A Dose Ranging Safety and Pharmacokinetic Study of Cannabidiol (CBD) in Children With Dravet Syndrome (GWPCARE1)

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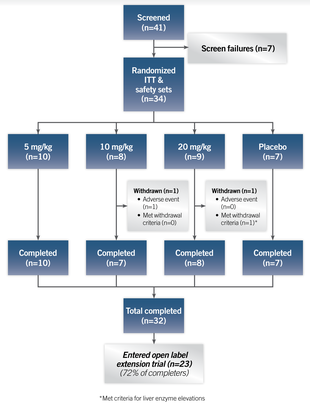
SUMMARY

- Exposure to CBD and its metabolites increased in a dose-proportional manner; 7-COOH-CBD was the major circulating metabolite.
- N-desmethylclobazam (N-CLB) levels increased in patients on CBD, except for those on concomitant stiripentol, which may reflect prior saturated inhibition of CYP2C19 enzyme by stiripentol.
- There was no demonstrable effect on other antiepileptic drugs (AEDs) tested (valproic acid, topiramate, stiripentol, or levetiracetam).
- CBD resulted in more adverse events than placebo, but it was generally well tolerated at all doses examined.
- 20 mg/kg/day was approved by the Data Safety Monitoring Committee for further investigation.

INTRODUCTION

- Data from a US expanded access program suggest that CBD reduces seizures in patients with Dravet syndrome (DS)[1].
- This randomized controlled study evaluated dose-ranging safety, tolerability, and pharmacokinetics (PK) of adjunctive CBD in children with DS in Part A.
- Data from Part A were used to determine the dose for Part B, which assessed safety and efficacy in a larger population.

Patient disposition and baseline demographics



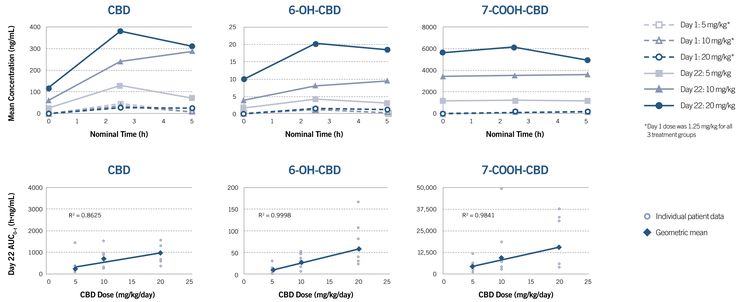
*Met criteria for liver enzyme elevations

Parameter	CBD			Placebo (n=7)
	5 mg/kg (n=10)	10 mg/kg (n=8)	20 mg/kg (n=9)	
Age (years)				
Mean (min, max)	7.2 (4.7, 10.9)	7.4 (4.0, 10.9)	8.7 (5.4, 10.7)	7.0 (6.1, 8.8)
Sex				
Male (%)	5 (50)	3 (38)	3 (33)	5 (71)
Number of Prior AEDs				
Median (min, max)	3 (0, 11)	3.5 (0, 5)	4 (2, 8)	5 (1, 5)
Number of Current AEDs*				
Median (min, max)	3 (1, 4)	3 (2, 3)	3 (1, 4)	2 (1, 3)

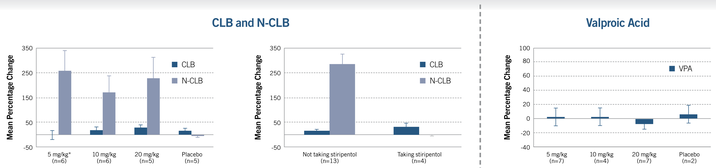
*The most commonly used AEDs were clobazam (68%) and valproic acid (65%).

PHARMACOKINETIC RESULTS

Plasma pharmacokinetics of CBD and metabolites



Mean percentage change in plasma concentrations of CLB, N-CLB, and valproic acid at Day 22



*2 patients in the 5 mg/kg group reduced CLB dose during the treatment period. Error bars: standard error of mean (SEM)

Error bars: SEM

- After single or twice-daily dosing of CBD, 7-COOH-CBD was the major circulating metabolite; by Day 22 it was approximately 13–17 times higher than CBD; 6-OH-CBD was a minor circulating metabolite.
- Exposure to CBD, 7-COOH-CBD, and 6-OH-CBD increased in a dose-proportional manner; qualitative data generated for the 7-OH-CBD metabolite also showed a dose-proportional increase.
- In patients on concomitant CLB, at Day 22, CLB plasma concentrations were unchanged; N-CLB concentration increased independent of CBD dose but did not increase in the patients on stiripentol.
- CBD had no obvious effect on drug levels of other AEDs tested: valproic acid (n=18), topiramate (n=8), stiripentol (n=4), or levetiracetam (n=7).

SAFETY RESULTS

Treatment-emergent adverse events (TEAEs)

	5 mg/kg (n=10) n (%)	10 mg/kg (n=8) n (%)	20 mg/kg (n=9) n (%)	Placebo (n=7) n (%)
All-causality TEAEs	8 (80)	5 (63)	7 (78)	6 (86)
Treatment-related TEAEs	6 (60)	3 (38)	4 (44)	1 (14)
TEAEs leading to withdrawal	0	1 (13)	1 (11)	0
Serious TEAEs	1 (10)	2 (25)	1 (11)	1 (14)
Treatment-related serious TEAEs	1 (10)	1 (13)	0	0
TEAEs reported in >10% of patients in either group by preferred term				
Somnolence	2 (20)	3 (38)	0	1 (14)
Pyrexia	3 (30)	3 (38)	0	0
Decreased appetite	0	1 (13)	4 (44)	0
Sedation	2 (20)	0	2 (22)	0

- 2 patients on CBD discontinued due to TEAEs (1 for abnormal liver enzymes meeting withdrawal criteria and decreased appetite on 20 mg/kg, and 1 for pyrexia and maculopapular rash on 10 mg/kg); each event was considered treatment-related but resolved following cessation of CBD.
- Increases in ALT or AST (levels >3× ULN) occurred in 6 CBD patients, all on valproic acid (4 had concomitant infections). No patients met standard criteria for drug-induced liver injury (Hy's law) with concurrent elevated bilirubin >2× ULN. One patient withdrew from treatment. All elevations resolved.

METHODS

- Patients were aged 4–10 years and had a documented history of DS with seizures inadequately controlled by ≥1 current AED(s).
- After a 4-week baseline period, patients with fewer than 4 convulsive seizures (ie, tonic–clonic, tonic, clonic, atonic seizures) were randomized to 1 of 3 doses of CBD (5, 10, 20 mg/kg/day) or placebo as add-on therapy for 3 weeks.
- CBD (25 or 100 mg/mL oral solution) was administered b.i.d. starting at 2.5 mg/kg/day and increasing by 2.5–5.0 mg/kg QOD to randomized dose.
- The treatment period consisted of both the titration and maintenance periods.
- PK blood samples were taken on the first day of dosing and again at 3 weeks (nominal times: pre-dose; 2.5 h and 5 h post-dose); PK exposures were expressed as $AUC_{0-\tau}$; dose proportionality was assessed on Day 22 by simple regression analysis.
- An independent Data Safety Monitoring Committee reviewed unblinded safety data during Part A of the trial in order to recommend the dose and dose regimen to be used in Part B.
- 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.

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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. **Contact Information:** medinfo.usa@gwpharm.com

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