

# Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

Thiele, EA. et al. *Lancet*. 2018. 391: 1085–96.

## Introduction

Lennox-Gastaut syndrome is a **severe form of epileptic encephalopathy** that typically manifests between 3-5 years of age and may account for up to 4% of paediatric epilepsy cases.

**This lifelong condition is often treatment-resistant** and is associated with high rates of progressive cognitive impairment. Less than 1 in 10 patients become seizure-free with current interventions.

Compared to approved antiepileptic drugs, **cannabidiol (CBD) is structurally unique and has potentially novel multimodal mechanisms of action**. With prior studies suggesting it may be a safe and effective intervention in drug-resistant epilepsy, this clinical trial sought to establish its efficacy and safety in patients with Lennox-Gastaut syndrome.

## Aim of the study

To assess the **efficacy and safety of CBD** compared with placebo as an add-on anticonvulsant therapy for **drop seizures** in patients with **treatment-resistant Lennox-Gastaut syndrome**.

## Methods and materials

A randomised, double-blind, placebo-controlled, multicentre **phase 3 trial of 171 adults and children aged between 2-55 years** with treatment-refractory Lennox-Gastaut syndrome.

Patients received **20mg/kg oral CBD daily** or matched placebo for 14 weeks, including a 2-week titration (dose escalation) period. The study design is shown in Figure 1.

The patient demographics were similar between the two groups. Their baseline characteristics included:

- 73.8 median monthly drop seizures
- Median of 6 failed prior interventions
- Median of 3 current interventions
- Most common current interventions: Clobazam, valproate, lamotrigine

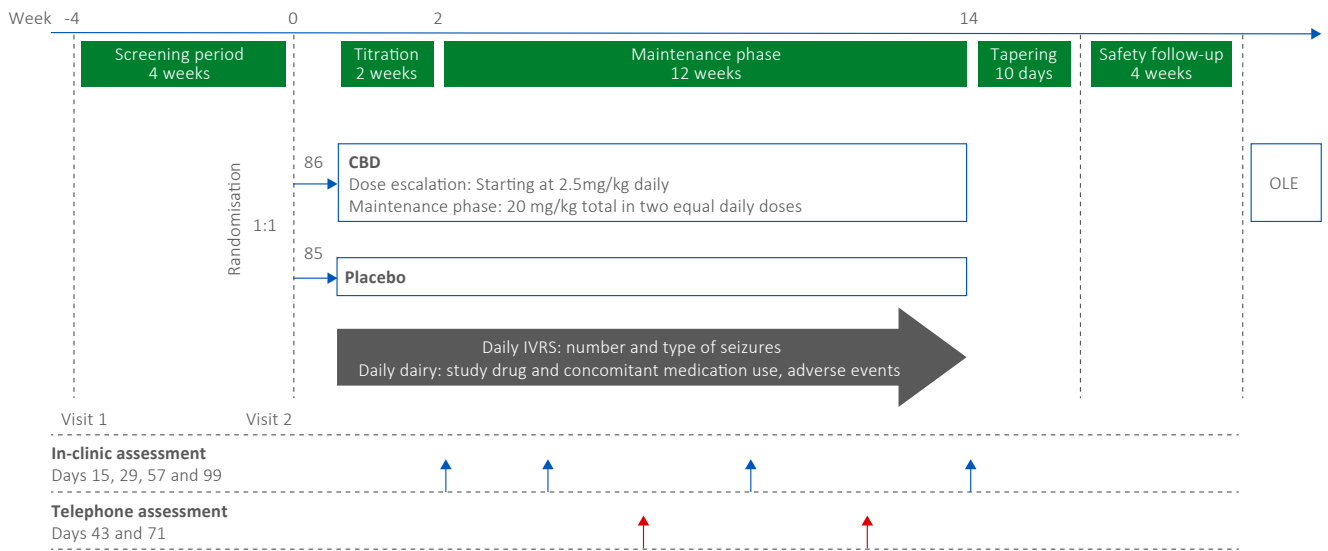


Figure 1: Trial design. IVRS; interactive voice recording system OLE; open-label extension

## Primary and secondary outcomes

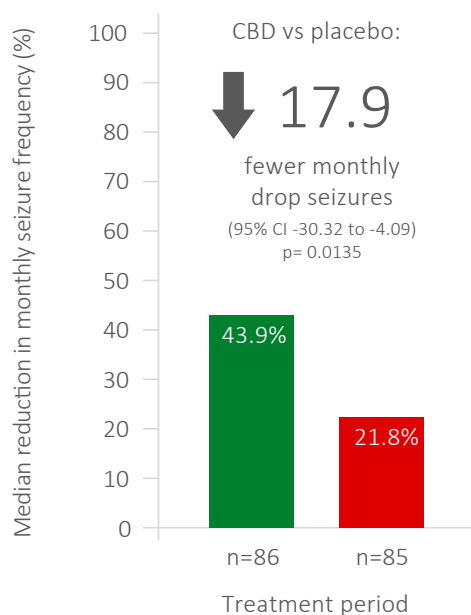
The primary endpoint was the percentage change in monthly frequency of drop seizures from baseline, measured during the 14-week treatment period.

The secondary safety endpoints included the proportion of patients with adverse events (mild, moderate, severe), cases of suicidal ideation and the frequency of episodes of status epilepticus.

## Results

**Patients treated with CBD had a median 43.9% reduction in monthly drop seizures** from baseline at 14 weeks compared to 21.8% in the placebo group (-17.21; 95% CI -30.32 to -4.09;  $p=0.0135$ ).

■ Add-on cannabidiol ■ Add-on placebo



During the 14-week treatment period, secondary outcomes in the CBD vs placebo group included:

- 44.1% vs 23.5% of patients achieving  $\geq 50\%$  reductions in the primary outcome (OR 2.57,  $p=0.0043$ )
- 41.2% vs 13.7% reduction in total monthly seizure frequency from baseline
- 58% vs 34% of patients reporting an improvement in their overall condition compared to baseline ( $p=0.0012$ )

## Safety outcomes

The safety analyses included all randomised patients who received at least one dose of the study drug.

More patients taking CBD experienced adverse events of any severity compared to placebo (86% vs 69%). **Most were mild to moderate**, were most commonly reported during the dose escalation period, and resolved with treatment.

In the CBD group:

- Common all-cause adverse events included diarrhoea, somnolence, fever, decreased appetite and vomiting
- 20 patients experienced severe adverse events
- 12 patients discontinued due to adverse events; most commonly due to transiently elevated liver enzymes
- 12 patients adjusted the dose of other antiepileptic drugs to manage adverse events
- 72/86 patients completed treatment
- The observed tolerability profile was consistent with other CBD studies in patients with severe refractory epilepsy

Status epilepticus was reported in one patient in each group; neither was considered treatment-related. No cases of study drug abuse or suicidal ideation were reported.

## Summary

This **highly treatment-resistant population** achieved **statistically significant and clinically meaningful improvements in seizure frequency** when CBD was added to their existing antiepileptic drug regimens compared with placebo.

The results establish add-on cannabidiol as **efficacious and generally well tolerated** in patients with drop seizures associated with Lennox-Gastaut syndrome. An open-label extension study is currently investigating long-term efficacy and safety.

## Declaration of interest

This study was funded by GW Pharmaceuticals (Cambridge, UK). Greenwich Biosciences (US subsidiary of GW Pharmaceuticals) also provided financial support for medical writing of the published clinical trial.

## References

Zhang, H., Xie, M., Archibald, S.D., Jackson, B.S. and Gupta, M.K., 2018. Association of marijuana use with psychosocial and quality of life outcomes among patients with head and neck cancer. *JAMA Otolaryngology – Head & Neck Surgery*, 144(11), pp.1017-1022.



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