposition available via QR code).

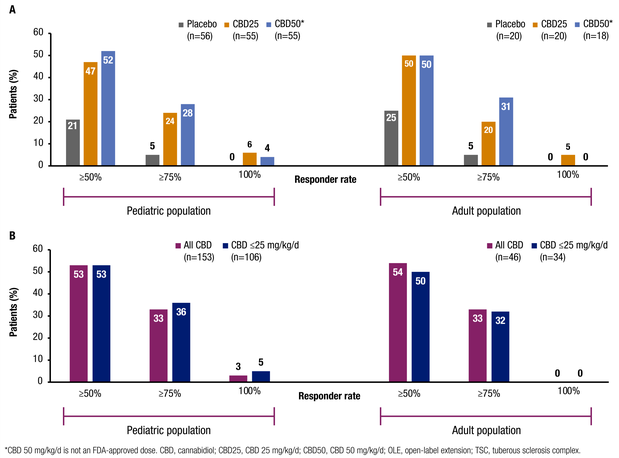
Table 1. Baseline characteristics and CBD exposure during the randomized phase and OLE

	Pediatric				Adult			
	Randomized phase			OLE	Randomized phase			OLE
	Placebo (n=56)	CBD25 (n=55)	CBD50[a] (n=55)	All CBD (n=153)	Placebo (n=20)	CBD25 (n=20)	CBD50[a] (n=18)	All CBD (n=46)
Median age at trial entry, years (min, max)	8.4 (1.2, 17.2)	8.7 (1.1, 17.6)	8.3 (1.8, 17.9)	8.3 (1.1, 17.9)	25.6 (18.2, 55.8)	25.9 (18.0, 56.8)	25.2 (18.2, 34.9)	24.6 (18.2, 56.8)
Age group, years, n (%)								
1–6	22 (39)	21 (38)	21 (38)	59 (39)	—	—	—	—
7–11	18 (32)	18 (33)	18 (33)	50 (33)	—	—	—	—
12–17	16 (29)	16 (29)	16 (29)	44 (29)	—	—	—	—
18–65	—	—	—	—	20 (100)	20 (100)	18 (100)	46 (100)
Sex, n (%)								
Male	31 (55)	31 (56)	32 (58)	87 (57)	14 (70)	12 (60)	11 (61)	31 (67)
No. of ASMs at baseline, median (min, max)	2 (1, 4)	3 (1, 4)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (0, 4)	3 (1, 5)	3 (0, 5)
Most common ASMs at baseline, n (%)								
Valproate	25 (45)	23 (42)	24 (44)	62 (41)	10 (50)	6 (30)	12 (67)	18 (39)
Vigabatrin	16 (29)	27 (49)	26 (47)	65 (43)	1 (5)	1 (5)	3 (17)	4 (9)
Clobazam	18 (32)	14 (26)	15 (27)	43 (28)	7 (35)	3 (15)	4 (22)	11 (24)
Levetiracetam	17 (30)	11 (20)	16 (29)	40 (26)	7 (35)	8 (40)	6 (33)	16 (35)
Median (Q1, Q3) monthly seizure frequency at randomized phase baseline								
TSC-associated seizures	58 (25, 139)	59 (29, 113)	74 (33, 131)	60 (29, 119)	51 (32, 67)	29 (14, 71)	52 (38, 76)	51 (28, 80)
Composite focal seizure score[b] [n]	106 (36, 196) [49]	120 (52, 207) [42]	110 (61, 233) [51]	109 (49, 218) [130]	55 (28, 114) [18]	33 (25, 101) [15]	54 (36, 96) [13]	53 (28, 101) [38]
CBD exposure								
Median time on CBD, days (range)	113 (106–123)	113 (9–121)	113 (10–125)	680 (18–1462)	113 (110–122)	113 (27–121)	113 (10–117)	383 (29–1289)
Mean modal dose, mg/kg/d (SD)	—	24 (2)	42 (10)	28 (9)	—	23 (4)	40 (9)	27 (10)

[a]CBD 50 mg/kg/d is not an FDA-approved dose. [b]Composite focal seizure score represents the weighted average of the 3 types of focal seizures included in the efficacy analysis.
ASM, antiseizure medication; CBD, cannabidiol; CBD25, CBD 25 mg/kg/d; CBD50, CBD 50 mg/kg/d; OLE, open-label extension; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

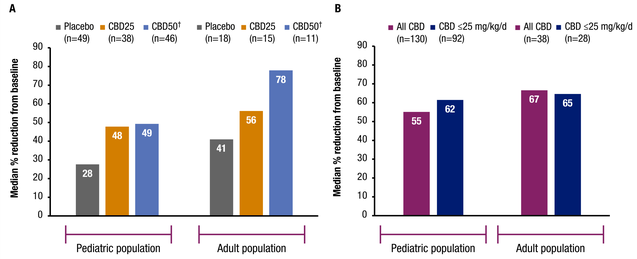
Efficacy results

Figure 2. TSC-associated seizure responder rates among pediatric and adult patients in the randomized phase maintenance period (A) and OLE phase (B)



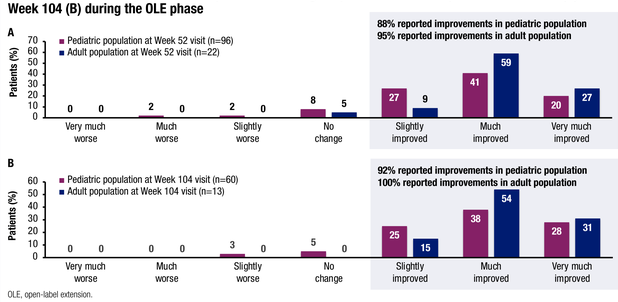
*CBD 50 mg/kg/d is not an FDA-approved dose. CBD, cannabidiol; CBD25, CBD 25 mg/kg/d; CBD50, CBD 50 mg/kg/d; OLE, open-label extension; TSC, tuberous sclerosis complex.

Figure 3. Change in TSC-associated composite focal seizure score* in pediatric and adult patients in the randomized phase maintenance period (A) and OLE phase (B)



*Composite focal seizure score represents the weighted average of the 3 types of focal seizures included in the efficacy analysis. †CBD 50 mg/kg/d is not an FDA-approved dose.
CBD, cannabidiol; CBD25, CBD 25 mg/kg/d; CBD50, CBD 50 mg/kg/d; OLE, open-label extension; TSC, tuberous sclerosis complex.

Figure 4. Subject/Caregiver Global Impression of Change in pediatric and adult patients at Week 52 (A) and Week 104 (B) during the OLE phase



OLE, open-label extension.

Safety results

Table 2. Summary of adverse events

	Pediatric				Adult			
	Randomized phase			OLE	Randomized phase			OLE
Patients, n (%)	Placebo (n=56)	CBD25 (n=55)	CBD50[a] (n=55)	All CBD (n=153)	Placebo (n=20)	CBD25 (n=20)	CBD50[a] (n=18)	All CBD (n=46)
TEAEs								
Patients reporting any AEs	53 (95)	53 (96)	55 (100)	148 (97)	19 (95)	17 (85)	18 (100)	42 (91)
AEs leading to permanent discontinuation[b]	1 (2)	4 (7)	5 (9)	1 (1)	1 (5)	4 (20)	5 (28)	1 (2)
Serious AEs	1 (2)	12 (22)	8 (15)	16 (11)	1 (5)	4 (20)	2 (11)	3 (7)
Deaths[c]	0	0	0	1 (1)	0	0	0	0
TEAEs reported in >20% of patients in any treatment group in randomized phase or OLE by MedDRA preferred term								
Diarrhea	14 (25)	14 (26)	27 (49)	53 (35)	5 (25)	9 (45)	14 (78)	19 (41)
Pyrexia	6 (11)	13 (24)	11 (20)	27 (18)	0	1 (5)	1 (6)	1 (2)
Decreased appetite	6 (11)	8 (15)	15 (27)	26 (17)	3 (15)	7 (35)	2 (11)	10 (22)
Somnolence	2 (4)	9 (16)	16 (29)	23 (15)	5 (25)	1 (5)	3 (17)	7 (15)
Nasopharyngitis	7 (13)	6 (11)	9 (16)	22 (14)	5 (25)	5 (25)	2 (11)	11 (24)
Gamma-glutamyltransferase increased	0	12 (22)	6 (11)	17 (11)	0	0	4 (22)	1 (2)
Alanine aminotransferase increased	0	6 (11)	10 (18)	14 (9)	0	3 (15)	6 (33)	4 (9)
Aspartate aminotransferase increased	0	6 (11)	10 (18)	13 (9)	0	2 (10)	4 (22)	2 (4)
Nausea	1 (2)	2 (4)	0	3 (2)	1 (5)	5 (25)	2 (11)	5 (11)

[a]CBD 50 mg/kg/d is not an FDA-approved dose. [b]Includes all patients with an AE listed as one of the reasons for discontinuation of the study drug. [c]Death due to cardiopulmonary failure was deemed not treatment-related by the investigator. AE, adverse event; CBD, cannabidiol; CBD25, CBD 25 mg/kg/d; CBD50, CBD 50 mg/kg/d; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; TEAE, treatment-emergent adverse event.

- The most frequently reported serious AEs among pediatric patients were elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (2% each) during both the randomized phase as well as during the OLE (3% each).
- The most frequently reported serious AE among adult patients was status epilepticus during both the randomized phase (5%) and OLE (4%).
- During the randomized phase, the most frequently reported AE leading to permanent discontinuation was somnolence (1%) among pediatric patients and rash (5%) among adult patients.
- In the OLE, permanent treatment discontinuation because of an AE was reported in 1 pediatric patient due to ataxia and in 1 adult patient due to agitation.

Laboratory investigations

- During the randomized phase, elevation in ALT/AST levels >3× the upper limit of normal (ULN) occurred in 20/166 (12%) pediatric patients and 8/58 (14%) adult patients, representing 9% and 4%, respectively, of the total number of patients (N=224) randomized in the trial.
- During the OLE, elevation in ALT/AST levels >3× ULN occurred in 17/153 (11%) pediatric patients and 3/45 (7%) adult patients representing 9% and 2%, respectively, of the total number of patients (N=199) enrolled in the OLE.

Conclusions

- In this post hoc analysis of pediatric and adult patients in the randomized and OLE phases of trial GWPCARE6, which assessed the safety and efficacy of add-on CBD in patients with TSC:
  - Patients enrolled are representative of the TSC population eligible for treatment with CBD and include patients as young as 1 year.
  - At approved doses, we observed substantial efficacy on seizure reduction which is similar between adults and pediatric patients.
  - During the randomized phase, ≥50%, ≥75%, and 100% responder rates were greater than placebo and similar between the adult and pediatric populations.
  - Responder rates in both the adult and pediatric populations were durable and maintained throughout the OLE.
  - A substantial proportion of patients/caregivers reported improvements for both pediatric and adult patients on the S/CGIC scale.
  - The safety profile was similar between the pediatric and adult populations, with diarrhea being the most frequently reported AE during the randomized phase and the OLE.

References: 1. Thiele EA et al. *JAMA Neurol.* 2021;78(3):285-292. **2.** Thiele EA et al. *Epilepsia.* 2022;63(2):426-439.

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Clinical Trial ID: NCT02544763 (GWPCARE6 randomized phase); NCT02544750 (GWPCARE6 OLE).

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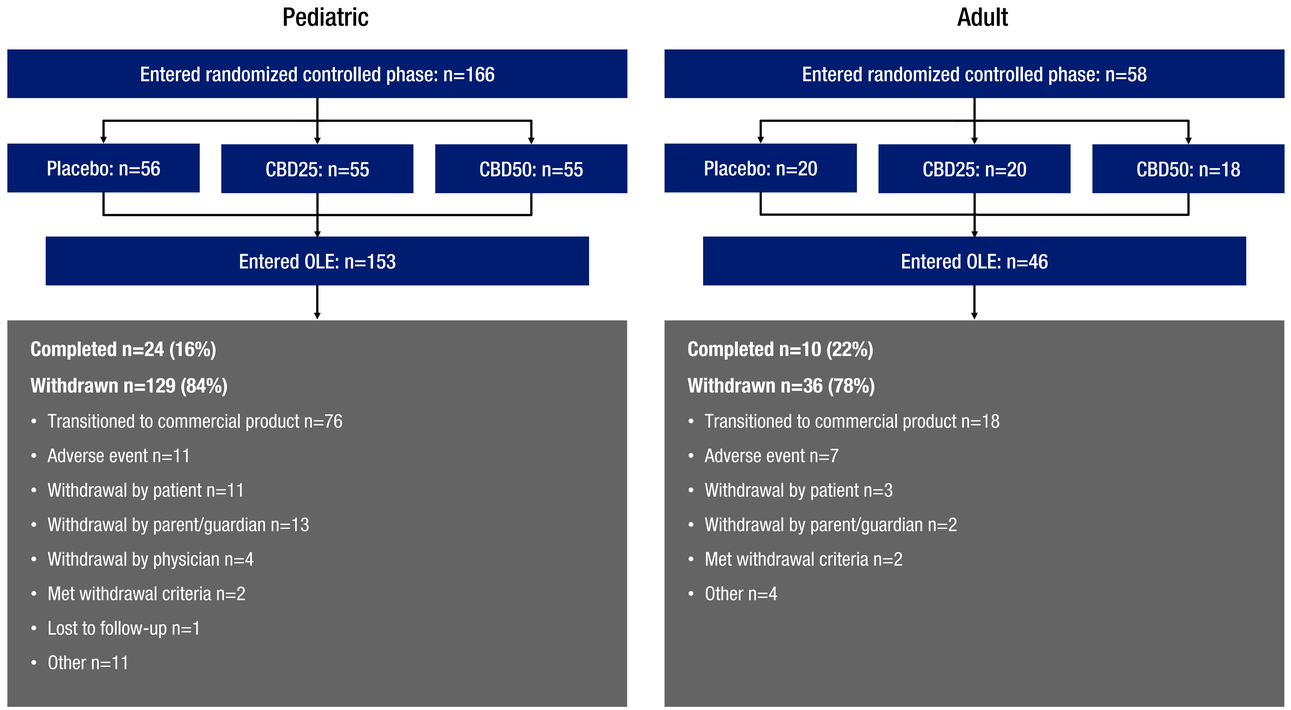
Supplementary Material

Figure S1. Patient disposition



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