# Cannabidiol (CBD) Significantly Reduces Convulsive Seizure Frequency in Dravet Syndrome (DS): Results of a Multi-center, Randomized, Double-blind, Placebo-controlled Trial (GWPCARE1)

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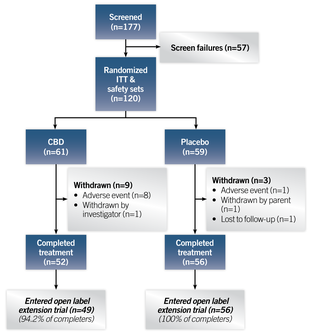
## SUMMARY

- The trial met its primary endpoint, demonstrating that CBD (20 mg/kg/day), as an add-on to standard of care, produced significantly greater reductions in convulsive seizures vs. placebo in patients with Dravet syndrome (DS).
- CBD resulted in significantly greater reductions in total seizure frequency vs. placebo.
- Compared to placebo, CBD caregivers were significantly more likely to report an improvement in overall condition, as measured on the Caregiver Global Impression of Change (CGIC) scale.
- CBD resulted in more adverse events than placebo, but it was generally well tolerated.

## INTRODUCTION

- Data from a US expanded access program suggest that CBD reduces seizures in patients with DS[1].
- This is the first randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of adjunctive CBD in children (2–18 years old) with DS.

### Patient disposition and baseline demographics



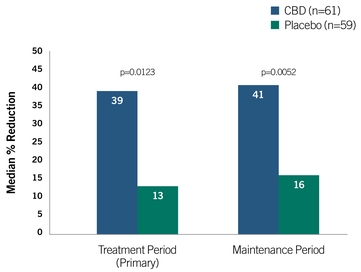

| Parameter | CBD (n=61) | Placebo (n=59) |
|---|---|---|
| **Age (years)** | | |
| Mean (min, max) | 9.7 (2.5, 18.0) | 9.8 (2.3, 18.4) |
| **Age Group [n (%)]** | | |
| 2–5 years | 18 (29.5) | 17 (28.8) |
| 6–12 years | 23 (37.7) | 24 (40.7) |
| 13–18 years | 20 (32.8) | 18 (30.5) |
| **Sex [n (%)]** | | |
| Male | 35 (57.4) | 27 (45.8) |
| **Number of Prior AEDs** | | |
| Median (min, max) | 4 (0, 26) | 4 (0, 14) |
| **Number of Current AEDs*** | | |
| Median (min, max) | 3 (1, 5) | 3 (1, 5) |
| **Seizure Frequency (per 28 Days) During Baseline** | | |
| Median Convulsive (Q1, Q3) | 12.4 (6.2, 28.0) | 14.9 (7.0, 36.0) |
| Median Total (Q1, Q3) | 24 (10.4, 141.0) | 41.5 (12.0, 367.0) |

*Most common antiepileptic drugs (AEDs) were clobazam (65%), valproic acid (57%), stiripentol (43%).

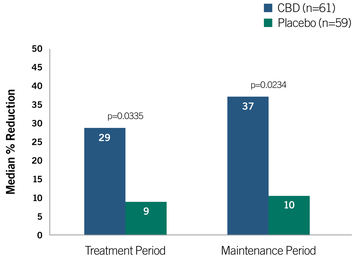
## EFFICACY RESULTS

### Percentage change in convulsive and total seizure frequency (28-day average)

**A | Convulsive Seizures**

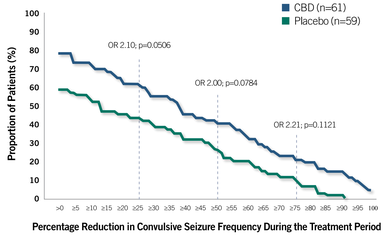



**B | Total Seizures**

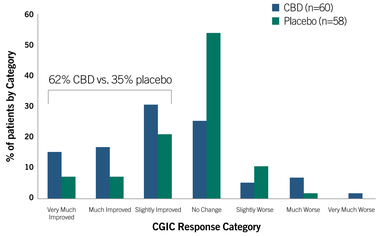



- Significantly greater reductions were reported for CBD than for placebo; this difference was established during the first 4 weeks of maintenance.
- Reduction in non-convulsive seizures was not statistically different for subgroup of patients with non-convulsive seizures who were taking CBD (n=37, 40%) vs. placebo (n=41, 35%).

### Convulsive seizure responder rates




### Caregiver global impression of change from baseline at last visit




- 43% of CBD patients had a ≥50% reduction in convulsive seizures compared to 27% of patients taking placebo.
- 3 CBD and no placebo patients achieved convulsive and total seizure freedom during the entire treatment period. An additional 4 CBD patients achieved convulsive seizure freedom during maintenance (no placebo); of these, 1 completed the trial.
- Caregivers of CBD patients were more likely to report an improvement in overall condition on CGIC (OR=2.29; p=0.0155).
- 93% of patients were on multiple concomitant AEDs. The effect of concomitant AEDs on efficacy will be explored in future pooled analyses.

## SAFETY RESULTS

### Summary of treatment-emergent adverse events (TEAEs)

| | CBD (n=61) n (%) | Placebo (n=59) n (%) |
|---|---|---|
| All-causality TEAEs | 57 (93.4%) | 44 (74.6%) |
| Treatment-related TEAEs | 43 (70.5%) | 16 (27.1%) |
| TEAEs leading to withdrawal | 9 (14.8%) | 1 (1.7%) |
| Serious TEAEs | 10 (16.4%) | 3 (5.1%) |
| Treatment-related serious TEAEs | 5 (8.2%) | 0 |
| **TEAEs reported in >10% of patients in either group by preferred term** | | |
| Somnolence | 22 (36.1%) | 6 (10.2%) |
| Diarrhea | 19 (31.1%) | 6 (10.2%) |
| Decreased appetite | 17 (27.9%) | 3 (5.1%) |
| Fatigue | 12 (19.7%) | 2 (3.4%) |
| Pyrexia | 9 (14.8%) | 5 (8.5%) |
| Vomiting | 9 (14.8%) | 3 (5.1%) |
| Lethargy | 8 (13.1%) | 3 (5.1%) |
| Upper respiratory tract infection | 7 (11.5%) | 5 (8.5%) |
| Convulsion | 7 (11.5%) | 3 (5.1%) |

- Of those who reported a TEAE, 84% of CBD and 95% of placebo patients reported it as mild or moderate.
- The pattern of serious TEAEs was consistent with the common TEAEs reported on CBD.
- There was no difference in the number of patients who experienced status epilepticus between CBD (n=4) and placebo (n=3); no episodes were deemed treatment-related nor led to withdrawal from treatment.
- There were no deaths.

### Laboratory investigations

- Increases in ALT or AST (> 3× ULN) occurred in 12 CBD and 1 placebo patient, all of whom were on concomitant valproic acid. No patients met standard criteria for drug-induced liver injury (Hy's law) with concurrent elevated bilirubin >2× ULN. Three of the CBD patients withdrew from treatment. All elevations resolved.

## METHODS

- Eligible patients were aged 2–18 years, with a clinical diagnosis of DS inadequately controlled by ≥1 current AED(s), and were experiencing ≥4 convulsive seizures during the 28-day baseline period.
- Patients were randomized (1:1) to 20 mg/kg/day of a pharmaceutical formulation of CBD (100 mg/mL) in oral solution or matched placebo, administered b.i.d. starting at 2.5 mg/kg/day and titrated up to 20 mg/kg/day over a 2-week period, followed by a 12-week dose maintenance period.
- Convulsive seizures were defined as tonic–clonic, tonic, clonic, and atonic seizures.
- The treatment period consisted of both the titration and maintenance periods.
- Caregivers recorded seizures daily using an automated interactive voice response system.
- DS diagnosis and classification of seizure types was confirmed by the Epilepsy Study Consortium.
- Patients who completed the trial were eligible to continue into an open-label extension study.

**Disclosures:** This study was sponsored by GW Pharmaceuticals plc, London, UK. Formatting and editorial assistance was provided to the authors by Hospicom, Cold Spring, NY and funded by GW Pharmaceuticals. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship. J. Helen Cross, Orrin Devinsky, Linda Laux, Eric Marsh, Ian Miller, Rima Nabbout, Ingrid E Scheffer, and Elizabeth A. Thiele have consulted for, conducted studies funded by, or received honoraria from GW Pharmaceuticals, plc. Stephen Wright is an employee of GW Research, Ltd. Findings reported in this study are specific to GW Pharmaceuticals' formulation of cannabidiol and cannot be extrapolated to other cannabidiol products.

**References:** 1. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2015;4422(15):1–9.

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**Presented:** The American Epilepsy Society Annual Meeting; Houston, TX; December 2–6, 2016.

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