1.285 Seizure-free Days as a Novel and Meaningful Outcome in Patients with Lennox-Gastaut Syndrome: Post Hoc Analysis of Patients Receiving Cannabidiol (CBD) in GWPCARE3 and GWPCARE4

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Introduction

- In two placebo-controlled, phase 3 randomized clinical trials (RCTs), add-on highly purified CBD (Epidiolex®) demonstrated efficacy with an acceptable safety profile in patients with Lennox-Gastaut syndrome (LGS).[1,2]
- Drop seizure frequency was evaluated as the primary endpoint reflecting its use as the established primary endpoint for clinical trials in LGS[3]; however, it may not adequately capture the impact of treatment on total seizure burden and quality of life.[3]
- Two vignette studies indicated the importance of considering the impact of seizure-free days as well as seizure frequency on everyday patient and caregiver health-related quality of life[4,5]; one of the studies linked seizure-free days to a greater impact on quality of life than a reduction in the frequency of seizures.[5]

Objective

- This post hoc analysis evaluated the number of seizure-free days as a potential new outcome measure to demonstrate the efficacy of antiseizure medications (ASMs) in patients with LGS.

Methods

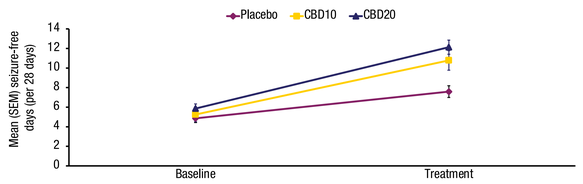
- Patients enrolled to GWPCARE3 and GWPCARE4 were 2–55 years of age with clinically confirmed LGS, with ≥2 drop seizures per week during the 4-week baseline period and seizures uncontrolled on ≥2 ASM. Patients were also required to take ≥1 ASM at a stable dose for ≥4 weeks prior to screening.
- During the RCTs, patients were randomized to add-on treatment with plant-derived highly purified CBD (Epidiolex®; 100 mg/mL oral solution) at 10 mg/kg/day (CBD10) or 20 mg/kg/day (CBD20) or matched placebo for a 14-week treatment period; the treatment period comprised a 2-week dose titration and a 12-week dose maintenance period.
- This post hoc analysis evaluated the number of drop seizure-free and total seizure-free days per 28 days.
- Results are reported for the pooled intention-to-treat (ITT) population of both RCTs and during the full treatment or maintenance periods.
- Least-squares (LS) mean changes from baseline in drop or total seizure-free days and difference versus placebo were estimated using an analysis of covariance model with categorical age and baseline number of drop or total seizure-free days as covariates, and treatment group as a fixed factor.
- The trials were conducted with Epidiolex® and results do not apply to other CBD-containing products.

Patient demographics and baseline characteristics

	Placebo (n=161)	CBD10 (n=73)	CBD20 (n=162)
Age, years			
Mean (SD)	15.3 (9.5)	15.4 (9.5)	15.7 (9.7)
Range	2.6, 45.1	2.6, 42.6	2.6, 48.0
Sex, n (%)			
Female	74 (46)	33 (45)	72 (44)
Race, n (%)			
White	148 (92)	62 (85)	142 (88)
Black/African American	6 (4)	4 (5)	6 (4)
Asian	5 (3)	1 (1)	4 (2)
Not applicable*	0	1 (1)	0
Other	2 (1)	5 (7)	10 (6)
Number of ASMs, median (range)			
Previous	6 (0, 28)	6 (0, 21)	6 (1, 18)
Current	3 (1, 5)	3 (1, 5)	3 (0, 5)
Concomitant ASMs, n (%)			
Clobazam	79 (49)	37 (51)	78 (48)
Valproate	63 (39)	27 (37)	64 (40)
Lamotrigine	56 (35)	22 (30)	53 (33)
Levetiracetam	58 (36)	22 (30)	47 (29)
Rufinamide	41 (25)	19 (26)	51 (31)
Baseline seizure frequency per 28 days, median (range)			
Drop	79.0 (8.7, 3174.6)	86.9 (14.0, 7494.0)	78.1 (10.3, 1092.0)
Seizure-free days per 28 days, median (range)			
Drop	2.0 (0, 19.3)	1.9 (0, 19.3)	3.9 (0, 21.7)
Total	0.8 (0, 18.0)	1.0 (0, 17.0)	0.9 (0, 20.0)

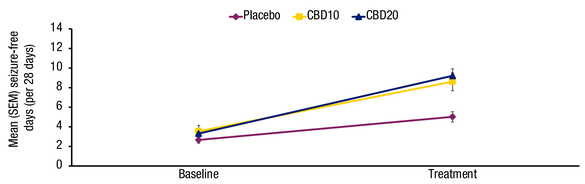
*Not applicable as per country-specific data protection law.
ASM, antiseizure medication; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; SD, standard deviation

Drop seizure-free days during treatment period



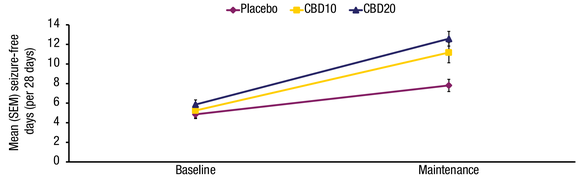
	Change from baseline	Treatment difference vs. placebo	
	LS mean (95% CI)	LS mean (95% CI)	P-value
Placebo (n=161)	2.8 (1.8, 3.9)		
CBD10 (n=73)	5.6 (4.1, 7.2)	2.8 (1.0, 4.7)	0.0028
CBD20 (n=162)	6.5 (5.4, 7.5)	3.6 (2.2, 5.1)	<0.0001

Total seizure-free days during treatment period



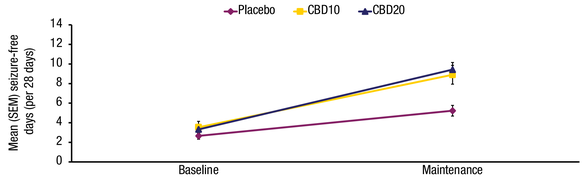
	Change from baseline	Treatment difference vs. placebo	
	LS mean (95% CI)	LS mean (95% CI)	P-value
Placebo (n=161)	2.3 (1.3, 3.3)		
CBD10 (n=73)	4.9 (3.5, 6.4)	2.6 (0.9, 4.3)	0.0026
CBD20 (n=162)	5.8 (4.8, 6.8)	3.5 (2.2, 4.9)	<0.0001

Drop seizure-free days during maintenance period



	Change from baseline	Treatment difference vs. placebo	
	LS mean (95% CI)	LS mean (95% CI)	P-value
Placebo (n=161)	3.1 (2.0, 4.2)		
CBD10 (n=73)	6.1 (4.4, 7.7)	3.0 (1.1, 5.0)	0.0027
CBD20 (n=162)	6.9 (5.8, 8.1)	3.9 (2.3, 5.4)	<0.0001

Total seizure-free days during maintenance period



	Change from baseline	Treatment difference vs. placebo	
	LS mean (95% CI)	LS mean (95% CI)	P-value
Placebo (n=161)	2.5 (1.5, 3.5)		
CBD10 (n=73)	5.2 (3.7, 6.7)	2.7 (0.9, 4.5)	0.0034
CBD20 (n=162)	6.0 (5.0, 7.0)	3.5 (2.1, 4.9)	<0.0001

Drop seizures were defined as tonic, atonic or tonic-clonic seizures involving the entire body, trunk or head leading to a fall, injury, slumping in a chair or hitting the patient's head on a surface. CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; CI, confidence interval; LS, least squares; SEM, standard error of the mean

AE summary

Patients, n (%)	Placebo (n=161)	CBD10 (n=67)	CBD20 (n=168)
AEs	114 (71)	56 (84)	151 (90)
AEs leading to permanent discontinuation	2 (1)	1 (1)	18 (11)
Serious AEs	12 (7)	13 (19)	33 (20)
Deaths	0	0	1* (<1)
AEs reported in ≥10% of all CBD patients by MedDRA preferred term			
Somnolence	12 (7)	14 (21)	38 (23)
Decreased appetite	8 (5)	11 (16)	32 (19)
Diarrhea	13 (8)	7 (10)	28 (17)
Pyrexia	19 (12)	6 (9)	21 (13)
Vomiting	23 (14)	4 (6)	19 (11)
Upper respiratory tract infection	17 (11)	11 (16)	13 (8)
Status epilepticus	4 (2)	7 (10)	5 (3)

*Death attributed to acute respiratory distress syndrome.
AE, treatment-emergent adverse event; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; MedDRA, Medical Dictionary for Regulatory Activities

Laboratory investigations

- Alanine aminotransferase (ALT) elevations (>3× upper limit of normal [ULN]) occurred in 1 patient (<1%) on placebo, 1 patient (1%) on CBD10, and 30 patients (18%) on CBD20; the patient on CBD10 and 23 of the 30 patients on CBD20 were on concomitant valproate.
- Aspartate aminotransferase (AST) elevations (>3× ULN) occurred in no patients on placebo, 2 patients (3%) on CBD10, and 10 patients (6%) on CBD20; 1 of the 2 patients on CBD10 and all of the patients on CBD20 were on concomitant valproate.

Conclusions

- In this post hoc analysis of GWPCARE3 and GWPCARE4:
  - For both drop and total seizures, improvements from baseline in seizure-free days were demonstrated overall and versus placebo at both doses of CBD during the treatment and maintenance periods of GWPCARE3 and GWPCARE4.
  - An increase in total seizure-free days may potentially correlate with improved patient quality of life and reduced caregiver burden.[4,5]
- CBD had an acceptable safety profile.
- Drop seizure-free and total seizure-free days represent potential new and clinically meaningful endpoints for seizure assessment in patients with LGS for future clinical trials.

References: 1. Devinsky O et al. *N Engl J Med.* 2018;378:1888–1897. **2.** Thiele EA et al. *Lancet.* 2018;391:1085–1096. **3.** Auvin S et al. *Epilepsia Open.* 2019;4:275–280. **4.** Lo SH et al. *Clin Ther.* 2021;43:1861–1876. **5.** Auvin S et al. *Epilepsy Behav.* 2021;123:108239.

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Contact information: medinfo@greenwichbiosciences.com. **Clinical Trial ID:** NCT02224560 (GWPCARE3); NCT02224690 (GWPCARE4).

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