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

SUMMARY

- The trial met its primary endpoint for both doses (20 mg/kg/day, 10 mg/kg/day) demonstrating that CBD (≥50% on 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 in the S/CGIC scale.
- More patients were significantly more likely to report an improvement in overall condition in the S/CGIC than in previous trials of CBD.

INTRODUCTION

- LGS is a rare form of epileptic encephalopathy and is often treatment-resistant.1
- Results from the first randomised, 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

- Included 76 patients (CBD 20 mg/kg n=76, CBD 10 mg/kg n=75, PLB n=76). 66% CBD 10 mg/kg vs 44% PBO (% Patients with ≥25% drop seizure reduction).
- The median% reduction in drop seizure frequency in the CBD 20 mg/kg group was 37%. The median % reduction in drop seizure frequency in the CBD 10 mg/kg and PLB groups was 25%. 99% of patients in the CBD 20 mg/kg group for the efficacy analysis. 70% of patients in the CBD 10 mg/kg group, 89% in the CBD 10 mg/kg group and 2 patients in the CBD 10 mg/kg group; 10 of those 13 patients were also taking valproic acid.
- 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.

Efficacy results

- 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% CBD 20 mg/kg, 7% (CBD 10 mg/kg) and 1% (PLB) 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 by the S/CGIC scale.
- Responders were defined as patients who were rated as much or very much improved.
- 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.

SAFETY RESULTS

- All-causality TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to withdrawal
- TEAEs caused by study treatment
- Crypto exposure
- Gastrointestinal

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 those 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 ≤3 (<3) spikewave/and-wave pattern electroencephalogram.
- Patients with 22 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 atomic, 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 defined 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.