004 Long-term Safety and Efficacy of Add-on Cannabidiol for Seizures Associated With Tuberous Sclerosis Complex: 3-year Results From the GWPCARE6 Open-Label Extension

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Introduction

- Add-on cannabidiol (CBD) produced a significant reduction in tuberous sclerosis complex (TSC)-associated seizures with an acceptable safety profile in a randomized, placebo-controlled phase 3 trial (GWPCARE6).[1]
- To assess the long-term safety and efficacy of CBD, patients who completed the randomized phase were enrolled in the open-label extension (OLE) of trial GWPCARE6.[2]

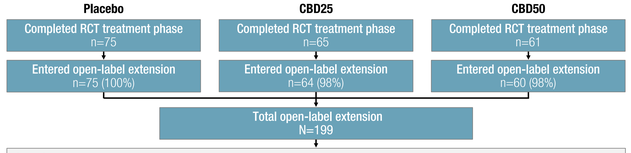
Objective

- To present the final analysis of the OLE, reporting safety for the full follow-up and efficacy for up to 156 weeks of treatment.

Methods

- The OLE enrolled patients who had completed treatment in the 16-week randomized controlled phase of GWPCARE6.
- Eligible patients (aged 1–65 years) had a clinical diagnosis of TSC and were experiencing ≥8 TSC-associated seizures during the 4-week baseline period of the randomized controlled trial (RCT), with ≥1 seizure in ≥3 out of 4 weeks, and were currently taking ≥1 antiseizure medication (ASM) at baseline.
- 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 entering 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 zero while simultaneously CBD was titrated up to 25 mg/kg/d; dose could then be decreased or increased up to maximum 50 mg/kg/d based on response and tolerability.
- Primary endpoint: long-term safety and tolerability of add-on CBD.
- Secondary endpoint: percentage change from the RCT baseline in TSC-associated seizures (average per 28 days) across 12-week treatment windows; ≥50%, ≥75%, and 100% responder rates across 12-week windows; and subject/caregiver-reported outcomes.
- This trial was conducted with Epidiolex®, and results do not apply to other CBD-containing products.

Patient disposition, baseline characteristics, and CBD exposure



Completed,* n=34

Withdrawn,† n=165

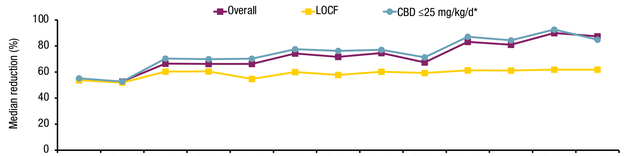
- Transitioned to commercial product, n=93
- Adverse event, n=18
- By patient, n=14
- By parent/guardian, n=15
- By investigator, n=4
- Met withdrawal criteria, n=4
- Lost to follow-up, n=1
- Other,‡ n=16

	CBD modal dose		
	≤25 mg/kg/d (n=140)	>25 mg/kg/d (n=59)	All CBD (N=199)
Median age at RCT entry (min, max), y	11.5 (1.1, 56.8)	9.5 (1.6, 32.6)	10.8 (1.1, 56.8)
Age group, n (%)			
1–6 y	43 (31)	16 (27)	59 (30)
7–11 y	29 (21)	21 (36)	50 (25)
12–17 y	34 (24)	10 (17)	44 (22)
18–65 y	34 (24)	12 (20)	46 (23)
Sex, n (%)			
Male, n (%)	85 (61)	33 (56)	118 (59)
Most common (>30% in any group) ASMs, n (%)			
Valproate	60 (43)	26 (44)	86 (43)
Vigabatrin	51 (36)	22 (37)	73 (37)
Clobazam	49 (35)	21 (36)	70 (35)
Levetiracetam	38 (27)	21 (36)	59 (30)
Lacosamide	33 (24)	18 (31)	51 (26)
Lamotrigine	27 (19)	18 (31)	45 (23)
Seizure frequency per 28 days at parent trial baseline, median (Q1, Q3)			
TSC-associated seizures	54 (27, 108)	66 (36, 125)	57 (28, 109)
CBD exposure during the OLE			
Median time on CBD (min, max), days	614 (18, 1462)	686 (92, 1458)	631 (18, 1462)
Mean of CBD modal dose (SD), mg/kg/d	23 (4)	39 (7)	28 (9)

*Patients received treatment in the open-label extension for a maximum of 1 year, except in the US and Poland, where patients could continue beyond 1 year. †Withdrawals are reported according to the primary reason reported by each patient. ‡Other reasons included a lack of efficacy (n=11); withdrawal by the physician/medical monitor (n=2) or parent/investigator (n=1); lack of compliance (n=1); and study completion (n=1). ASM, antiseizure medication; CBD25, cannabidiol 25 mg/kg/d group of parent trial; CBD50, cannabidiol 50 mg/kg/d group of parent trial; OLE, open-label extension; Q1, first quartile; Q3, third quartile; RCT, randomized-controlled trial; SD, standard deviation.

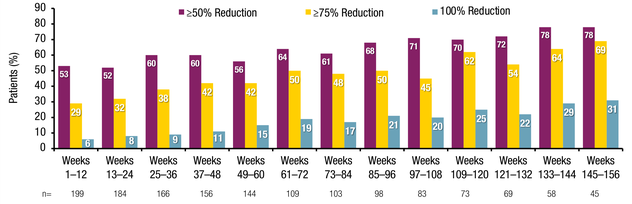
Efficacy results

Percentage change in TSC-associated seizures per 28 days

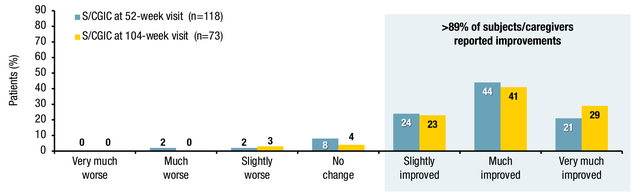


Overall, n	199	184	166	156	144	109	103	98	83	73	69	58	45
LOCF, n	199	199	199	199	199	198	198	199	199	199	199	199	199
≤25 mg/kg/d,* n	140	126	111	104	99	77	73	70	58	51	48	40	30

Overall TSC-associated seizure responder rates



Subject/Caregiver Global Impression of Change



*Dose category based on patient's modal dose. CBD, cannabidiol; LOCF, last observation carried forward. S/CGIC, Subject/Caregiver Global Impression of Change; TSC, tuberous sclerosis complex.

Safety results

AE summary

	CBD modal dose		
Patients, n (%)	**≤25 mg/kg/d (n=140)**	**>25 mg/kg/d (n=59)**	**All CBD (n=199)**
AEs	133 (95)	59 (100)	192 (96)
AEs leading to permanent discontinuation[a]	14 (10)	4 (7)	18 (9)
Serious AEs	35 (25)	21 (36)	56 (28)
Deaths	1 (1)[b]	0 (0)	1 (0.5)[b]
AEs reported in ≥10% of all CBD patients by MedDRA preferred term			
Diarrhea	62 (44)	31 (53)	93 (47)
Seizure	41 (29)	18 (31)	59 (30)
Pyrexia	30 (21)	18 (31)	48 (24)
Decreased appetite	29 (21)	18 (31)	47 (24)
Vomiting	22 (16)	18 (31)	40 (20)
Somnolence	21 (15)	18 (31)	39 (20)
Nasopharyngitis	21 (15)	14 (24)	35 (18)
Upper respiratory tract infection	22 (16)	10 (17)	32 (16)
Cough	17 (12)	9 (15)	26 (13)
Constipation	16 (11)	5 (8)	21 (11)
Fall	13 (9)	8 (14)	21 (11)
Influenza	14 (10)	6 (10)	20 (10)

AE, treatment-emergent adverse event; CBD, cannabidiol; MedDRA, Medical Dictionary for Regulatory Activities. [a]Includes all patients with an AE listed as one of the reasons for discontinuation of the study drug. [b]Death due to cardiopulmonary failure was deemed not treatment-related by the investigator.

- Most frequently reported serious AEs included seizure (8%), status epilepticus (5%), and dehydration (3%).
- Most frequently reported AEs leading to permanent discontinuation included diarrhea (2%) and seizure (2%).

Laboratory investigations

- Elevation in ALT/AST levels >3× ULN occurred in 20 patients (10%), 15 (75%) of whom were on concomitant valproate.
- No patient met the criteria for severe drug-induced liver injury (Hy's law).
- At the time of this analysis, 18 of 20 cases of ALT/AST elevation had resolved.
  - Spontaneously in 5 patients (3 of 5 taking concomitant valproate)
  - Following treatment discontinuation in 2 patients (both taking concomitant valproate)
  - After CBD or ASM dose reduction in 11 patients (8 of 11 taking concomitant valproate; 3 on reduced valproate)

Conclusions

- In this final analysis of the OLE phase of trial GWPCARE6 that evaluated add-on CBD in patients with TSC:
  - CBD was well tolerated, and the safety profile was similar to that observed during the randomized phase
  - Seizure frequency remained lower than the RCT baseline throughout the treatment period in the OLE
  - A ≥50% reduction in TSC-associated seizures was reported in 52%–78% of patients, and a ≥75% reduction was reported in 29%–69% of patients across 12-week windows through 156 weeks
  - Seizure freedom was reported in 6%–31% of patients across the 12-week windows through 156 weeks of treatment
  - Improvements on the S/CGIC scale were reported by 89% of patients/caregivers at the 52-week visit and by 93% of patients/caregivers at the 104-week visit

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 RCT); NCT02544750 (GWPCARE6 OLE).

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