Cannabidiol (CBD) Significantly Reduces Drop Seizure Frequency in Lennox-Gastaut Syndrome (LGS): Results of a Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial (GWPCARE3)

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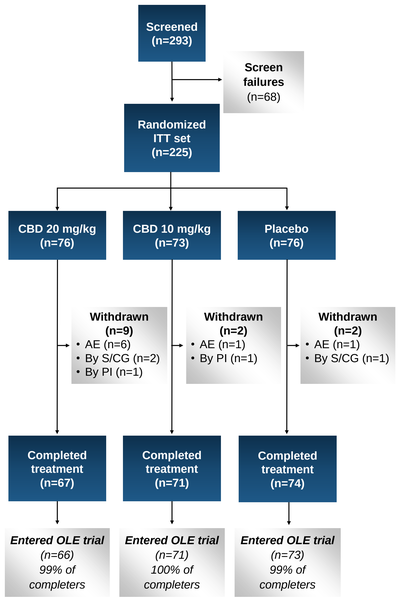
SUMMARY

- The trial met its primary endpoint for both doses (20 mg/kg/day, 10 mg/kg/day), demonstrating that CBD as an add-on to standard of care, produced significantly greater reductions in drop seizures vs placebo in patients with LGS.
- Responder rates were significantly higher with both CBD doses vs placebo.
- CBD patients/caregivers were significantly more likely to report an improvement in overall condition on the Subject/Caregiver Global Impression of Change (S/CGIC) scale.
- CBD resulted in more adverse events (AEs) than placebo; there were fewer AEs in the low-dose group.
- Both doses were generally well tolerated, with a similar safety profile to that observed in previous trials of CBD.

INTRODUCTION

- LGS is a rare form of epileptic encephalopathy and is often treatment-resistant.[1]
- Results from the first randomized, double-blind, placebo-controlled trial (RCT) of CBD 20 mg/kg/day in LGS patients demonstrated a significant reduction in drop seizure frequency.
- This is the second RCT of adjunctive CBD in LGS, and the first to evaluate 2 doses.

Patient disposition and baseline demographics



Safety set*	CBD 20 mg/kg (n=82)	CBD 10 mg/kg (n=67)	Placebo (n=76)
Age, y			
Mean (min, max)	16.54 (2.6-48.0)	14.73 (2.6-38.2)	15.28 (2.6-43.4)
2-5 y, n (%)	9 (11.0)	8 (11.9)	9 (11.8)
6-11 y, n (%)	27 (32.9)	22 (32.8)	24 (31.6)
12-17 y, n (%)	21 (25.6)	18 (26.9)	20 (26.3)
18-55 y, n (%)	25 (30.5)	19 (28.4)	23 (30.3)
Sex, n (%)			
Male	49 (59.8)	36 (53.7)	44 (57.9)
Number of previous AEDs			
Median (min, max)	6.79 (1-19)	6.82 (0-21)	7.18 (1-22)
Number of current AEDs†			
Median (min, max)	2.84 (0-5)	2.94 (1-5)	2.92 (1-5)

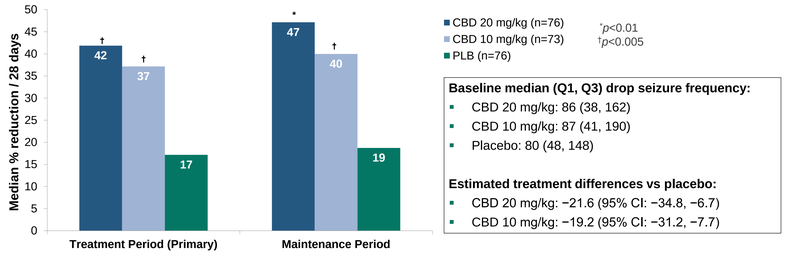
*Six patients randomized to 10 mg/kg transiently titrated to 20 mg/kg; these patients were included in the 20-mg/kg group for the safety analysis and in the 10-mg/kg group for the efficacy analysis.

†The most common AEDs were clobazam (49%), valproic acid (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).

AE=adverse event; ITT=intent-to-treat; OLE=open-label extension; PI=principle investigator; S/CG=subject/caregiver.

EFFICACY RESULTS

Reduction in drop seizures (ITT)

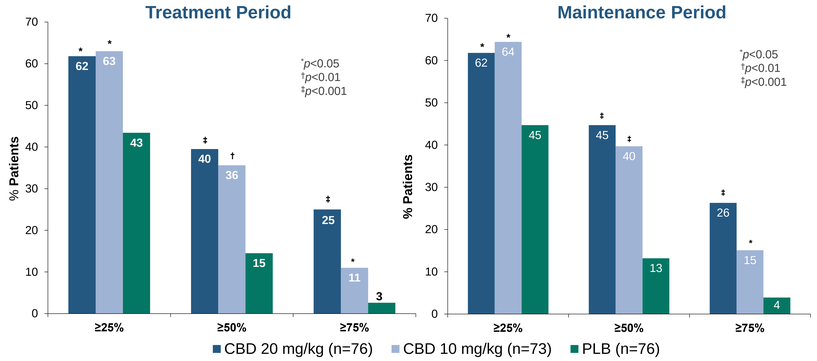


Baseline median (Q1, Q3) drop seizure frequency:
- CBD 20 mg/kg: 86 (38, 162)
- CBD 10 mg/kg: 87 (41, 190)
- Placebo: 80 (48, 148)

Estimated treatment differences vs placebo:
- CBD 20 mg/kg: −21.6 (95% CI: −34.8, −6.7)
- CBD 10 mg/kg: −19.2 (95% CI: −31.2, −7.7)

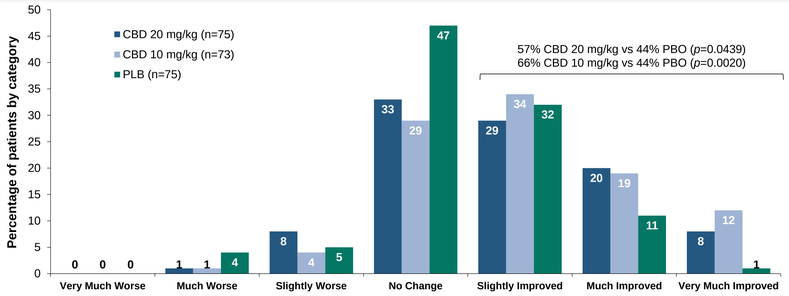
- Differences were established in the first 4 weeks of the maintenance period and persisted until the end of treatment.

Drop seizure responder rates (ITT)



- Significantly greater proportion of CBD vs placebo patients achieved ≥25%, ≥50%, and ≥75% reductions in drop seizure frequency.
- 5 (7%) CBD 20 mg/kg, 3 (4%) CBD 10 mg/kg, and 1 (1%) placebo patient achieved drop seizure freedom during the maintenance period.

Subject/caregiver global impression of change from baseline at last visit (ITT)*



- CBD patients/caregivers were significantly more likely to report an improvement in overall condition in the S/CGIC (OR=1.83-2.57; $p<0.05$).

SAFETY RESULTS

Treatment-emergent AEs (TEAEs) in safety set

	CBD 20 mg/kg (n=82) n (%)	CBD 10 mg/kg (n=67) n (%)	Placebo (n=76) n (%)
All-causality TEAEs	77 (94)	56 (84)	55 (72)
Treatment-related TEAEs	51 (62)	20 (30)	15 (20)
TEAEs leading to withdrawal	6 (7)	1 (1.5)	1 (1)
Serious TEAEs	13 (16)	13 (19.4)	8 (11)
Treatment-related serious TEAEs	5 (6)	2 (3)	0
TEAEs reported in >10% of patients in any group by preferred term			
Somnolence	25 (31)	14 (21)	4 (5)
Decreased appetite	21 (26)	11 (16)	6 (8)
Diarrhea	12 (15)	7 (10)	6 (8)
Upper respiratory tract infection	11 (14)	11 (16)	11 (15)
Pyrexia	10 (12)	6 (9)	12 (16)
Vomiting	10 (12)	4 (6)	9 (12)
Nasopharyngitis	9 (11)	3 (5)	5 (7)
Status epilepticus	4 (5)	7 (10)	3 (4)

- Of those who reported a TEAE, 88% in the CBD 20-mg/kg group, 89% in the CBD 10-mg/kg group, and 89% in the placebo group reported it as mild or moderate in severity.
- One of the status epilepticus cases led to discontinuation of CBD (in the 20-mg/kg group).
- No deaths occurred during the trial.

Laboratory investigations

- Increases in alanine transaminase (ALT) or aspartate transaminase (AST) (>3× upper limit of normal [ULN]) occurred in 11 patients in the CBD 20-mg/kg group and 2 patients in the CBD 10-mg/kg group; 10 of these 13 patients were also taking valproic acid.
- No patient met standard criteria for drug-induced liver injury (Hy's Law) with concurrent elevated bilirubin >2×ULN.
- 4 CBD 20 mg/kg and 1 CBD 10 mg/kg patient withdrew from treatment due to elevated ALT or AST.
- All transaminase elevations resolved.

METHODS

- Eligible patients were aged 2 to 55 years with a clinical diagnosis of LGS inadequately controlled by ≥1 current AED(s); patients had a history of slow (<3 Hz) spike-and-wave pattern electroencephalogram.
- Patients with ≥2 drop seizures per week during the 4-week baseline (minimum of 8 drop seizures) were randomized (1:1:1) to 20 mg/kg/day (titrated over 11 days) or 10 mg/kg/day (titrated over 7 days) of a pharmaceutical formulation of CBD (100 mg/mL) in oral solution or matched placebo, administered BID; the treatment period consisted of 2 weeks for titration followed by a 12-week dose-maintenance period.
- The primary efficacy outcome was the percentage change from baseline in number of drop seizures (average per 28 days) during the 14-week treatment period.
  - A drop seizure was defined as an atonic, tonic, or tonic-clonic seizure involving the entire body, trunk, or head that led (or could have led) to a fall, injury, slumping in a chair, or hitting the patient's head on a surface.
- Classification of seizure types was confirmed by the Epilepsy Study Consortium.
- Caregivers recorded seizures daily using an automated interactive voice response system.
- Patients who completed the treatment period of the trial were eligible to continue into an open-label extension (OLE) study.

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References: 1. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol.* 2009;8(1):82-93. 2. 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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