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2.362: Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet Syndrome: results of a multi-centered, randomized, controlled study (GWPCARE1)

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Rationale
The efficacy and safety of CBD in the treatment of seizures associated with Dravet syndrome (DS) has not been previously demonstrated in controlled trials, although data from an expanded access program conducted in the US suggest that CBD may provide meaningful clinical benefit.

Methods
This randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of CBD added to concomitant antiepileptic drug (AED) treatment in children and adolescents with treatment-resistant DS, treated over a 14-week period, including a 14-day dose-escalation. Patients were randomized to receive placebo or a pharmaceutical formulation of CBD in oral solution (100 mg/mL). The CBD dose of 20 mg/kg/day, in two divided doses, was recommended by an independent Data Safety Monitoring Committee, following a 22-day dose-ranging pharmacokinetic and safety evaluation (to be reported separately). The diagnosis of DS and the classification of seizures were confirmed by a committee from the Epilepsy Study Consortium. The primary efficacy endpoint was the percent change from baseline in convulsive seizure frequency over the entire treatment period for patients on CBD vs. placebo. Secondary outcome measures were also assessed.

Results
A total of 120 patients (USA 72, Europe 48) were randomized to CBD (n=61) or placebo (n=59). Nine CBD and 3 placebo patients withdrew early. The groups were well-balanced at baseline for demographics. The mean age overall was 10 years, with 29% of patients aged less than 6 years. Patients had previously tried a median 4 AEDs, and were currently taking a median 3 AEDs. CBD resulted in a significant reduction in convulsive seizure frequency assessed over both the 14-week treatment period and the 12-week stable dose maintenance period. The median reduction in seizure frequency during the treatment period was 39% on CBD vs. 13% on placebo (p=0.0123). A series of prospectively planned sensitivity analyses confirmed the robustness of this result. The difference between CBD and placebo was established by the end of the first 4 weeks of stable dose treatment. Complete seizure freedom was seen in 3 patients throughout the 14-week treatment period. Secondary efficacy endpoint analyses supported the result of the primary analysis. Adverse events (AEs) occurred in 93.4% of CBD and 74.6% of placebo patients; of patients on CBD who reported an AE, it was deemed to be mild or moderate in 84%. The most common AEs (occurring in ?10% of CBD-treated patients) were somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection, and convulsion. Serious AEs were reported in 16.4% of CBD and

5.1% of placebo patients; considered treatment-related in 8.2% of CBD patients. There were no deaths.

Conclusions
This phase 3 study of CBD in the adjunctive treatment of drug-resistant epilepsy in children with Dravet syndrome supports open-label study reports and provides Class 1 evidence of the efficacy and tolerability of CBD in this population. (NCT02091375)

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