

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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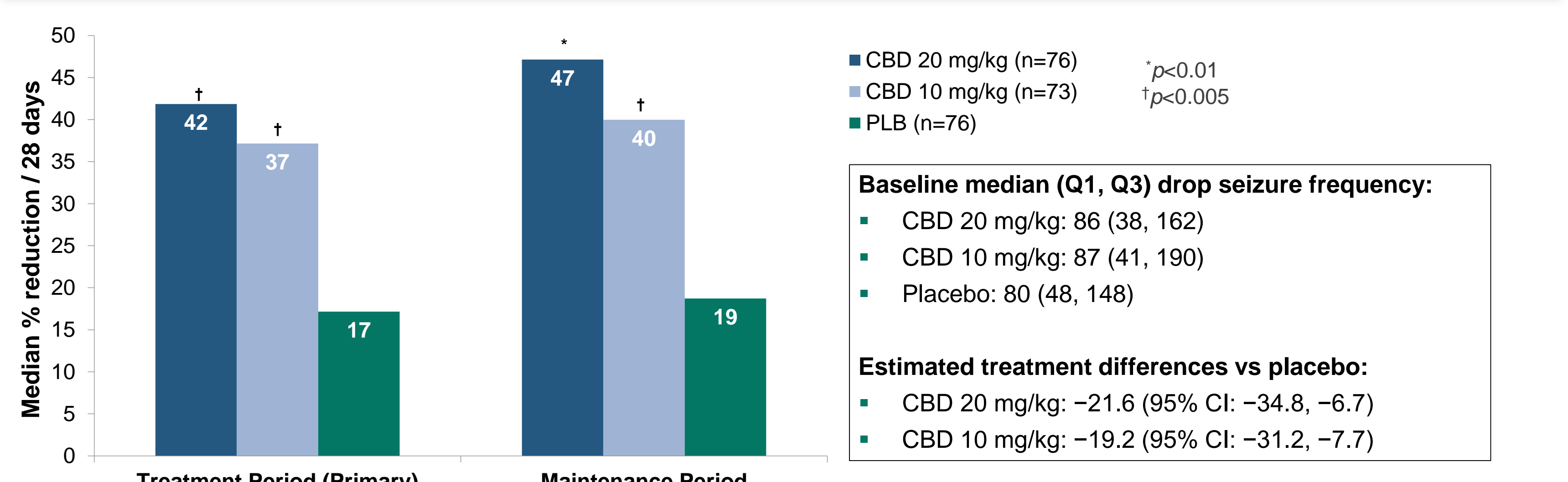
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SUMMARY

- 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.

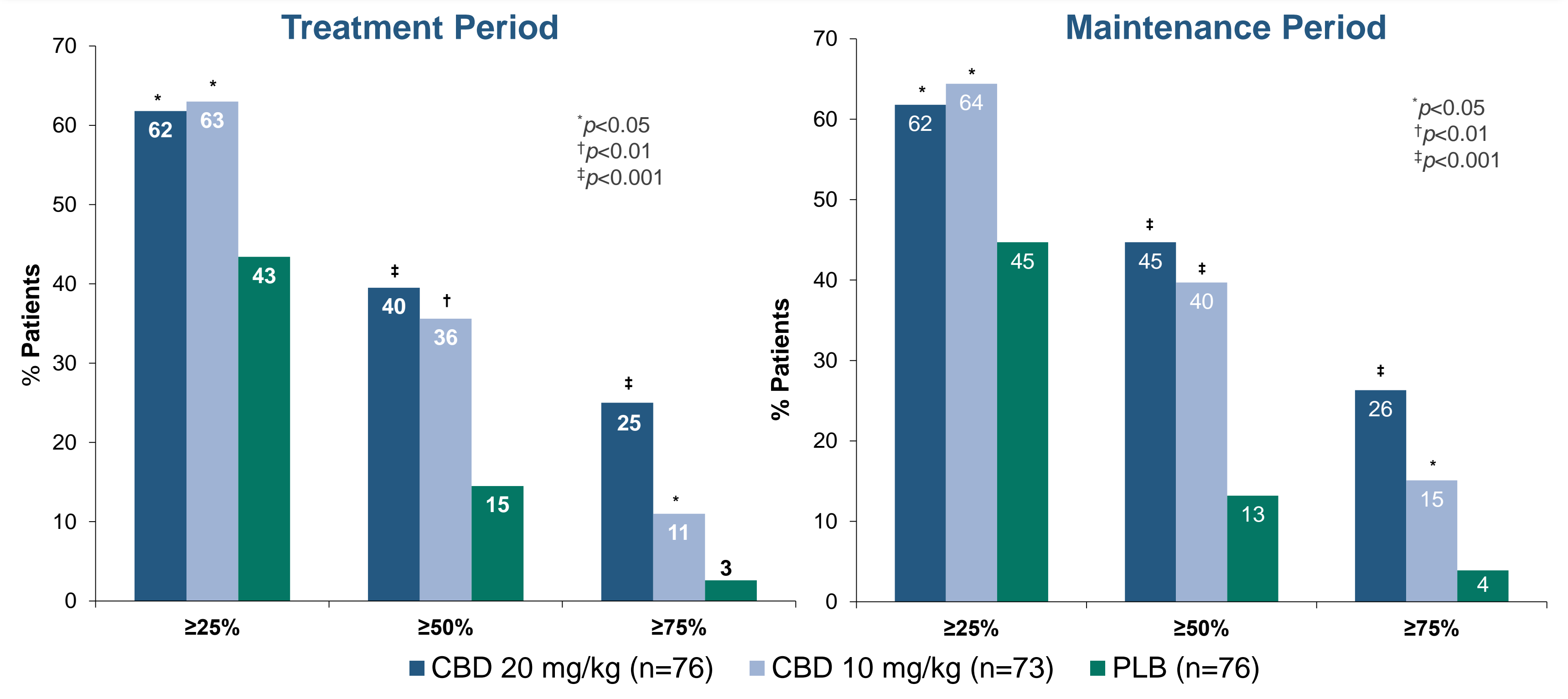
EFFICACY RESULTS

Reduction in drop seizures (ITT)



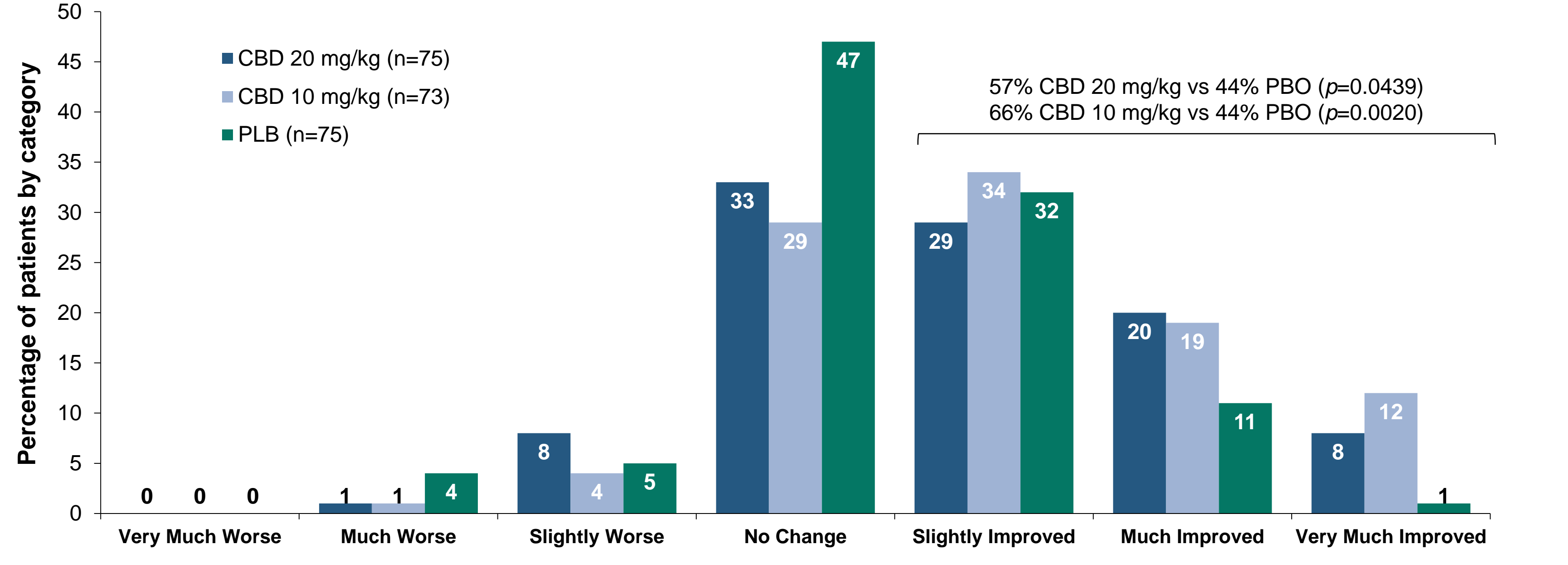
Differences were established in the first 4 weeks of the maintenance period and persisted until the end of treatment.

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)	CBD 10 mg/kg (n=67)	Placebo (n=76)
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)
Nausea/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.

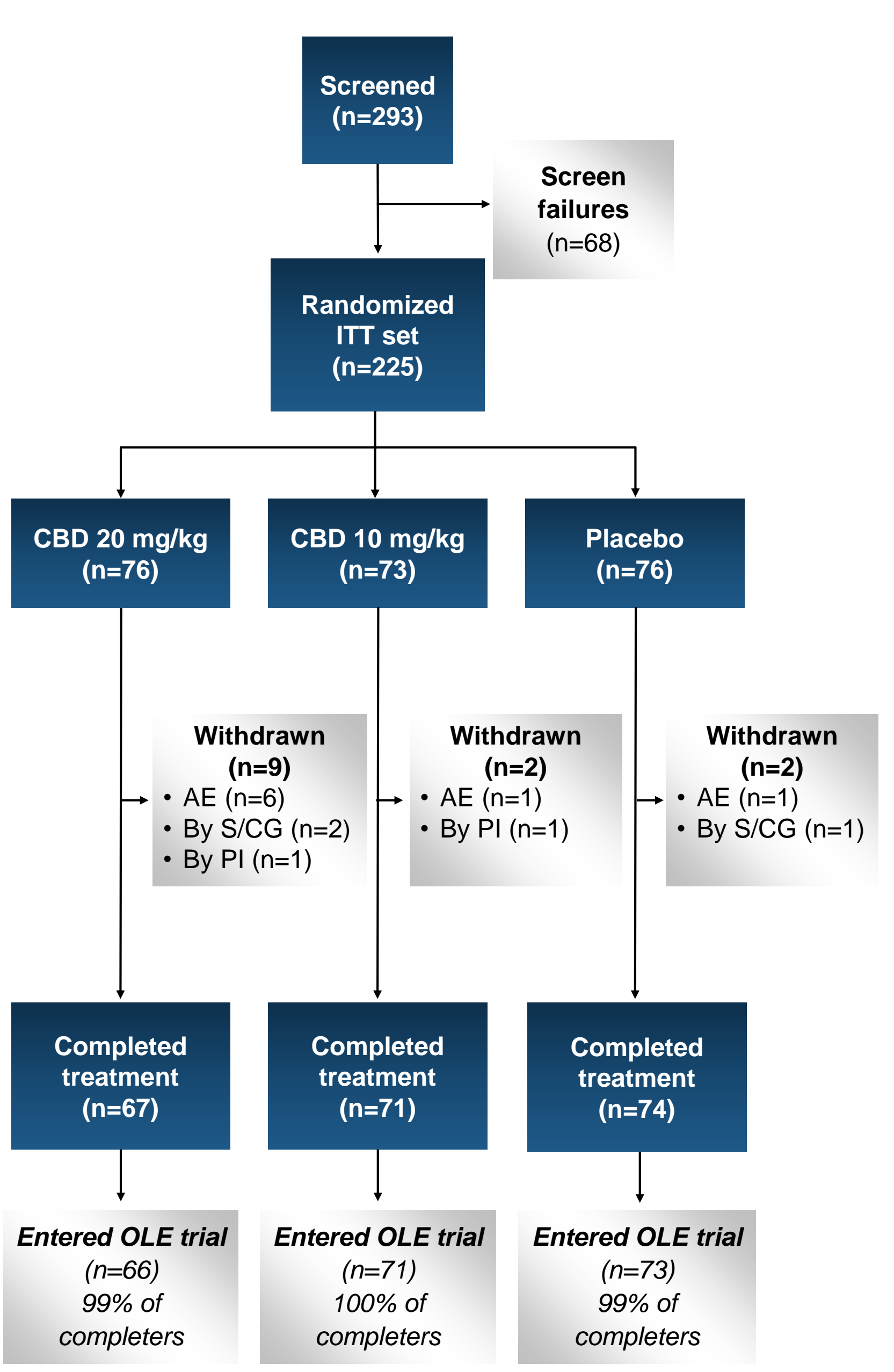
METHODS

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.

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=principal investigator; S/CG=subject/caregiver.

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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;14(2):151-160. Contact Information: medinfo.usa@greenwichbiosciences.com.