# #66 Efficacy and Safety of Add-on Cannabidiol for Seizures Associated With Tuberous Sclerosis Complex in Pediatric Patients Enrolled in a Phase 3 Trial With an Open-Label Extension

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## Background

- Add-on cannabidiol (CBD) produced a significant reduction in seizures associated with tuberous sclerosis complex (TSC) with an acceptable safety profile in a randomized, placebo-controlled phase 3 trial (GWPCARE6).[1]
- Long-term CBD treatment in the open-label extension (OLE) of GWPCARE6 showed a safety profile consistent with the randomized controlled phase and reduction in the frequency of TSC-associated seizures through 156 weeks of treatment.[2]
- This post hoc analysis was conducted to evaluate the effect of add-on CBD treatment in pediatric (aged <18 years) patients of GWPCARE6.

## Objective

- To present efficacy and safety outcomes of CBD treatment in pediatric 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 (ASM) 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.
- 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 zero while simultaneously CBD was titrated up to 25 mg/kg/d; 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 patients by calculating the ≥50%, ≥75%, and 100% reductions from baseline in TSC-associated seizures during the randomized phase maintenance period and the OLE. Improvement or worsening 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

### Patient disposition

- Of 224 patients enrolled in the randomized phase, 166 (74%) were pediatric patients with a median age of 8 years.
- Of 166 pediatric patients in the randomized phase, 153 (92%) enrolled in the OLE.
- Twenty-four patients (16%) completed the OLE, and 129 patients (84%) withdrew.
  - Reasons for withdrawal of pediatric patients from the OLE included:
    - Transition to commercial product (n=76)
    - Withdrawal by parent/guardian (n=13)
    - Adverse event (n=11)
    - Other (n=11)
    - Withdrawal by patient (n=11)
    - Physician decision (n=4)
    - Met withdrawal criteria (n=2)
    - Lost to follow-up (n=1)

### Baseline characteristics and CBD exposure during randomized phase and OLE

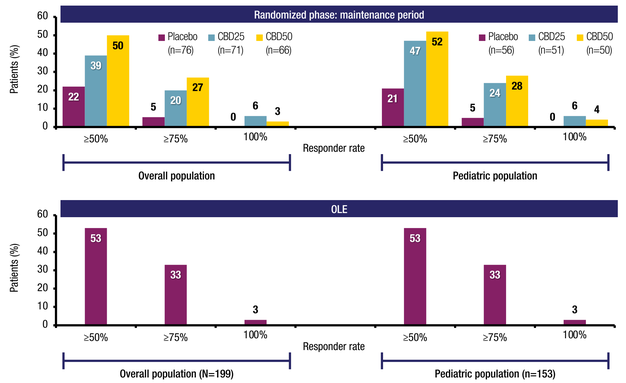
| | Randomized phase | | | | OLE |
|---|---|---|---|---|---|
| | Placebo (n=56) | CBD25 (n=55) | CBD50 (n=55) | All (N=166) | All CBD (N=153) |
| **Median age at trial entry (min, max), y** | 8.4 (1.2, 17.2) | 8.7 (1.1, 17.6) | 8.3 (1.8, 17.9) | 8.3 (1.1, 17.9) | 8.3 (1.1, 17.9) |
| **Age group, n (%)** | | | | | |
| 1–6 y | 22 (39) | 21 (38) | 21 (38) | 64 (39) | 59 (39) |
| 7–11 y | 18 (32) | 18 (33) | 18 (33) | 54 (33) | 50 (33) |
| 12–17 y | 16 (29) | 16 (29) | 16 (29) | 48 (29) | 44 (29) |
| **Sex, n (%)** | | | | | |
| Male | 31 (55) | 31 (56) | 32 (58) | 94 (57) | 87 (57) |
| **Common ASMs at randomized phase baseline, n (%)** | | | | | |
| Valproate | 25 (45) | 23 (42) | 24 (44) | 72 (43) | 62 (41) |
| Vigabatrin | 16 (29) | 27 (49) | 26 (47) | 69 (42) | 65 (42) |
| Clobazam | 18 (32) | 14 (25) | 15 (27) | 47 (28) | 43 (28) |
| Levetiracetam | 17 (30) | 11 (20) | 16 (29) | 44 (27) | 40 (26) |
| **Seizure frequency per 28 days at randomized phase baseline, median (Q1, Q3)** | | | | | |
| TSC-associated seizures | 58 (25, 139) | 59 (29, 113) | 74 (33, 131) | 62 (29, 125) | 60 (29, 119) |
| **CBD exposure** | | | | | |
| Median time on CBD (min, max) | 113 (106, 123) | 113 (9, 121) | 113 (10, 125) | 113 (9, 125) | 680 (18, 1462) |
| Mean of CBD modal dose (SD) mg/kg/d | — | 24 (2) | 42 (10) | — | 28 (9) |

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.

- At baseline, pediatric patients were taking a median of 3 ASMs and had a median (interquartile range) of 62 (29–125) TSC-associated seizures/28 days.

## Efficacy results

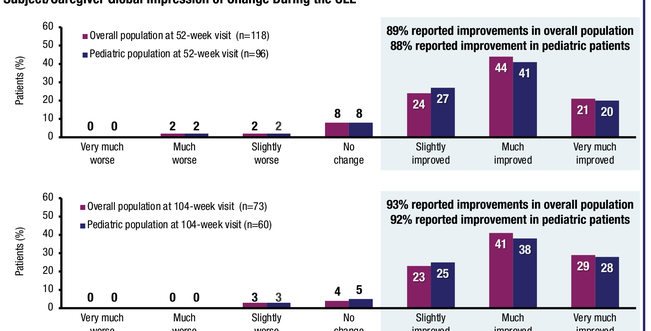
### TSC-associated seizure responder rates




CBD25, cannabidiol 25 mg/kg/d; CBD50, cannabidiol 50 mg/kg/d; OLE, open-label extension; TSC, tuberous sclerosis complex.

- The ≥50%, ≥75%, and 100% responder rates in the pediatric population were similar to those in the overall population during both the randomized phase and the OLE.

### Subject/Caregiver Global Impression of Change During the OLE




OLE, open-label extension.

- Similar to the overall population, a substantial proportion of patients or caregivers reported improvements in the overall condition of patients during the OLE.

## Safety results

### TEAE summary

| | Randomized phase | | | | OLE |
|---|---|---|---|---|---|
| **Patients, n (%)** | Placebo (n=56) | CBD25 (n=55) | CBD50 (n=55) | All (N=166) | All CBD (N=153) |
| **TEAEs** | | | | | |
| Patients reporting any AEs | 53 (95) | 53 (96) | 55 (100) | 161 (97) | 148 (97) |
| AEs leading to permanent discontinuation[a] | 1 (2) | 4 (7) | 5 (9) | 10 (6) | 1 (1) |
| Serious AEs | 1 (2) | 12 (22) | 8 (15) | 21 (13) | 16 (11) |
| Deaths[b] | 0 | 0 | 0 | 0 | 1 (1) |
| **TEAEs reported in ≥10% of patients in any group in the randomized phase or in the OLE by MedDRA preferred term** | | | | | |
| Diarrhea | 14 (25) | 14 (25) | 27 (49) | 55 (33) | 53 (35) |
| Pyrexia | 6 (11) | 13 (24) | 11 (20) | 30 (18) | 27 (18) |
| Decreased appetite | 6 (11) | 8 (15) | 15 (27) | 29 (17) | 26 (17) |
| Vomiting | 6 (11) | 11 (20) | 11 (20) | 28 (17) | 27 (18) |
| Somnolence | 2 (4) | 9 (16) | 16 (29) | 27 (16) | 23 (15) |
| Nasopharyngitis | 7 (13) | 6 (11) | 9 (16) | 22 (13) | 22 (14) |
| Upper respiratory tract infection | 8 (14) | 6 (11) | 7 (13) | 21 (13) | 20 (13) |
| Gamma-glutamyltransferase increased | 0 | 12 (22) | 6 (11) | 18 (11) | 17 (11) |
| Constipation | 5 (9) | 6 (11) | 5 (9) | 16 (10) | 15 (10) |
| Alanine aminotransferase | 0 | 6 (11) | 10 (18) | 16 (10) | 14 (9) |
| Aspartate aminotransferase increased | 0 | 6 (11) | 10 (18) | 16 (10) | 13 (8) |
| Seizure | 4 (7) | 3 (5) | 8 (15) | 15 (9) | 13 (8) |
| Cough | 4 (7) | 6 (11) | 3 (5) | 13 (8) | 12 (8) |

[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.
AEs, adverse events; CBD, cannabidiol; CBD25, cannabidiol 25 mg/kg/d; CBD50, cannabidiol 50 mg/kg/d; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; TEAE, treatment-emergent adverse event

- Diarrhea was the most frequently reported AE during the randomized phase and OLE, in both pediatric patients and the overall population.
- The most frequently reported AE leading to permanent discontinuation among pediatric patients in the randomized phase was somnolence (1%); in the OLE one patient permanently discontinued treatment due to the AE of ataxia.
- The most frequently reported serious AEs were elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (2% each) during the randomized phase as well as during the OLE (3% each).

### Laboratory investigations

- During the randomized phase, elevation in ALT/AST levels >3× upper limits of normal (ULN) occurred in 20 pediatric patients (12%), representing 9% of the overall population of pediatric and adult patients (N=224) enrolled in the trial.
- During the OLE, elevation in ALT/AST levels >3× ULN occurred in 17 pediatric patients (11%), representing 9% of the overall population of pediatric and adult patients (N=199) treated in the OLE.

## Conclusions

- In this post hoc analysis of pediatric patients in the randomized and OLE phases of the trial GWPCARE6, which assessed the efficacy and safety of add-on CBD:
  - Efficacy of CBD in pediatric patients was consistent with the overall population during the randomized phase and the OLE.
  - During the randomized phase, ≥50%, ≥75%, and 100% responder rates were greater than placebo and consistent with the overall population.
    - Responder rates were durable and maintained throughout the OLE.
  - During the OLE, consistent with the overall population, a substantial proportion of patients/caregivers reported improvements in the overall condition of pediatric patients using the S/CGIC scale.
  - CBD was well-tolerated, and the safety profile was consistent with that observed in the overall population during the OLE and randomized phase, with higher dose associated with an increased incidence of AEs and liver enzyme elevations.

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

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**Clinical Trial ID:** NCT02544763 (GWPCARE6 RCT); NCT02544750 (GWPCARE6 OLE).

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