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

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Summary

Background Patients with Lennox-Gastaut syndrome, a rare, severe form of epileptic encephalopathy, are frequently treatment resistant to available medications. No controlled studies have investigated the use of cannabidiol for patients with seizures associated with Lennox-Gastaut syndrome. We therefore assessed the efficacy and safety of cannabidiol as an add-on anticonvulsant therapy in this population of patients.

Methods In this randomised, double-blind, placebo-controlled trial done at 24 clinical sites in the USA, the Netherlands, and Poland, we investigated the efficacy of cannabidiol as add-on therapy for drop seizures in patients with treatment-resistant Lennox-Gastaut syndrome. Eligible patients (aged 2–55 years) had Lennox-Gastaut syndrome, including a history of slow (<3 Hz) spike-and-wave patterns on electroencephalogram, evidence of more than one type of generalised seizure for at least 6 months, at least two drop seizures per week during the 4-week baseline period, and had not responded to treatment with at least two antiepileptic drugs. Patients were randomly assigned (1:1) using an interactive voice response system, stratified by age group, to receive 20 mg/kg oral cannabidiol daily or matched placebo for 14 weeks. All patients, caregivers, investigators, and individuals assessing data were masked to group assignment. The primary endpoint was percentage change from baseline in monthly frequency of drop seizures during the treatment period, analysed in all patients who received at least one dose of study drug and had post-baseline efficacy data. All randomly assigned patients were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02224690.

Findings Between April 28, 2015, and Oct 15, 2015, we randomly assigned 171 patients to receive cannabidiol (n=86) or placebo (n=85). 14 patients in the cannabidiol group and one in the placebo group discontinued study treatment; all randomly assigned patients received at least one dose of study treatment and had post-baseline efficacy data. The median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannibidiol group and 21·8% (IQR −45·7 to 1·7) in the placebo group. The estimated median difference between the treatment groups was −17·21 (95% CI −30·32 to −4·09; p=0·0135) during the 14-week treatment period. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate. The most common adverse events were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. 12 (14%) patients in the cannabidiol group and one (1%) patient in the placebo group withdrew from the study because of adverse events. One patient (1%) died in the cannabidiol group, but this was considered unrelated to treatment.

Interpretation Add-on cannabidiol is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated. The long-term efficacy and safety of cannabidiol is currently being assessed in the open-label extension of this trial.

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Introduction

Lennox-Gastaut syndrome is a rare, severe form of epileptic encephalopathy with early childhood onset. The syndrome typically manifests by 8 years of age with peak incidence between age 3 and 5 years.[1] Lennox-Gastaut syndrome is characterised by the occurrence of multiple seizure types, including so-called drop attacks (ie, sudden falls due to seizures), slow spike-and-wave activity on electroencephalograms, and cognitive impairment. Lennox-Gastaut syndrome is typically a lifelong condition in which the phenotype and nature of seizures often vary with age.[2] Although 20–60% of patients with Lennox-Gastaut syndrome have delayed cognitive development at disease onset,[3] 75–95% of patients become cognitively impaired with increasing age.[3] Few robust, population-based epidemiological studies of Lennox-Gastaut syndrome have been done, but regional studies[4,5] have reported that Lennox-Gastaut syndrome accounts for 1–4% of cases of paediatric epilepsy.

The drugs approved for Lennox-Gastaut syndrome in the USA and Europe include felbamate, lamotrigine, topiramate, rufinamide, clobazam, and clonazepam.[6]

Research in context

Evidence before this study

We searched PubMed for English-language studies published between Jan 1, 1973, and June 1, 2017, using the search terms "cannabidiol" AND "(epilepsy OR seizures OR anticonvulsant)". Preclinical data have shown that cannabidiol has activity against seizures in in-vitro and in-vivo models. An open-label expanded access programme has indicated that GW Pharmaceutical's (Cambridge, UK) specific formulation of cannabidiol might be safe and efficacious in children and young adults with drug-resistant epilepsy, and results from a previous multicentre, randomised, placebo-controlled trial have suggested the formulation might also be safe and efficacious in children with Dravet syndrome.

Added value of this study

This is the first randomised, placebo-controlled trial to assess the efficacy and safety of a pharmaceutical formulation of purified cannabidiol as add-on therapy to existing antiepileptic drugs for the treatment of seizures associated with Lennox-Gastaut syndrome in children and adults.

Implications of all the available evidence

In addition to the available evidence, the results of this randomised, placebo-controlled trial suggest that the use of cannabidiol (20 mg/kg daily) as an add-on therapy for existing antiepileptic drug regimens might significantly reduce the frequency of seizures in patients with Lennox-Gastaut syndrome. The results also indicate that cannabidiol might lead to additional adverse events, but in general it appears to be well tolerated.

Although not approved for Lennox-Gastaut syndrome, valproate is also used on the basis of clinical experience and study data.[7] Hancock and Cross[8] identified nine randomised controlled trials of monotherapies for Lennox-Gastaut syndrome to assess treatment effects on specific seizure types, adverse events, and mortality. Although a meta-analysis was not possible because of different patient populations and outcome measures, the authors concluded that adjunctive therapy with felbamate, lamotrigine, topiramate, and rufinamide might be beneficial, and clobazam might be efficacious for drop seizures.[8] In a separate randomised, placebo-controlled trial of more than 200 patients, Ng and colleagues[9] showed that clobazam significantly decreased drop seizure frequency. Non-pharmacological treatments, including a ketogenic diet,[10] vagus nerve stimulation,[11,12] and surgery, including resective surgery and corpus callosotomy,[13] have been shown to be effective in some patients.[14] However, despite the number of available treatments, less than 10% of patients become seizure free with existing treatments.[15]

In comparison to approved antiepileptic drugs, cannabidol is structurally unique and has potentially novel multimodal mechanisms of action.[16,17] Preclinical data have shown cannabidiol to have activity against seizures in in-vitro and in-vivo models.[18] Results of an open-label expanded access programme[19] in 214 children and young adults suggested that cannabidiol might be safe and efficacious in patients with drug-resistant epilepsy, and results from a randomised, controlled trial[20] in 120 children indicated that cannabidiol might be safe and efficacious in Dravet syndrome. Dravet syndrome is a severe, treatment-resistant, and rare genetic epilepsy syndrome with childhood onset that is associated with life-long seizures and considerable intellectual and physical disabilities. The GWPCARE4 study was designed to assess the efficacy and safety of cannabidiol compared with placebo as add-on therapy to existing antiepileptic drugs for the treatment of seizures associated with Lennox-Gastaut syndrome in children and adults.

See Online for appendix

Methods

Study design and patients

We did a randomised, double-blind, placebo-controlled, phase 3 trial at 24 clinical sites in the USA (n=17), the Netherlands (n=1), and Poland (n=6). Eligible patients were aged between 2 and 55 years, with a clinical diagnosis of Lennox-Gastaut syndrome (including documented history of slow [<3·0 Hz] spike-and-wave electroencephalograms), and evidence of more than one type of generalised seizure, including drop seizures, for at least 6 months. The definition of Lennox-Gastaut syndrome chosen for this trial was the same as has been used in other multicentre trials.[9,21] Patients who were refractory (ie, inadequately managed on at least two antiepileptic drugs, inclusive of previous and current treatments), were taking one to four antiepileptic drugs, and had at least two drop seizures per week during the 4-week baseline period were eligible. Patients in whom all medications and interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) were stable for 4 weeks before screening were included. Patients who had a clinically significant unstable illness (other than epilepsy) in the 4 weeks before screening or randomisation, had a history of alcohol or substance misuse, were recreational or medicinal cannabis users, had taken corticotrophins in the previous 6 months, or who had been taking felbamate for less than 1 year before screening were excluded. Patients with a positive urine tetrahydrocannabinol screen at the beginning of the study, and female patients who were pregnant, lactating, or planning pregnancy during or within 3 months of completing the trial were also ineligible.

The study protocol (appendix) was approved by the institutional review board or independent ethics committee

for each study site. The study was done in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. All patients or their caregivers were required to provide written informed consent before enrolment.

Randomisation and masking

Following a 4-week screening period, patients with Lennox-Gastaut syndrome who were eligible for the study were randomly assigned to receive a pharmaceutical formulation of purified cannabidiol or matching placebo solution in addition to existing medications. At visit 1, each patient was assigned a unique number via an interactive voice response system (IVRS) and then at visit 2 the IVRS was used to randomly assign eligible participants to treatment in a 1:1 ratio. The randomisation schedule was produced by an independent statistician, and was stratified by age group (2–5, 6–11, 12–17, and 18–55 years). Both cannabidiol and placebo were provided in identical 100 mL amber glass bottles and could not be distinguished visually. GW Pharmaceuticals manufactured and supplied the study drug. All patients, caregivers, investigators, and individuals assessing data were masked to group assignment.

Procedures

All patients received treatment for 14 weeks, which included 2 weeks of dose escalation (starting at a daily dose of 2·5 mg/kg, followed by 12 weeks of stable dosing [maintenance]), a tapering period of up to 10 days, and a 4-week safety follow-up period (appendix).

Patients received 20 mg/kg of a pharmaceutical formulation of purified cannabidiol (100 mg/mL, GW Pharmaceuticals (Cambridge, UK) in oral solution daily, or matching placebo solution. Cannabidiol or placebo was administered orally in two equally divided doses (morning and evening) for 14 weeks. The 20 mg/kg dose of cannabidiol was approved by an independent data safety monitoring committee (DSMC), who reviewed data from a dose-ranging safety and pharmacokinetic evaluation[22] of three doses of cannabidiol (5, 10, and 20 mg/kg daily) in Dravet syndrome and identified 20 mg/kg per day as a safe dose without unacceptable side-effects.

Following randomisation (day 1), patients were assessed in the clinic on days 15, 29, 57, and 99, and by telephone on days 43 and 71 (appendix). Full details of the assessment and procedures at each trial visit are available in the study protocol (appendix).

Patients or caregivers recorded the number and type of seizures, including drop seizures, each day using an IVRS. Patients or caregivers recorded information on study drug use (ie, cannabidiol or placebo), concomitant medications, and adverse events in a paper diary.

Patients who completed treatment were eligible to enrol in an open-label extension trial (NCT02224573). A data safety monitoring committee was used to monitor ongoing patient safety during the trial and an adjudication board was used to determine any potential signals of abuse or misuse of the study drug.

Outcomes

The primary endpoint was the percentage change in monthly frequency of drop seizures from baseline, measured during the 14-week treatment period. For group analyses, we intended to use the mean to assess percentage change in seizures, unless the data were non-normally distributed. Data were subsequently shown to be non-normally distributed and therefore non-parametric analyses using median were used; the parametric analyses were still done, but as sensitivity analyses.

1 month was defined as 28 days. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic-clonic) 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. The functional definition of drop seizure used in this trial was reviewed and approved by the US Food and Drug Administration, the European Medicines Agency, and an independent committee of experts from the Epilepsy Study Consortium, and was similar to that used in a previous clobazam trial.[9] All seizure types or descriptions given by each patient were confirmed by the Epilepsy Study Consortium.

The key secondary endpoints were the proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of drop seizures, percentage change in total seizure frequency from baseline during the treatment period (ie, sum of all individual seizure subtypes reported), and change from baseline in patient and caregiver global impression of change (GIC) at the end of treatment.

Other secondary endpoints included a responder analysis (ie, the proportion of patients who achieved a ≥25%, ≥50%, ≥75%, or 100% reduction in drop seizures from baseline) and percentage change in the frequency of non-drop, convulsive (tonic-clonic, tonic, clonic, or atonic seizures), non-convulsive (myoclonic, countable focal, other focal, or absence seizures), and individual seizure types. We also assessed patient and caregiver GIC in seizure duration, and change in sleep disruption and daytime sleepiness, quality of life, and adaptive behaviours. The number of hospital admissions due to epilepsy were recorded, and cognitive function was assessed during the trial.

Secondary safety endpoints included the proportion of patients with adverse events measured by the investigators using standard severity measures (ie, mild, moderate, or severe), Columbia Suicide Severity Rating Scale (C-SSRS) scores, and frequency of episodes of status epilepticus.

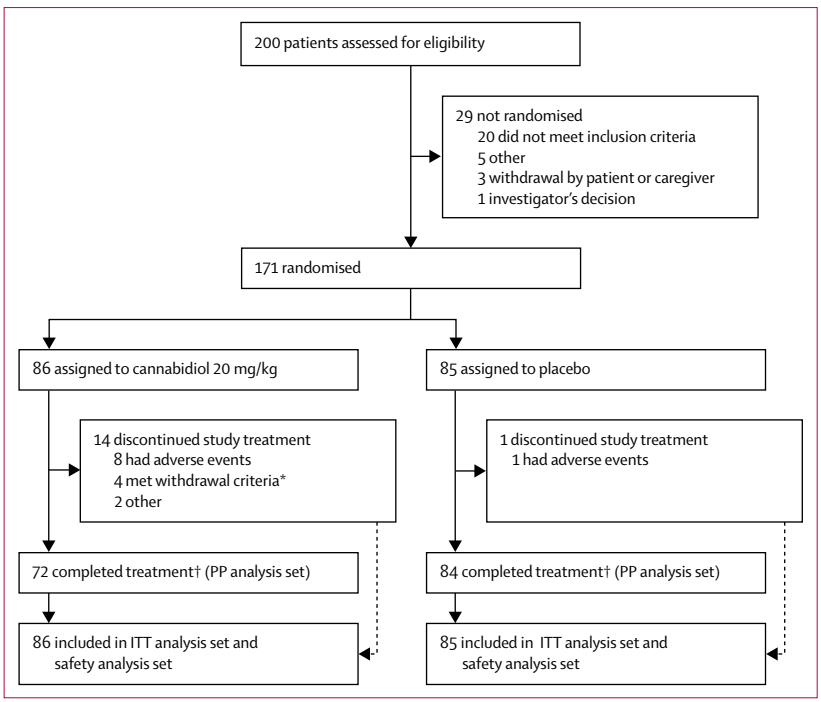

Figure 1: **Trial profile**
PP=per-protocol. ITT=intention-to-treat. *Three of the patients who met withdrawal criteria had elevations in liver transaminases that were considered adverse events. One patient who withdrew for other reasons had a viral infection that was considered an adverse event. †72 patients in the cannabidiol group and 84 in the placebo group were enrolled in the open-label extension trial.

Statistical analysis

On the basis of the reduction in seizure frequency reported for patients on placebo in the literature,[9,23] and considering the additional placebo effect from the expectation of cannabidiol, we hypothesised that the placebo group would have a mean percentage reduction in monthly frequency of drop seizures from baseline of 18%. Thus, a sample size of 100 patients (50 per group) was calculated to provide 80% power with a two-tailed significance level of 0·05.

The primary endpoint was analysed in the intention-to-treat analysis dataset, which included all randomly assigned patients who received at least one dose of cannabidiol or placebo and had post-baseline efficacy data. Secondary endpoints were also analysed in the intention-to-treat dataset, apart from seizure reduction during the maintenance period and patient or caregiver GIC, which were analysed in all patients who had post-baseline efficacy data for those endpoints.

Analyses using the per-protocol analysis set were additionally performed for the primary and key secondary endpoints only. Because the seizure data had a non-normal distribution, non-parametric statistical tests were used for all analyses of the percentage change in seizure frequency. The safety analyses included all randomised patients who received at least one dose of the study drug.

The primary endpoint was assessed using a Wilcoxon rank-sum test, and the estimated median difference (with 95% CI) between the cannabidiol and placebo groups was compared using the Hodges-Lehmann method. Prespecified sensitivity analyses of the primary endpoint included repeat analysis using the per-protocol analysis set, analysis over the maintenance period alone and during weeks 1–4, 5–8, and 9–12 separately, analyses accounting for missing values with alternative methods, and parametric analyses.

According to our statistical analysis plan, if the primary endpoint was met (ie, statistical significance was reached), the key secondary endpoints were to be tested in the following hierarchical order, whereby each successive endpoint was only tested if the previous test identified a statistically significant difference. The proportion of patients who achieved a reduction in drop seizure frequency of 50% or more was compared between treatment groups using the Cochran-Mantel-Haenszel test, which was expressed as an odds ratio (OR) with 95% CI, stratified by the age groups used for randomisation. The percentage change in total seizure frequency from baseline during the treatment period was analysed as per the primary endpoint assessed using a Wilcoxon rank-sum test, and the median difference (with 95% CI) between the treatment groups was compared using the Hodges-Lehmann method. The change from baseline in patient and caregiver GIC scores was compared between the groups using an ordinal logistic regression model (ordinal values ranged from 7–1 [7=very much worse, 1=very much improved]). SAS software (version 9.3) was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT02224690.

Role of the funding source

The funder was responsible for the study design (following input from investigators and other experts), management, monitoring, pharmacovigilance, statistical and data analysis, and supply of the investigational medicinal products. The trial protocol and procedures were reviewed before the start of the trial at investigator meetings. Third party services were used for clinical laboratory analyses (ACM Global Central Laboratory [York, UK; Rochester, NY, USA]) and bioanalytical laboratory analyses (LGC [Teddington, UK]; Covance Laboratories [Maidenhead, UK]), design of case report forms and data management (Quanticate [Hitchin, UK]), distribution (Catalent Pharma Solutions [Morrisville, NC, USA]), return (Danox Environmental Services (Cumming, GA, USA), and destruction (KATO Labs [Warsaw, Poland]) of investigational medicinal products, supply of the IVRS (Perceptive eClinical [Basingstoke, UK]), seizure type classification (DSMC; The Epilepsy Study Consortium [Herndon, VA, USA]), and translation of documents (Wessex Translations [Romsey, UK]). The funder was involved in data collection, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 28, 2015, and Oct 15, 2015, 200 patients were screened for eligibility, of whom 171 were randomly assigned to receive add-on cannabidiol (n=86) or add-on placebo (n=85; figure 1) at 24 study sites. The proportion of patients who were ineligible after screening was half of what was expected. Additionally, after notification of pending recruitment closure to sites, the number of patients referred for screening increased. These two factors contributed to more patients being randomised than originally planned. 14 patients in the cannabidiol group and one in the placebo group withdrew from the trial; in nine (60%) of these patients, adverse events were the primary reason for study discontinuation.

All 15 patients who withdrew early from the trial were excluded from the per-protocol analysis set (used in sensitivity analyses). Of the 156 patients who completed the trial, all entered the open-label extension study (figure 1).

Patient demographics and baseline characteristics were similar across the two treatment groups (table 1). The study population was mostly white and from the USA, with similar numbers of female and male patients. The mean age of patients was 15·4 years (SD 9·2). At baseline patients had previously tried, and stopped taking, a median of six antiepileptic drugs (IQR 3–9; range 0–28) and took a median of three concomitant antiepileptic drugs (IQR 2–4; range 1–5) during the trial; the most common were clobazam, valproate, and lamotrigine. The median monthly frequency of drop seizures in all patients was 73·8 (IQR 32·0–148·0).

In the cannabidiol group, the monthly frequency of drop seizures decreased by a median of 43·9% (IQR –69·6 to –1·9) from baseline (figure 2) over the 14-week treatment period (from a median of 71·4 drop seizures per patient per month at baseline [IQR 27·0 to 156·0] to 31·4 [14·4 to 92·0]). In the placebo group, the monthly frequency of drop seizures decreased by a median of 21·8% (IQR –45·7 to 1·7) from baseline (figure 2) over the 14-week treatment period (from a median of 74·7 drop seizures per patient per month at baseline [IQR 47·3 to 144·0] to 56·3 [29·7 to 129·3]). The estimated median difference between the treatment groups was –17·21 (95% CI –30·32 to –4·09; p=0·0135) during the 14-week treatment period and –19·45 (–33·05 to –4·68; p=0·0096) during the 12-week maintenance period alone (figure 2).

Because the primary endpoint reached statistical significance, formal statistical analysis of the key secondary endpoints was permitted. We analysed all three key secondary endpoints in accordance with the hierarchical gate-keeping procedure outlined in the statistical analysis plan.

38 (44%) of 86 patients in the cannabidiol group had a reduction in drop seizure frequency of 50% or more from baseline during the treatment period compared with 20 (24%) of 85 patients in the placebo group (OR 2·57, 95% CI 1·33–4·97; p=0·0043; figure 3).

	Cannabidiol (n=86)	Placebo (n=85)
Age (years)		
Mean (SD)	15·5 (8·7)	15·3 (9·8)
Median (range)	14·2 (2·7–39·0)	13·3 (2·8–45·1)
Age group (years)		
2–5	11 (13%)	12 (14%)
6–11	26 (30%)	27 (32%)
12–17	19 (22%)	18 (21%)
18–55	30 (35%)	28 (33%)
Sex		
Female	41 (48%)	42 (49%)
Male	45 (52%)	43 (51%)
Race		
White	75 (87%)	79 (93%)
Other*	11 (13%)	6 (7%)
Region		
USA	62 (72%)	66 (78%)
Rest of world	24 (28%)	19 (22%)
AED status		
Previous AEDs per patient†	6 (1–18)	6 (0–28)
Concomitant AEDs per patient†	3 (1–5)	3 (1–4)
Current AEDs		
Clobazam	41 (48%)	43 (51%)
Valproate (all forms)	36 (42%)	33 (39%)
Lamotrigine	33 (38%)	31 (36%)
Levetiracetam	24 (28%)	34 (40%)
Rufinamide	24 (28%)	22 (26%)
Other concomitant interventions		
Ketogenic diet	4 (5%)	10 (12%)
Vagus nerve stimulation	26 (30%)	25 (29%)
Monthly frequency of seizures at baseline		
Drop seizures	71·4 (27·0–156·0)	74·7 (47·3–144·0)
Total seizures	144·6 (72·0–385·7)	176·7 (68·6–359·5)
Non-drop seizures	94·0 (19·8–311·0)‡	85·0 (20·5–220·0)§

Data are n (%), mean (SD), or median (IQR). AED=antiepileptic drug. *Includes patients who identified as black or African American, Asian, Hispanic, Latino, and Arabian. †One patient was reported as having no previous treatment with AEDs and current treatment with four AEDs, and seven patients were reported as having previous treatment with one AED and current treatment with one or more AEDs; all other patients were reported as having previous treatment with two or more AEDs. All patients met the International League Against Epilepsy definition of refractory Lennox-Gastaut syndrome (ie, inadequately managed on two or more AEDs). ‡n=77. §n=79.

Table 1: **Patient demographics and baseline characteristics**

Additionally, significantly more patients in the cannabidiol group than the placebo group achieved reductions of 25% or more or 75% or more in monthly frequency of drop seizures from baseline during the treatment and maintenance periods (figure 3). None of the patients were free of drop seizures throughout the entire 14-week treatment period, but three patients in the cannabidiol group who completed treatment were drop seizure free throughout the 12-week maintenance period (day 15 onwards); their monthly frequency of drop

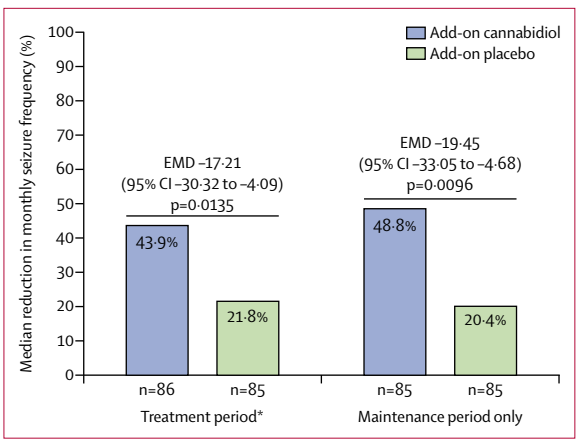

Figure 2: **Reduction in drop seizure frequency during the treatment and maintenance period**

Median percentage reduction in monthly drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference. *Primary endpoint.

seizures at baseline ranged from 15·6 to 99·2. Two additional patients in the cannabidiol group were seizure free during the maintenance period, but they did not complete the trial; one withdrew due to serious adverse events and the other was withdrawn because they required the drug to be administered via gastric tube. No patients in the placebo group were free of drop seizures throughout the 12-week maintenance period.

In the cannabidiol group, monthly frequency of total seizures decreased by a median of 41·2% (IQR –62·9 to –13·0) from baseline over the 14-week treatment period (from a median of 144·6 to 83·8 seizures per month). In the placebo group, monthly frequency of total seizures decreased by a median of 13·7% from baseline (IQR –45·0 to 7·3) over the 14-week treatment period (from a median of 176·7 to 128·7 seizures per month). The estimated median difference was –21·1 (95% CI –33·3 to –9·4; p=0·0005) during the treatment period and –23·3 (95% CI –36·3 to –10·5; p=0·0004) during the 12-week maintenance period (figure 4).

At their last visit to the clinic, patients in the cannabidiol group or their caregivers were significantly more likely than patients in the placebo group or their caregivers to report an improvement in the patient's overall condition compared with baseline, measured using the patient and caregiver GIC scale (OR 2·54, 95% CI 1·5–4·5; p=0·0012; figure 5). 49 (58%) of 84 patients in the cannabidiol group reported an improvement in their overall condition (ie, a score of 1, 2, or 3) compared with 29 (34%) of 85 patients in the placebo group, with three times as many patients in the cannabidiol group than the placebo group reporting their overall condition as very much improved (15 [18%] patients *vs* five [6%] patients; figure 5).

Similar to the results observed for drop and total seizures, cannabidiol significantly reduced median monthly non-drop seizure frequency by 49·4% (IQR –81·6 to –25·3; from a median of 94·0 [19·8–311·0] to 39·4 [4·7–136·2]) compared with 22·9% (IQR –67·8 to 31·7; from a median of 85·0 [20·5–220·0] to 57·7 [11·3–186·4]) in the placebo group (figure 4). The estimated median difference was –26·1 (95% CI –46·1 to –8·3; p=0·0044) during the treatment period and –31·0% (95% CI –52·0 to –10·4; p=0·0008) during the 12-week maintenance period (figure 4). Analyses for the other secondary endpoints are presented in the appendix, with the exception of the Cannabis Withdrawal Scale, number of hospital admissions, and cognitive function, for which insufficient data was collected.

Safety analyses were done in 86 patients in the cannabidiol group and 85 patients in the placebo group. All-cause adverse events of any severity were reported in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group. All adverse events are listed in the appendix. 58 (78%) of 74 patients in the cannabidiol group and 57 (97%) of 59 patients in the placebo group reported adverse events that were mild or moderate in severity. The first occurrence of an adverse event was most commonly reported during the 2-week dose escalation period in both treatment groups (42 [57%] of 74 patients in the cannabidiol group *vs* 33 [56%] of 59 patients in the placebo group). In the cannabidiol group, 53 (62%) of 86 patients had treatment-related adverse events compared with 29 (34%) of 85 patients in the placebo group. Common adverse events (occurring in more than 10% of patients) in the cannabidiol group were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting (table 2). Of the patients who had all-cause adverse events, the events resolved by the end of the trial in 45 (61%) patients in the cannabidiol group and 38 (64%) patients in the placebo group.

Adverse events led to study withdrawal in 12 (14%) of 86 patients in the cannabidiol group and one (1%) of 85 patients in the placebo group. The most common treatment-related adverse events leading to withdrawal were collectively reported in three patients and comprised increased alanine aminotransferase concentrations (all three patients), increased aspartate aminotransferase concentrations (all three patients), and increased γ-glutamyltransferase concentrations (two patients). One additional patient in the cannabidiol group was withdrawn due to treatment-related alanine aminotransferase and aspartate aminotransferase elevations, defined using a different Medical Dictionary for Regulatory Activities preferred term (transaminases increased). All other adverse events leading to discontinuation, which occurred in no more than one patient each in the cannabidiol group, included diarrhoea, vomiting, acute hepatic failure, hepatic failure, viral infection, increased concentration of another antiepileptic drug in the blood, convulsion, lethargy, restlessness, acute respiratory distress syndrome, acute respiratory failure, hypercapnia, hypoxia, pneumonia aspiration, and

rash. The two cases in the cannabidiol group reported as hepatic failure did not meet diagnostic criteria for hepatic failure or Hy's law criteria for severe liver injury because the events were without elevations in bilirubin,[24] and patients had complete recovery. One patient in the cannabidiol group died due to respiratory failure, which was considered unrelated to treatment. One patient in the placebo group withdrew due to monoplegia that was considered treatment related. Six (7%) of 86 patients in the cannabidiol group and one (1%) of 85 in the placebo group had adverse events that led to a dose reduction of the investigational medicinal product; the most common events were vomiting (two patients in the cannabidiol group *vs* one in the placebo group) and sedation (two patients in the cannabidiol group). All but two events (aggression [one in the cannabidiol group] and vomiting [one in the placebo group]) resolved after dose reduction.

Serious adverse events were reported in 20 (23%) of 86 patients in the cannabidiol group and four (5%) of 85 in the placebo group. Two patients in the cannabidiol group had serious adverse events that were ongoing at the end of the trial: one patient died due to acute respiratory distress syndrome, as previously described, and one patient had ongoing sleep apnoea (considered treatment related) and status epilepticus (not considered treatment related). Status epilepticus was not reported as an adverse event or serious adverse event in any other patients in the cannabidiol group, but was reported as an adverse event in one patient in the placebo group (not considered treatment related).

The most common serious treatment-related adverse events (occurring in >3% of patients) were collectively reported in four patients in the cannabidiol group and comprised increased alanine aminotransferase concentration (all four patients), increased aspartate aminotransferase concentrations (all four patients), and increased γ-glutamyltransferase concentrations (three patients). Additionally, pneumonia and acute respiratory failure were reported in two patients in the cannabidiol group on clobazam, pneumonia alone was reported in three patients in the cannabidiol group (all but one on clobazam) and one placebo patient on clobazam, and acute respiratory failure alone was reported in one cannabidiol patient on clobazam. Only the serious adverse event that occurred in the placebo patient was considered treatment related.

Increases in alanine aminotransferase or aspartate aminotransferase (>three times the upper limit of normal), irrespective of whether they were reported as adverse events, occurred in one patient in the placebo group and 20 patients in the cannabidiol group; 16 of these patients in the cannabidiol group were on concomitant valproate. No patients met standard criteria for drug-induced severe liver injury (Hy's law). Six patients in the cannabidiol group withdrew from treatment because of adverse events associated with increases in alanine or aspartate aminotransferase concentrations. A seventh patient met criteria for withdrawal (alanine aminotransferase concentrations >three times the upper limit of normal, with fatigue and vomiting) but was discontinued for non-compliance. All elevations in alanine or aspartate aminotransferases resolved either spontaneously during treatment (eight patients in the cannabidiol group *vs* one in the placebo group), after a reduction in concomitant valproate dose (three patients in the cannabidiol group), after tapering or cessation of cannabidiol (six patients in the cannabidiol group), or after entry into the open-label extension trial (three patients in the cannabidiol group).

80 (93%) of 86 patients in the cannabidiol group and 81 (95%) of 85 patients in the placebo group were on multiple concomitant antiepileptic drugs. Concomitant antiepileptic drug doses were adjusted during the trial for 20 (23%) of 86 patients in the cannabidiol group and eight (9%) of 85 patients in the placebo group. Doses were changed in response to adverse events for 12 patients in

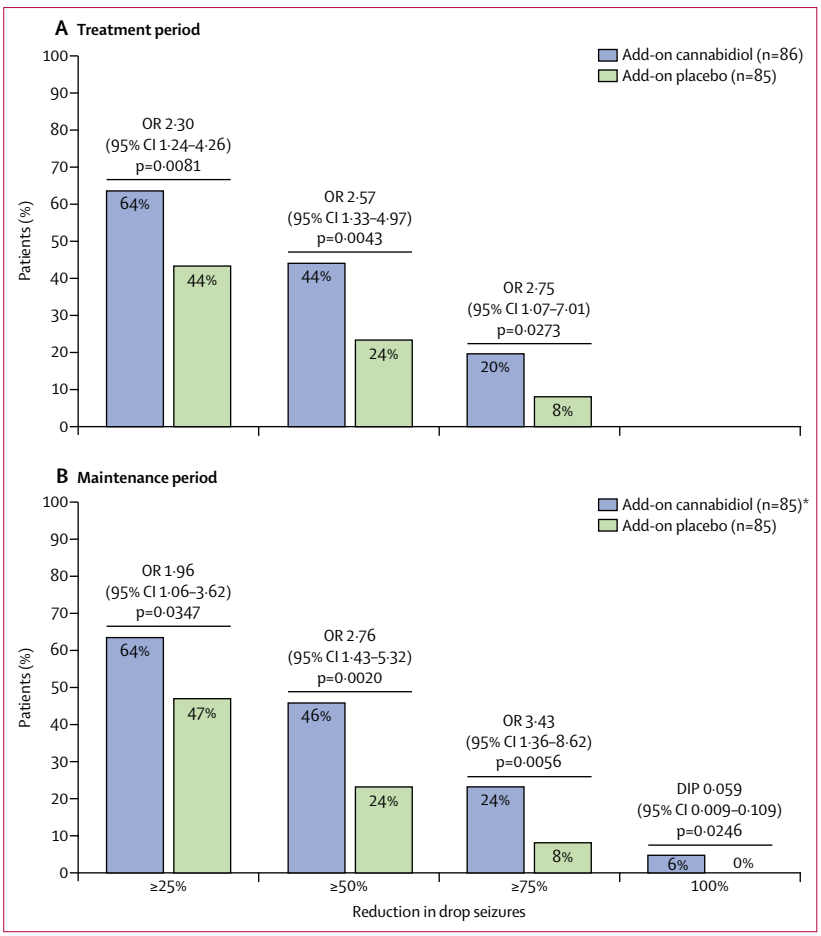

Figure 3: **Patients who responded to treatment as measured by reduction in drop seizures**
The proportion of patients who had a reduction in drop seizure frequency of 25% or more, 50% or more, 75% or more, or 100% during the treatment period (A) and the maintenance period alone (B). Because no patients in the placebo group were free of drop seizures during the maintenance period, DIP was used to analyse the difference between groups. Of the five patients in the cannabidiol group who were free of drop seizures during the maintenance period, three patients completed the trial. OR=odds ratio. DIP=difference in proportions. *One patient in the cannabidiol group did not reach the maintenance phase.

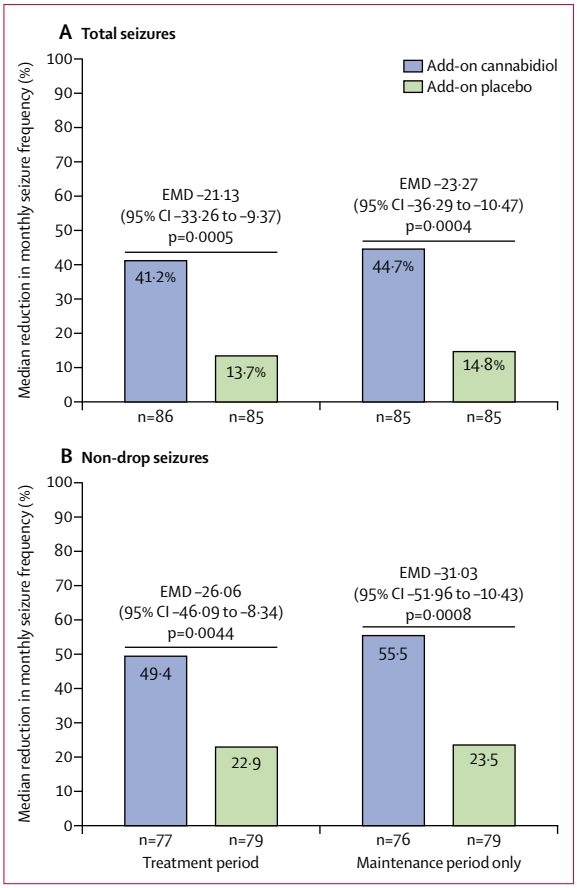

Figure 4: **Reduction in seizure frequency during the treatment and maintenance period**

Median percentage reduction in monthly (A) total seizures and (B) non-drop seizures during the 14-week treatment period (2 weeks of dose escalation plus 12-week maintenance period alone) in cannabidiol and placebo treatment groups. EMD=estimated median difference.

the cannabidiol group and three in the placebo group. A higher occurrence of somnolence was observed in patients on antiepileptic drug regimens that included clobazam than those that did not include clobazam for both the cannabidiol (nine [22%] of 41 patients *vs* four [9%] of 45 patients) and placebo (seven [16%] of 43 patients *vs* one [2%] of 42 patients) groups. Of the patients on clobazam during the trial, clobazam dose was reduced in 11 (27%) of 41 patients in the cannabidiol group, and four (9%) of 43 patients in the placebo group. Of the 14 patients in the cannabidiol group who discontinued the trial, eight were on clobazam. In the cannabidiol group, a higher incidence of elevated transaminases was observed in patients on antiepileptic drug regimens that included valproate than those that did not (19% *vs* 5%).

No cases of study drug abuse or misuse (ie, triggering adverse events of interest) occurred. No cases of suicidal ideation were reported, as measured on the C-SSRS (data not shown), although the applicability of the C-SSRS to this population is unclear because most patients had cognitive impairment.

Sensitivity analyses confirmed that the treatment effect of cannabidiol on the primary endpoint was established during the first 4 weeks of the maintenance period and was maintained during the full treatment period. Of the 14 sensitivity analyses done, all except the analysis using ANCOVA showed statistically significant treatment differences in favour of cannabidiol; however, ANCOVA is not considered appropriate for non-normally distributed data (figure 6). Sensitivity analyses of the three key secondary endpoints also showed significant treatment differences in favour of cannabidiol (appendix).

Discussion

This is the first randomised, double-blind trial to assess the efficacy and safety of cannabidiol as add-on anticonvulsant therapy for patients with Lennox-Gastaut syndrome. Patients in this study were highly treatment resistant; at baseline, they had previously not responded to a median of six antiepileptic drugs, were taking a median of three concomitant antiepileptic drugs, and had a median of 73·8 drop seizures every 28 days. The urgent need for novel treatment options for patients with Lennox-Gastaut syndrome was reinforced by the rapid patient recruitment and low dropout rates.

Even in this highly treatment-resistant population, statistically significant and clinically meaningful improvements in seizure frequency were observed following the addition of cannabidiol to existing antiepileptic drug regimens compared with placebo. The percentage reduction in the monthly frequency of drop seizures during the 14-week treatment period was significantly higher for the cannabidiol group than the placebo group. Moreover, the treatment effect of cannabidiol was established early—during the first 4 weeks of the maintenance period—and was maintained for the full treatment period.

Significantly higher percentages of patients in the cannabidiol group achieved 25% or more, 50% or more, and 75% or more reductions in monthly frequency of drop seizures compared with patients in the placebo group. Although no patients were free of drop seizures throughout the whole 14-week treatment period, three patients in the treated cannabidiol group who completed the trial were free of drop seizures during the entire 12-week maintenance period. Similarly, treatment with cannabidiol significantly reduced the median frequency of total seizures and non-drop seizures during the 14-week treatment period compared with placebo, suggesting that add-on cannabidiol might have broad spectrum effects on seizure reduction. Sensitivity analyses of these endpoints confirmed conclusions from our data were robust.

Results from the patient and caregiver GIC questionnaire showed that a significantly higher proportion of patients and caregivers in the cannabidiol group than patients and caregivers in the placebo group perceived the patients' condition to have improved; three times as many patients in the cannabidiol group reported that their overall condition was very much improved. These

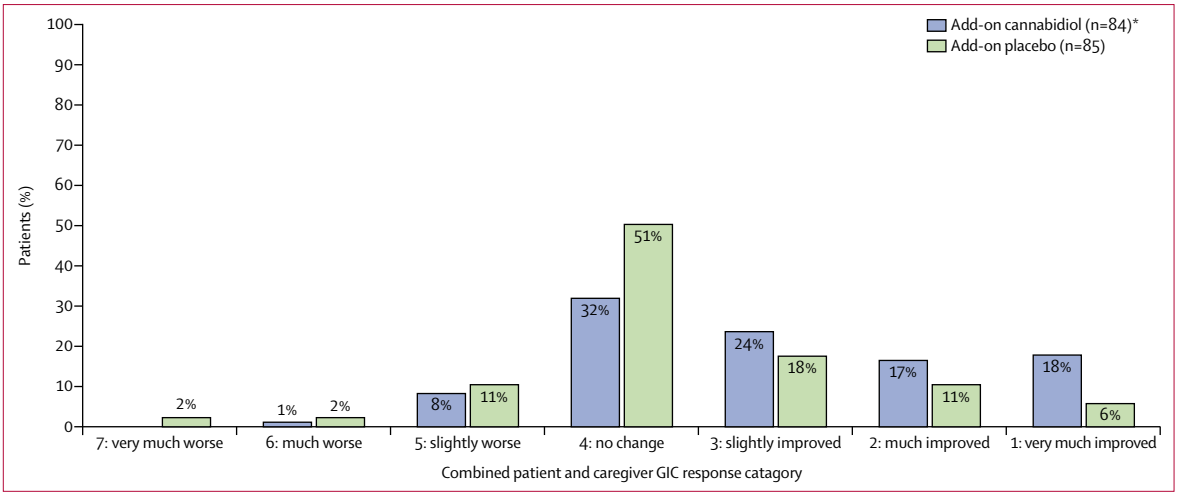

Figure 5: **Patient and caregiver GIC scores**
For the ordinal logistic regression analysis, scores ranged from 7–1 (7=very much worse, 1=very much improved). If both caregiver GIC and patient GIC questionnaires were completed, the caregiver GIC score was used. If only the caregiver GIC was completed, the caregiver GIC was used, and if only the patient GIC was completed, the patient GIC was used. GIC=global impression of change. *The questionnaire was not completed for two patients in the cannabidiol group.

results suggest that treatment with cannabidiol has an overall positive effect in this patient population. The high rate of enrolment into the open-label extension trial further reinforces the perception of improvement in seizure frequency held by patients and caregivers.

Most patients reported mild to moderate adverse events during the trial, with higher proportions of adverse events and serious adverse events considered to be treatment related in the cannabidiol group than the placebo group. The most frequent adverse events leading to withdrawal from the trial were transient elevations in liver enzymes. For 61% of patients in the cannabidiol group and 64% in the placebo group, adverse events resolved during the trial. The observed tolerability profile for cannabidiol was consistent with that reported in a previous open-label, investigator led trial[19] in patients with severe refractory epilepsy. No adverse events related to so-called stoned-like effects were reported in the trial, which is consistent with a previous trial[25] assessing cannabidiol abuse liability in people who smoke marijuana. The proportion of patients who withdrew due to adverse events were similar or lower than those associated with the use of other antiepileptic drugs.[9,26]

Although some transaminase elevations were observed, patients recovered, and none of the elevations suggested lasting liver damage because concomitant increases in bilirubin concentration were not observed. Of the 20 patients in the cannabidiol group who had elevations, 16 were also taking valproate. The elevations tended to appear early in treatment and reversed spontaneously or following dose reduction or discontinuation of valproate or cannabidiol. Because 16 of the 36 patients on valproate had transaminase elevations, it would be prudent for clinicians to monitor transaminases in all patients taking concomitant cannabidiol and valproate. Overall, cannabidiol was well

	Cannabidiol (n=86)		Placebo (n=85)	
	All cause	Treatment related	All cause	Treatment related
Diarrhoea				
Mild	12 (14%)	9 (10%)	6 (7%)	3 (4%)
Moderate	3 (3%)	2 (2%)	1 (1%)	0
Severe	1 (1%)	0	0	0
All	16 (19%)	11 (13%)	7 (8%)	3 (4%)
Somnolence*				
Mild	5 (6%)	5 (6%)	5 (6%)	4 (5%)
Moderate	8 (9%)	7 (8%)	3 (4%)	3 (4%)
All	13 (15%)	12 (14%)	8 (9%)	7 (8%)
Pyrexia				
Mild	7 (8%)	0	5 (6%)	1 (1%)
Moderate	4 (5%)	1 (1%)	2 (2%)	0
All	11 (13%)	1 (1%)	7 (8%)	1 (1%)
Decreased appetite				
Mild	7 (8%)	5 (6%)	1 (1%)	0
Moderate	3 (3%)	2 (2%)	1 (1%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	11 (13%)	8 (9%)	2 (2%)	1 (1%)
Vomiting				
Mild	3 (3%)	3 (3%)	9 (11%)	3 (4%)
Moderate	5 (6%)	2 (2%)	5 (6%)	1 (1%)
Severe	1 (1%)	1 (1%)	0	0
All	9 (10%)	6 (7%)	14 (16%)	4 (5%)

Data are n (%). The most common adverse events, defined using Medical Dictionary for Regulatory Activities preferred terms, were events that occurred in more than 10% of patients. Event names were defined according to the Medical Dictionary for Regulatory Activities. *Nine (69%) of 13 patients in the cannabidiol group and seven (88%) of eight patients in the placebo group with somnolence were taking concomitant clobazam.

Table 2: **Most common adverse events**

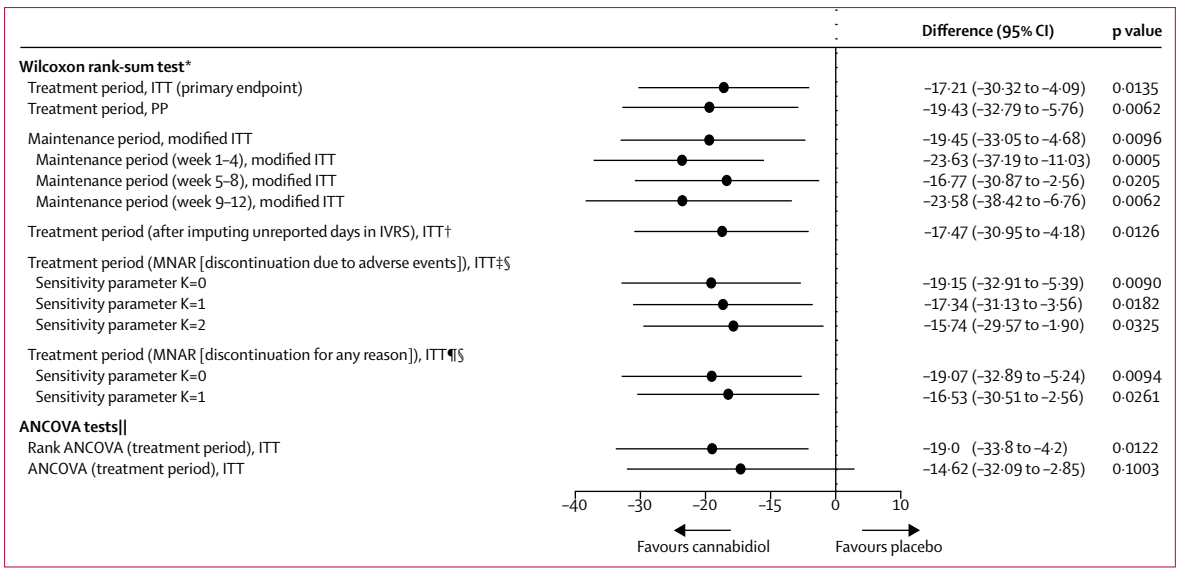

Figure 6: **Sensitivity analyses of the primary endpoint**

ITT=intention to treat. PP=per protocol. IVRS=interactive voice response system. MNAR=missing not at random. *Hodges–Lehmann median difference and 95% CI and the p value from the Wilcoxon rank-sum test are presented for the Wilcoxon rank-sum test analyses. †Missing data from the treatment period (ie, unreported days in the IVRS) were imputed using the highest number of seizures from the following for each patient: last observation carried forward, next observation carried backward, and the mean daily number of seizures during the treatment period (using non-missing data). ‡Multiple imputation assuming MNAR for missing values for discontinuation due to adverse events in the cannabidiol group. §Sensitivity parameter represents the extent of decrease (positive *k* values) or increase (negative k values) in efficacy. The increment in the positive k value continues until the overall p value is higher than 0·05. The decrease in the negative k value continues until the overall p value becomes smaller than the p value from the primary efficacy analysis. ¶Multiple imputation assuming MNAR for missing values for either discontinuation for any reason, or any other monotone missing data in the cannabidiol group. ||The difference in least squares means, 95% CI, and p value for the difference are presented for the ANCOVA analyses. All ANCOVA analyses used baseline monthly drop seizure frequency and age group (2–5, 6–11, 12–17, and 18–55 years) as covariates and treatment as a fixed factor. Log-transformed ANCOVA was also performed; the results were in favour of cannabidiol (treatment ratio 0·69, 95% CI 0·54–0·87; p=0·0024).

tolerated by patients during the course of treatment in this study.

Of the cases of pneumonia and respiratory failure in the cannabidiol group, none were considered treatment related, and all but one of the patients in the cannabidiol group were on concomitant clobazam. The prescribing information for clobazam indicates pneumonia as a common adverse reaction, and profound sedation and respiratory depression can occur with concomitant use of benzodiazepines and opioids.[27] Cannabidiol is known to increase concentrations of N-desmethylclobazam—clobazam's active metabolite—with both anticonvulsant and side-effects (eg, somnolence) via inhibition of CYP2C19.[22,28] Thus, some adverse events could be caused by, at least in part, increased concentrations of N-desmethylclobazam. Clinicians might choose to observe patients on concomitant clobazam and adjust doses as necessary to manage adverse events; during this trial clobazam dose was decreased in 27% of patients in the cannabidiol group.

Although this is the first randomised, controlled, clinical trial of add-on cannabidiol in Lennox-Gastaut syndrome, this pharmaceutical formulation of purified cannabidiol has been investigated previously in an open-label, multicentre expanded access programme[19] in patients with epilepsy. The subset of patients with Lennox-Gastaut syndrome (n=30) in the study had a 36·8% median reduction in motor seizures (primary endpoint), similar to the 43·9% reduction in drop seizures observed in the current trial, suggesting that the treatment effect with this formulation of cannabidiol is likely to be consistent across different settings.

Our trial is not without limitations. Cannabidiol was used as add-on therapy to conventional antiepileptic drugs, with most patients taking multiple medications, thus the potential for drug–drug interactions and the subsequent effect on safety and efficacy should be explored further. In particular, the potential interactions with valproate and clobazam require additional investigation. Additionally, only a single dose of cannabidiol was tested in this trial; dose–response effects will be assessed further in the GWPCARE3 study (NCT02224560). The use of various scales such as the C-SSRS in patients with mental disabilities might represent another limitation. The ethnic diversity in this trial was poor (90% of patients were white), which is likely to reflect the demographics of the included study sites. Furthermore, the long-term efficacy and safety of cannabidiol should be assessed in the ongoing open-label extension of this trial and using real-world data, once available.

In this randomised, placebo-controlled trial, a 20 mg/kg daily dose of cannabidiol as add-on therapy to existing antiepileptic drugs significantly reduced the frequency of drop, non-drop, and total seizures in highly

treatment-resistant patients with Lennox-Gastaut syndrome, with a small number of patients becoming free of drop seizures during the entire 12-week maintenance period. The treatment effect was established early, during the first 4 weeks of the maintenance period, and was maintained throughout treatment. Add-on cannabidiol was generally well tolerated in this population, and although cannabidiol was associated with more adverse events than placebo, most events were mild or moderate, resolved on treatment, and were consistent with previous clinical trial reports of the use of cannabidiol in patients with epilepsy.

Contributors

EAT was involved with data collection, analysis, and interpretation, and manuscript preparation. EDM was involved with patient recruitment, data collection and interpretation, and manuscript preparation. JAF contributed to trial design and analysis, data interpretation, and manuscript editing. MM-B was involved with data collection, analysis, and interpretation, literature searches, and manuscript preparation. SRB contributed to data collection, analysis, and interpretation, and manuscript preparation. CJ contributed to data collection, analysis, and interpretation, and manuscript preparation and reviewed the manuscript. PDL was involved in protocol development, the literature search, and manuscript writing. AT was involved with the trial design and protocol development, data interpretation, clinical study report writing, literature search, and initial drafting of the manuscript (text and figures). CR was involved with the trial design and data interpretation, and manuscript preparation. KS was involved in the trial design, data collection, analysis, and interpretation, and manuscript preparation.

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Declaration of interests

EAT received grants from GW Research Pharmaceuticals; was the principal investigator on clinical trials for GW Pharmaceuticals and Zogenix, outside the submitted work; and serves as a consultant for Eisai Medical Research, Greenwich Biosciences, Ovid Therapeutics, UCB, Aquestive, and Zogenix. EDM received grants from GW Pharmaceuticals during the conduct of the trial; received a grant from GW Pharmaceuticals outside the submitted work; received personal fees from Stanley Brothers Social Enterprises, Eisai Pharma, and Cydan Co; and is the principal investigator for studies sponsored by Neuren Pharma and Zogenix Pharma. JAF receives New York University salary support from the Epilepsy Foundation and for consulting work on behalf of the Epilepsy Study Consortium for Acadia Acorda, Adamas, Alexza, Anavex, Axcella Health, Biogen, BioPharm Solutions, Cavion, Cerecor, Concert Pharmaceuticals, Covance, CuroNZ, Eisai, Empatica, Engage, Georgia Regents University, GlaxoSmithKline, GW Pharmaceuticals, Johnson & Johnson Pharmaceuticals, Marinus, MonosolRx, Monteris, Nestle-Health Science, Neurelis, Novartis, Otsuka, Ovid, Pfizer, Pfizer-Neusentis, Sage Therapeutics, Shire, SK Life Sciences, Sunovion, Takeda, UCB, Upsher Smith, Ultragenyx, Xenon Pharmaceuticals, Xeris, Zogenix, and Zynerba; has received research grants from Acorda, Alexza, Eisai Medical Research, LCGH, Lundbeck, Pfizer, SK Life Sciences, Sunovion, Takeda, and UCB; has grants from the Epilepsy Research Foundation, Epilepsy Study Consortium, Epilepsy Therapy Project, and National Institute of Neurological Disorders and Stroke; is on the Scientific Advisory Board of Ovid, Sage Therapeutics, and Blackfynn; is on the editorial board of *Lancet Neurology*, *Neurology Today*, and *Epileptic Disorders*; is scientific officer for the Epilepsy Foundation for which New York University receives salary support; and has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Biogen, Eisai, Engage, GW Pharmaceuticals, GlaxoSmithKline, Novartis, Otsuka, Ovid, Pfizer, Sage, Sunovion, SK Life Sciences, Takeda, UCB, Ultragenyx, Upsher-Smith, Zogenix, and Zynerba. SRB received grants from GW Pharmaceuticals during the conduct of this study; and serves as a speaker or consultant for Eisai Medical Research, Livanova, Lundbeck, Neuropace, Sunovion, and UCB. CJ has a patent pending for the use of cannabidiol in febrile infection-related epilepsy syndrome. AT and CR are employed by GW Research and own shares or stock options in GW Pharmaceuticals. KS is full-time employee of Greenwich Biosciences and owns stock options in GW Pharmaceuticals. MM-B and PDL have nothing to disclose.

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References

1 van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. *Neuropsychiatr Dis Treat* 2008; **4:** 1001–19.
2 Autry AR, Trevathan E, Van Naarden Braun K, Yeargin-Allsopp M. Increased risk of death among children with Lennox-Gastaut syndrome and infantile spasms. *J Child Neurol* 2010; **25:** 441–47.
3 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:** 82–93.
4 Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. *J Child Neurol* 2007; **22:** 823–28.
5 Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. *Epilepsia* 1997; **38:** 1283–88.
6 Doring JH, Lampert A, Hoffmann GF, Ries M. Thirty years of orphan drug legislation and the development of drugs to treat rare seizure conditions: a cross sectional analysis. *PLoS One* 2016; **11:** e0161660.
7 Montouris GD, Wheless JW, TA. The efficacy and tolerability of pharmacologic treatment options for Lennox-Gastaut syndrome. *Epilepsia* 2014; **55** (suppl 4)**:** 10–20.
8 Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2013; CD003277.
9 Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA, OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011; **77:** 1473–81.
10 Kang HC, Kim YJ, Kim DW, Kim HD. Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multicentric experience. *Epilepsia* 2005; **46:** 272–79.
11 Cersosimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. *Epileptic Disord* 2011; **13:** 382–88.
12 Lancman G, Virk M, Shao H, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. *Seizure* 2013; **22:** 3–8.
13 Douglass LM, Salpekar J. Surgical options for patients with Lennox-Gastaut syndrome. *Epilepsia* 2014; **55** (suppl 4)**:** 21–28.
14 Kossoff EH, Shields WD. Nonpharmacologic care for patients with Lennox-Gastaut syndrome: ketogenic diets and vagus nerve stimulation. *Epilepsia* 2014; **55** (suppl 4)**:** 29–33.
15 Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. *Epilepsia* 2014; **55** (suppl 4)**:** 4–9.
16 Ibeas Bih C, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics* 2015; **12:** 699–730.

17 Turner SE, Williams CM, Iversen L, Whalley BJ. Molecular pharmacology of phytocannabinoids. In: Kinghorn AD, Falk H, Gibbons S, Kobayashi J, eds. Phytocannabinoids: unraveling the complex chemistry and pharmacology of *cannabis sativa*. Basel, Switzerland: Springer International Publishing, 2017: 61–101.

18 Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther* 2010; **332:** 569–77.

19 Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2016; **15:** 270–78.

20 Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. *N Engl J Med* 2017; **376:** 2011–20.

21 Kothare S, Kluger G, Sachdeo R, et al. Dosing considerations for rufinamide in patients with Lennox-Gastaut sundrome: phase III trial results and real-world clinical data. *Seizure* 2017; **47:** 25–33.

22 Devinsky O, Patel AD, Thiele EA, et al. A randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* (in press).

23 Purcarin G, Ng YT. Experience in the use of clobazam in the treatment of Lennox-Gastaut syndrome. *Ther Adv Neurol Disord* 2014; **7:** 169–76.

24 US Department of Health and Human Services. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. 2009. https://www.fda.gov/downloads/Guidances/UCM174090.pdf (accessed Dec 12, 2017).

25 Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend* 2017; **172:** 9–13.

26 Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; **70:** 1950–58.

27 Lundbeck. ONFI® (clobazam): full prescribing information. 2016. www.accessdata.fda.gov/drugsatfda_docs/label/2016/203993s005lbl.pdf (accessed Dec 12, 2017).

28 Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015; **56:** 1246–51.