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Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials

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Objectives: To assess the efficacy and safety profile of add-on cannabidiol (CBD) in patients with Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) on clobazam and in the overall population of four randomized, controlled phase 3 trials.

Methods: Patients received plant-derived, highly purified CBD medicine (Epidiolex® in the USA; Epidyolex® in Europe; 100 mg/ml oral solution) at a dose of 10 or 20 mg/kg/day, or placebo for 14 weeks. A subgroup analysis of patients on clobazam and meta-analysis by syndrome were conducted. The primary endpoint was percentage reduction in primary seizure type during the treatment period.

Results: 396 patients with LGS (49% on clobazam) and 318 patients with DS (64% on clobazam) were included. CBD treatment resulted in a reduction in primary seizure frequency vs placebo in the overall population (treatment ratio [95% confidence interval]: LGS, 0.70 [0.62-0.80]; DS, 0.71 [0.60-0.83]) and in patients receiving clobazam (LGS, 0.56 [0.47-0.67]; DS, 0.63 [0.52-0.77]). The antiseizure efficacy of CBD was also demonstrated across other endpoints vs placebo (≥50% responder rate, total seizure frequency, number of seizure-free days, and Subject/Caregiver Global Impression of Change scores) in the overall populations and in patients receiving clobazam. There were higher incidences of somnolence and sedation in patients on CBD and clobazam. Most incidences of elevated transaminases occurred in patients on concomitant valproate and, to a lesser extent, clobazam.

Conclusions: Add-on CBD was effective in reducing seizures in the overall populations and in conjunction with clobazam. Somnolence and sedation occurred more frequently in patients on CBD and clobazam.

KEYWORDS
cannabidiol, clobazam, epilepsies, myoclonic, epilepsy, lennox–gastaut syndrome, seizures

Trial registration: GWPCARE1A, NCT02091206; GWPCARE1B, NCT02091375; GWPCARE2, NCT02224703; GWPCARE3, NCT02224560; GWPCARE4, NCT02224690.

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) are rare, severe epileptic encephalopathies with early childhood onset that highly impact mortality and quality of life.[1-10] Prescribing appropriate treatments for patients with LGS and DS can be complex, due to the prevalence of multiple seizure types and a high degree of treatment resistance.[4,11,12]

LGS is characterized by drop seizures, which can result in falls and injuries, tonic seizures, and non-convulsive seizures.[3,13] Patients with DS present with different seizure types, but most patients experience combinations of severe convulsive seizures, primarily generalized tonic–clonic, and clonic seizures, as well as focal, myoclonic, and atypical absence seizures.[11,14] Seizure types change over time in both LGS and DS.[5,11,15,16] Current guidelines for LGS recommend the use of valproate as first-line treatment, followed by add-on therapy including lamotrigine and rufinamide.[12] The treatment recommendation for DS is valproate or clobazam as first-line therapy, with add-on stiripentol or topiramate if seizure control is suboptimal.[11,14]

Adequate seizure control remains a concern in both syndromes despite currently available treatment options;[12,14] no single treatment has been shown to be highly efficacious, and many patients receive multiple antiepileptic drugs (AEDs) without seizure control.[14,17] There is a need for new treatment options for patients with LGS and DS, as better seizure control may lead to reduced mortality[1] and improvements in quality of life.[11,18,19]

Highly purified cannabidiol (CBD; Epidyolex® in Europe, GW Pharma [International] B.V., and Epidiolex® in the USA, Greenwich Biosciences, Inc.) is structurally distinct from other AEDs. While its mechanism of action has not been fully elucidated, it has multimodal effects including reducing neuronal hyperexcitability through transient receptor potential vanilloid 1 (TRPV1) channels, antagonizing G protein-coupled receptor 55 (GPR55) receptors, and inhibiting equilibrative nucleoside transporter 1 (ENT1) adenosine reuptake pumps.[20,21] In four phase 3 randomized, controlled trials, add-on CBD demonstrated efficacy with an acceptable safety profile in patients with LGS (GWPCARE3/NCT02224560 and GWPCARE4/NCT02224690) and DS (GWPCARE1B/NCT02091375 and GWPCARE2/NCT02224703).[22-25] CBD is approved as Epidiolex® in the USA for the treatment of seizures associated with LGS, DS, or tuberous sclerosis complex in patients ≥1 years of age;[26] CBD (as Epidyolex®) is approved in the EU for the adjunctive treatment of seizures associated with LGS or DS, in conjunction with clobazam, in patients ≥2 years of age.[27]

The overall population for the phase 3 trials comprised patients who were taking CBD as add-on therapy to a number of different AEDs, most commonly clobazam (LGS, 49%; DS, 64%) and valproate (LGS, 39%; DS, 66%). As a result of the current EU labeling, this article will focus on the efficacy and safety profile of CBD in patients on clobazam and the overall population. To further understand the magnitude of the treatment effect and safety profile of CBD as an add-on treatment in patients with LGS and DS, a post hoc meta-analysis by syndrome was also conducted.

2 | METHODS

2.1 | Patients

Key inclusion/exclusion criteria for the four pivotal trials of add-on CBD in LGS and DS have been published previously.[22-25,28] In brief, for the two trials evaluating CBD in LGS, eligible patients were aged 2-55 years, had documented failures on one or more AEDs, were currently taking one or more AEDs, and had at least two drop seizures per week in the 4-week baseline period. For the two trials evaluating CBD in DS, eligible patients were aged 2-18 years, were taking one or more AEDs, were not completely controlled by current AEDs, and had at least four convulsive seizures in the 4-week baseline period. In all trials, concomitant medications and interventions needed to be stable for 4 weeks prior to screening and remain unchanged throughout the trial.

2.2 | Trial design

All trials followed a similar design where eligible patients were randomized following a 4-week baseline period. Patients received a pharmaceutical formulation of highly purified CBD derived from *Cannabis sativa L.* plant (100 mg/ml oral solution; Epidyolex® in the EU; Epidiolex® in the USA) or placebo. In GWPCARE3 (LGS) and GWPCARE2 (DS), patients were randomized to receive 10 mg/kg/day (CBD10) or 20 mg/kg/day (CBD20), or matched placebo. In GWPCARE4 (LGS) and GWPCARE1B (DS), patients were randomized to receive CBD20 or matched placebo. In all trials, patients received double-blind treatment for 14 weeks, which included a 2-week titration period (7 days [CBD10] or 11 days [CBD20] of dose escalation, starting daily dose of 2.5 mg/kg/day) and a maintenance period of 12 weeks of stable dosing. This was followed by a tapering period of 10 days and a 4-week safety follow-up period, or entry into an open-label extension trial (GWPCARE5, NCT02224573).

Protocols were approved by institutional review boards or independent ethics committees at each trial site. Trials were performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients or their caregivers provided written informed consent before enrollment.

2.3 | Outcome measures

Patients or caregivers recorded the number and type of seizures each day using an interactive voice response system. All seizure types or descriptions given were confirmed independently by an independent epilepsy study consortium using a standard protocol. The primary seizure type in the LGS trials was drop seizures, defined as tonic, tonic–clonic, or atonic seizures that could have led to a fall or injury. The primary seizure type in the DS trials was convulsive seizures, defined as tonic, tonic–clonic, clonic, or atonic seizures. The safety profile was evaluated by recording adverse events.

TABLE 1 Demographics and baseline characteristics for pooled LGS and DS populations, overall and on clobazam (intention-to-treat population)

	Pooled LGS						Pooled DS					
	LGS overall			LGS on clobazam			DS overall			DS on clobazam		
	Placebo (*n* = 161)	CBD10 (*n* = 73)	CBD20 (*n* = 162)	Placebo (*n* = 79)	CBD10 (*n* = 37)	CBD20 (*n* = 78)	Placebo (*n* = 124)	CBD10[a] (*n* = 66)	CBD20 (*n* = 128)	Placebo (*n* = 79)	CBD10 (*n* = 45)	CBD20 (*n* = 80)
Age, years												
Mean	15.3	15.4	15.7	12.5	14.7	15.2	9.7	9.2	9.5	9.7	9.1	9.3
SD	9.5	9.5	9.7	7.5	7.8	9.3	4.7	4.3	4.5	5.0	4.1	4.3
Sex, n (%)												
Male	87 (54)	40 (55)	90 (56)	42 (53)	16 (43)	43 (55)	58 (47)	27 (41)	71 (56)	35 (44)	23 (51)	45 (56)
Region, n (%)												
USA	128 (80)	60 (82)	121 (75)	71 (90)	36 (97)	70 (90)	69 (56)	30 (46)	66 (52)	52 (66)	22 (49)	44 (55)
Rest of world	33 (21)	13 (18)	41 (25)	8 (10)	1 (3)	8 (10)	55 (44)	36 (55)	62 (48)	27 (34)	23 (51)	36 (45)
Weight at baseline, kg												
Mean	44.2	44.3	41.9	40.6	42.0	42.5	34.6	32.8	34.0	34.9	33.5	34.8
SD	23.0	26.2	21.6	21.9	21.0	21.4	16.5	16.6	18.0	17.5	17.3	20.0
Body mass index at baseline, kg/m^2												
Mean	20.5	20.9	20.1	19.9	20.0	21.1	18.9	18.5	18.6	19.0	18.9	19.0
SD	6.3	7.6	8.3	5.3	5.6	10.0	4.3	4.5	4.5	3.8	5.0	4.9
Baseline primary seizure frequency, per 28 days[b]												
Median	79.0	86.9	78.1	80.5	87.0	64.9	15.5	13.5	10.4	17.0	13.1	10.4
Range	8.7, 3174.6	14.0, 7494.0	10.3, 1092.0	8.7, 3174.6	14.0, 7494.0	10.3, 682.3	3.0, 770.5	0.0, 467.0	3.9, 1716.7	3.0, 448.9	4.0, 238.4	3.9, 661.2
Number of AEDs, median (range)												
Previous AEDs	6 (0, 28)	6 (0, 21)	6 (1, 18)	5 (0, 16)	6 (1, 19)	5 (1, 18)	4 (0, 14)	4 (0, 19)	4 (0, 26)	4 (0, 14)	4 (0, 12)	4 (0, 20)
Current AEDs	3 (1, 5)	3 (1, 5)	3 (0, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)
Most common (>25% in any group) AEDs currently being taken, n (%)												
Clobazam	79 (49)	37 (51)	78 (48)	79 (100)	37 (100)	78 (100)	79 (64)	45 (68)	80 (63)	79 (100)	45 (100)	80 (100)
Valproate[c]	63 (39)	27 (37)	64 (40)	24 (30)	7 (19)	22 (28)	82 (66)	44 (67)	84 (66)	50 (63)	30 (67)	56 (70)
Levetiracetam	58 (36)	22 (30)	47 (29)	32 (41)	9 (24)	26 (33)	31 (25)	19 (29)	37 (29)	17 (22)	11 (24)	15 (19)
Lamotrigine	56 (35)	22 (30)	53 (33)	22 (28)	10 (27)	29 (37)	5 (4)	0	2 (2)	3 (4)	0	1 (1)
Topiramate	24 (15)	13 (18)	22 (14)	12 (15)	4 (11)	11 (14)	32 (26)	11 (17)	34 (27)	18 (23)	8 (18)	18 (23)
Rufinamide	41 (26)	19 (26)	51 (32)	19 (24)	12 (32)	22 (28)	3 (2)	2 (3)	9 (7)	3 (4)	1 (2)	5 (6)
Stiripentol	-	-	-	-	-	-	45 (36)	25 (38)	52 (41)	31 (39)	17 (38)	41 (51)

Abbreviations: AED, antiepileptic drug; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; SD, standard deviation.

[a]One patient randomized to CBD10 was not treated and was withdrawn by the principal investigator.

[b]Baseline period included all seizure data prior to day 1.

[c]Valproate includes Ergenyl Chrono for all trials.

The primary efficacy endpoint for all trials was the change from baseline in primary seizure type frequency (over 28 days) during the entire treatment period (14 weeks). Key secondary endpoints were ≥50% responder rate, defined as the proportion of patients with ≥50% reduction in primary seizure type frequency during the treatment period, change from baseline in total seizure frequency over the treatment period, and Subject/Caregiver Global Impression of Change (S/CGIC) at the last visit. Other secondary endpoints included ≥75% responder rate, defined as the proportion of patients with ≥75% reduction in primary seizure type frequency during the treatment period and the number of primary seizure type-free days.

2.4 | Statistical analyses

The safety and intention-to-treat analysis sets included all randomized patients who took at least one dose of CBD or placebo.

The similar trial designs across the pivotal trials allowed for pooling of the outcome data. Efficacy data (primary endpoint and ≥50% responder rates) are presented for the pooled LGS and DS populations (CBD20 and all CBD [CBD10 and CBD20] groups), as well as by trial. The safety outcomes are presented for the pooled LGS and DS populations (CBD20 group); individual trial results for the CBD10 groups are also presented. The pooled DS safety population additionally included 24 patients from GWPCARE1A, a preceding dose-defining and pharmacokinetic trial, who had received CBD10 (n = 8), CBD20 (n = 9), or matched placebo (n = 7).[28] Additional efficacy data and safety data by trial are shown in the Supporting Information.

For by-trial analyses, the primary endpoint, change from baseline in primary seizure type frequency, was analyzed in GWPCARE1B, GWPCARE3, and GWPCARE4 using the Wilcoxon rank-sum test; the overall effect size was measured using the Hodges–Lehmann estimate of median difference. For GWPCARE2, the primary endpoint was analyzed using a mixed-effects model with repeated-measures implemented within the framework of general linear models using the negative binomial response distribution. The model included stratified age-group, time (baseline period or treatment period), treatment arm, and treatment arm-by-time interaction as fixed effects and patient as a random effect. The log-transformed number of days in which seizure data were reported was included as an offset.

In the meta-analysis, the primary endpoint was re-analyzed in GWPCARE1B, GWPCARE3, and GWPCARE4, using the same negative binomial regression (NBR) analysis used for GWPCARE2.

For the responder endpoint, ≥50% responder rates were analyzed by trial using the Cochran–Mantel–Haenszel test stratified by age-group. In the meta-analysis, the endpoint was re-analyzed using logistic regression, including stratified age-group and treatment arm as fixed effects.

Fixed-effects meta-analysis techniques were then used to combine the log treatment ratios (from NBR analysis of the primary seizure count) and log odds ratios (from logistic regression analysis ≥50% responder rates) from the individual trials. The interaction p-value tested the null hypothesis of homogeneity of the treatment effect across trials/dose comparisons.

Other secondary endpoints were analyzed by trial. The percentage change in total seizure frequency in GWPCARE1B, GWPCARE3, and GWPCARE4 was analyzed using the Wilcoxon rank-sum test; the overall effect size was measured using the Hodges–Lehmann estimate of median difference. GWPCARE2 was analyzed using the same NBR analysis stated above. Across all trials, S/CGIC was analyzed using ordinal logistic regression and the ≥75% responder rates analyzed using the Cochran–Mantel–Haenszel test. The change from baseline in the number of primary seizure type-free days was analyzed using analysis of covariance (ANCOVA).

To assess the effect of concomitant clobazam within each trial, the primary endpoint and total seizure endpoint were analyzed using the NBR described above including stratified age-group, time (baseline period or treatment period), treatment arm, treatment arm-by-time interaction, clobazam use, clobazam use-by-treatment arm interaction, and clobazam use-by-treatment arm-by-time interaction as fixed effects and patient as a random effect. The responder endpoints and S/CGIC were analyzed separately using logistic regression, and the change from baseline in the number of primary seizure type-free days was analyzed using ANCOVA. Each analysis included stratified age-group, treatment arm, clobazam use, and clobazam use-by-treatment arm-by-time interaction as fixed effects. The same fixed-effects meta-analysis techniques were then used to combine the treatment effects from the individual trials.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

Demographic and baseline characteristics are shown for the pooled LGS and DS populations in Table 1 and by trial in Table S1 and Table S2.

Overall, the pooled intention-to-treat populations consisted of 396 patients with LGS and 318 patients with DS. In the LGS trials, 161 and 235 patients received placebo and CBD, respectively, of whom 79 (49%) and 115 (49%) were on clobazam. In the DS trials, 124 and 194 patients received placebo and CBD, respectively, of whom 79 (64%) and 125 (64%) were on clobazam.

Demographics and baseline characteristics for patients with LGS were generally similar between treatment arms, both in the overall population and in patients on clobazam. The mean age across both LGS trials was 15 years. Demographics and baseline characteristics were also similar between treatment arms for patients with DS. The mean age across DS trials was 9 years.

In the overall trial populations, the median number of concomitant AEDs was 3; the most common AEDs (>25% of patients) were clobazam, valproate, levetiracetam, lamotrigine, and rufinamide in patients with LGS and valproate, clobazam, stiripentol, levetiracetam, and topiramate in patients with DS.

The median baseline drop seizure frequency (per 28 days) for patients with LGS was 79.0 for placebo, 86.9 for the CBD10 group, and 78.1 for the CBD20 group. The median baseline convulsive seizure frequency (per 28 days) for patients with DS was 15.5 for placebo, 13.5 for the CBD10 group, and 10.4 for the CBD20 group.

3.2 | Efficacy outcome measures in patients with LGS

The re-analysis by trial and meta-analysis for overall and on-clobazam populations for drop seizure reduction and ≥50% responder rate are shown in Table 2. Original by-trial data for the LGS population are shown in Table S3.

In the meta-analysis of the overall population, CBD resulted in a greater reduction in drop seizures compared with placebo (treatment ratio 0.70 [95% confidence interval {CI}, 0.62-0.80], $p < 0.0001$). In the subgroups of patients on clobazam, there was also a marked reduction in drop seizure frequency versus placebo (0.56 [0.47-0.67], $p < 0.0001$). This effect was also reflected in the ≥50% responder odds ratios (overall population, 3.14 [2.04-4.81], $p < 0.0001$; patients on clobazam, 3.48 [1.96-6.17], $p < 0.0001$).

Other secondary endpoints by trial are shown in Table S4. Patients receiving either dose of CBD experienced a greater percentage reduction in total seizures compared with placebo, both in the overall population and in patients on clobazam. Similarly, a higher percentage of patients in the overall population and the subgroup of patients on clobazam reported an improvement in overall condition on the S/CGIC with either dose of CBD compared with placebo. CBD led to a greater rate of patients achieving ≥75% reduction in seizure frequency compared with placebo at CBD20; this effect appeared to be more pronounced in patients on clobazam treated with CBD20. The number of seizure-free days (per 28 days) was also greater in patients treated with either dose of CBD compared with placebo, both in the overall population and in patients on clobazam.

3.3 | Efficacy outcome measures in patients with DS

The re-analysis by trial and meta-analysis for overall and on-clobazam populations for convulsive seizure reduction and ≥50% responder rate are shown in Table 3. Original by-trial data for the DS population are shown in Table S5.

In the overall DS population, CBD resulted in a greater reduction in convulsive seizures (0.71 [0.60-0.83], $p < 0.0001$) and higher ≥50% responder rates (2.34 [1.51-3.63], $p = 0.0001$) compared with placebo. Similarly, in subgroups of patients on clobazam, there was a reduction in convulsive seizure frequency (0.63 [0.52-0.77], $p < 0.0001$) and higher ≥50% responder rates (2.78 [1.62-4.77], $p = 0.0002$) in patients treated with CBD compared to those treated with placebo.

Other secondary endpoints by trial are shown in Table S6. Patients receiving either dose of CBD experienced a greater percentage reduction in total seizures compared with placebo, both in the overall population and in patients on clobazam. Similarly, a greater percentage of patients reported improvements in overall condition on the S/CGIC with both doses of CBD compared with

TABLE 2 Meta-analyses of reduction from baseline in primary seizures and ≥50% responder rates for LGS populations, overall and on clobazam (intention-to-treat population)

		Overall			On clobazam		
Trial	Treatment arm vs placebo	Interaction *p*-value	Treatment/odds ratio[a] (95% CI)	*p*-value	Interaction *p*-value	Treatment/odds ratio[a] (95% CI)	*p*-value
Reduction in drop seizure frequency							
GWPCARE3	CBD10		0.71 (0.56-0.89)	0.0032	0.9727	0.70 (0.51-0.98)	0.0355
	CBD20		0.66 (0.53-0.83)	0.0005	0.0067	0.46 (0.33-0.64)	<0.0001
GWPCARE4	CBD20		0.73 (0.59-0.90)	0.0036	0.0123	0.54 (0.40-0.73)	<0.0001
Meta-analysis	CBD10 + CBD20	0.8244	0.70 (0.62-0.80)	<0.0001	0.1948	0.56 (0.47-0.67)	<0.0001
	CBD20	0.5363	0.70 (0.60-0.82)	<0.0001	0.4734	0.51 (0.41-0.63)	<0.0001
≥50% responder rate							
GWPCARE3	CBD10		3.30 (1.48-7.35)	0.0035	0.5021	2.72 (0.96-7.67)	0.0584
	CBD20		3.87 (1.76-8.53)	0.0008	0.7015	5.12 (1.81-14.54)	0.0021
GWPCARE4	CBD20		2.61 (1.35-5.06)	0.0044	0.6190	3.14 (1.26-7.81)	0.0140
Meta-analysis	CBD10 + CBD20	0.7482	3.14 (2.04-4.81)	<0.0001	0.6720	3.48 (1.96-6.17)	<0.0001
	CBD20	0.4545	3.07 (1.85-5.10)	<0.0001	0.4879	3.88 (1.95-7.71)	<0.0001

Note: Results are based on a fixed-effects meta-analysis. The interaction *p*-value tested the null hypothesis of homogeneity of the treatment effect across trials/dose comparisons.

Abbreviations: CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; CI, confidence interval; LGS, Lennox–Gastaut syndrome.

[a]Reductions in drop seizure frequency are displayed using treatment ratios; ≥50% responder rates are displayed using odds ratios.

TABLE 3 Meta-analyses of reduction from baseline in primary seizures and ≥50% responder rates for DS populations, overall and on clobazam (intention-to-treat population)

		Overall			On clobazam		
Trial	**Treatment arm vs placebo**	**Interaction *p*-value**	**Treatment/odds ratio[a] (95% CI)**	***p*-value**	**Interaction *p*-value**	**Treatment/odds ratio[a] (95% CI)**	***p*-value**
Reduction in convulsive seizure frequency							
GWPCARE2	CBD10		0.70 (0.54-0.92)	0.0095	0.1691	0.63 (0.46-0.86)	0.0042
	CBD20		0.74 (0.57-0.97)	0.0299	0.5702	0.69 (0.50-0.96)	0.0297
GWPCARE1	CBD20		0.67 (0.50-0.90)	0.0082		0.57 (0.40-0.83)	0.0032
Meta-analysis	CBD10 + CBD20	0.8808	0.71 (0.60-0.83)	<0.0001	0.7490	0.63 (0.52-0.77)	<0.0001
	CBD20	0.6170	0.71 (0.58-0.86)	0.0006	0.4490	0.64 (0.50-0.81)	0.0003
≥50% responder rate							
GWPCARE2	CBD10		2.24 (1.06-4.73)	0.0346	0.9722	2.33 (0.96-5.68)	0.0623
	CBD20		2.77 (1.32-5.82)	0.0073	0.8188	3.26 (1.28-8.26)	0.0130
GWPCARE1	CBD20		2.04 (0.93-4.51)	0.0768	0.2517	2.88 (1.06-7.84)	0.0382
Meta-analysis	CBD10 + CBD20	0.8512	2.34 (1.51-3.63)	0.0001	0.8763	2.78 (1.62-4.77)	0.0002
	CBD20	0.5837	2.40 (1.40-4.13)	0.0015	0.8612	3.08 (1.56-6.08)	0.0012

Note: Results are based on a fixed-effects meta-analysis. The interaction *p*-value tested the null hypothesis of homogeneity of the treatment effect across trials/dose comparisons.

Abbreviations: CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; CI, confidence interval; DS, Dravet syndrome.

[a]Reductions in convulsive seizure frequency are displayed using treatment ratios; ≥50% responder rates are displayed using odds ratios.

placebo, in the overall population, and in the subgroup of patients on clobazam. CBD led to higher ≥75% responder rates compared with placebo in the overall population; this effect was more prominent in GWPCARE2 and generally comparable in the overall population and on-clobazam groups. Finally, the number of seizure-free days (per 28 days) was greater in patients treated with CBD20 compared with placebo in GWPCARE1, and in patients treated with CBD10 in GWPCARE2, both in the overall population and in patients on clobazam.

3.4 | Safety and tolerability

Adverse events for the pooled LGS and DS populations are summarized by syndrome in Table 4.

The overall incidence of treatment-emergent adverse events (TEAEs) was greater in patients taking CBD compared with placebo; the incidence was similar between patients with LGS and DS. In the subgroup of patients on clobazam, there also appeared to be a similar proportion of patients experiencing TEAEs compared with the overall population across the CBD dose groups.

Most adverse events were mild to moderate in severity. The most common TEAEs in any patient group were somnolence, decreased appetite, diarrhea, pyrexia, fatigue, and vomiting.

More patients treated with CBD compared with placebo reported serious TEAEs and TEAEs leading to discontinuation, both in the overall population and in patients on clobazam. In the overall LGS and DS populations, there were a greater number of patients experiencing TEAEs leading to discontinuation in the CBD20 group compared with CBD10; however, the numbers of serious TEAEs were similar across the two CBD doses. In patients on clobazam, the incidence of serious TEAEs and TEAEs leading to discontinuation appeared to be similar to the overall population.

Somnolence was the most commonly reported TEAE and was not considered dose-related. In patients treated with CBD, somnolence was reported in 52/235 (22%) of patients with LGS and 57/211 (27%) of patients with DS, of whom 35/52 (67%) and 48/57 (84%) were on clobazam. Comparatively, somnolence was reported in 12/161 (7%) and 16/131 (12%) of patients with LGS and DS treated with placebo, of whom 8/12 (67%) and 13/16 (81%) were on clobazam. Similarly, the majority of CBD patients in the LGS and DS populations who experienced sedation were also on clobazam (LGS, 11/12 patients, 92%; DS, 6/7 patients, 86%). Other common TEAEs, such as decreased appetite and diarrhea, did not appear to be more common in patients on clobazam.

Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were the most common causes of treatment discontinuation in patients with LGS (AST, 6/235, 3%; ALT, 7/235, 3%), and DS (AST, 4/211, 2%; ALT 2/211, 1%) taking CBD. In patients treated with CBD, increased AST was reported as a TEAE in 11/235 (5%) patients with LGS and 14/211 (7%) with DS, of whom 6/11 (55%) and 13/14 (93%) were on clobazam. The majority of patients reporting increased AST as a TEAE were taking valproate (LGS, 9/11 patients, 82%; DS, 14/14 patients, 100%). Similarly, increased ALT was reported as a TEAE in 15/235 (6%) patients with LGS and 12/211 (6%) patients with DS, of whom 8/15 (53%) with LGS and

TABLE 4 Treatment-emergent adverse event summary for pooled LGS and DS populations, overall and on clobazam (safety population)

	Pooled LGS						Pooled DS					
	LGS overall			LGS on clobazam			DS overall			DS on clobazam		
Number of patients (%)	Placebo (*n* = 161)	CBD10 (*n* = 67)	CBD20 (*n* = 168)	Placebo (*n* = 80)	CBD10 (*n* = 35)	CBD20 (*n* = 79)	Placebo (*n* = 131)	CBD10 (*n* = 72)	CBD20 (*n* = 139)	Placebo (*n* = 84)	CBD10 (*n* = 50)	CBD20 (*n* = 88)
TEAEs	114 (71)	56 (84)	151 (90)	58 (73)	31 (89)	74 (94)	108 (82)	61 (85)	126 (91)	73 (87)	44 (88)	83 (94)
TEAEs leading to discontinuation	2 (1)	1 (2)	18 (11)	0	1 (3)	11 (14)	1 (1)	1 (1)	15 (11)	1 (1)	0	10 (11)
Serious TEAEs	12 (8)	13 (19)	33 (20)	6 (8)	8 (23)	18 (23)	14 (11)	15 (21)	28 (20)	9 (11)	11 (22)	20 (23)
Deaths	0	0	1 (1)	0	0	1 (1)	0	0	0	0	0	0
TEAEs reported in ≥10% of patients in any group by preferred term												
Somnolence	12 (8)	14 (21)	38 (23)	8 (10)	11 (31)	24 (30)	16 (12)	19 (26)	38 (27)	13 (16)	17 (34)	31 (35)
Decreased appetite	8 (5)	11 (16)	32 (19)	4 (5)	4 (11)	10 (13)	14 (11)	12 (17)	41 (30)	8 (10)	9 (18)	30 (34)
Diarrhea	13 (8)	7 (10)	28 (17)	7 (9)	2 (6)	9 (11)	15 (12)	11 (15)	37 (27)	9 (11)	7 (14)	22 (25)
Pyrexia	19 (12)	6 (9)	21 (13)	11 (14)	3 (9)	14 (18)	16 (12)	18 (25)	24 (17)	13 (16)	11 (22)	17 (19)
Nasopharyngitis	9 (6)	3 (5)	13 (8)	6 (8)	0	6 (8)	9 (7)	5 (7)	12 (9)	5 (6)	5 (10)	8 (9)
Vomiting	23 (14)	4 (6)	19 (11)	13 (16)	2 (6)	7 (9)	7 (5)	5 (7)	21 (15)	5 (6)	3 (6)	14 (16)
Fatigue	4 (3)	5 (8)	13 (8)	0	5 (14)	7 (9)	11 (8)	5 (7)	28 (20)	7 (8)	4 (8)	24 (27)
Convulsion	12 (8)	2 (3)	12 (7)	4 (5)	1 (3)	7 (9)	10 (8)	7 (10)	11 (8)	7 (8)	5 (10)	5 (6)
URTI	17 (11)	11 (16)	13 (8)	10 (13)	5 (14)	6 (8)	8 (6)	3 (4)	11 (8)	4 (5)	3 (6)	9 (10)
Status epilepticus	4 (3)	7 (10)	5 (3)	0	3 (9)	2 (3)	12 (9)	5 (7)	11 (8)	6 (7)	5 (10)	5 (6)
Lethargy	2 (1)	3 (5)	10 (6)	2 (3)	2 (6)	9 (11)	5 (4)	1 (1)	9 (7)	5 (6)	1 (2)	9 (10)
Constipation	7 (4)	3 (5)	10 (6)	4 (5)	2 (6)	8 (10)	5 (4)	2 (3)	2 (1)	3 (4)	1 (2)	2 (2)
AST increased	2 (1)	2 (3)	9 (5)	1 (1)	2 (6)	4 (5)	0	3 (4)	11 (8)	0	3 (6)	10 (11)
Pneumonia	0	4 (6)	6 (4)	0	4 (11)	4 (5)	2 (2)	6 (8)	6 (4)	0	6 (12)	5 (6)
Rash	2 (1)	0	10 (6)	1 (1)	0	9 (11)	1 (1)	3 (4)	6 (4)	0	3 (6)	5 (6)
Sedation	2 (1)	2 (3)	10 (6)	1 (1)	2 (6)	9 (11)	0	1 (1)	6 (4)	0	1 (2)	5 (6)
Other TEAEs of interest												
Irritability	3 (2)	6 (9)	6 (4)	2 (3)	3 (9)	3 (4)	2 (2)	4 (6)	9 (7)	2 (2)	4 (8)	7 (8)
ALT increased	3 (2)	3 (5)	12 (7)	1 (1)	3 (9)	5 (6)	0	3 (4)	9 (7)	0	2 (4)	6 (7)
GGT increased	3 (2)	2 (3)	6 (4)	1 (1)	2 (6)	2 (3)	3 (2)	4 (6)	8 (6)	2 (2)	0	7 (8)
Aggression	1 (1)	2 (3)	7 (4)	0	2 (6)	5 (6)	2 (2)	1 (1)	8 (6)	1 (1)	1 (2)	3 (3)
Weight decreased	3 (2)	2 (3)	6 (4)	2 (3)	1 (3)	4 (5)	1 (1)	0	7 (5)	1 (1)	0	5 (6)
Liver function abnormal	0	0	6 (4)	0	0	4 (5)	1 (1)	0	6 (4)	1 (1)	0	4 (5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; GGT, gamma-glutamyl transpeptidase; LGS, Lennox–Gastaut syndrome; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

8/12 (67%) with DS were taking clobazam and 11/15 (73%) with LGS and 12/12 (100%) with DS were taking valproate.

4 | DISCUSSION

As a result of the current EU indication for CBD, the primary aim of this manuscript was to assess the efficacy and safety profile of CBD in patients with LGS and DS on clobazam and in the overall population of four randomized controlled phase 3 trials. The overall trial population comprised patients who were taking CBD as an add-on to a number of different AEDs; the on-clobazam population across the trials accounted for 49% of patients with LGS and 64% of patients with DS. Pooled data for subgroups of patients with and without clobazam have been recently published.[29-31]

In a meta-analysis of the phase 3 trials, CBD was effective at reducing seizures in patients with LGS and DS in the overall population and in patients on clobazam. Compared with placebo, CBD resulted in a greater reduction in drop seizures in patients with LGS and convulsive seizures in patients with DS. The antiseizure effect of CBD was also seen in the ≥50% responder odds ratios in both syndromes. Across the trials, there were a greater number of patients receiving CBD20 compared with CBD10; however, there seemed to be no consistent dose response between the two doses. The recommended maintenance CBD dose is therefore 10 mg/kg/day in patients with LGS or DS. As individual patients may show greater efficacy at higher doses, CBD may be titrated up to a maximum dose of 20 mg/kg/day.[27]

The number of seizure-free days is an important endpoint in patients with severe epilepsy, as it represents a reduction in overall seizure burden. Patients treated with CBD experienced more seizure-free days than those in the placebo group, both in the overall population and in patients on clobazam. Importantly, the effects on seizure reduction are reflected by the improvements in patient-reported outcomes such as the S/CGIC scores seen across all CBD groups compared with placebo.

The meta-analysis shows similar antiseizure efficacy for the overall population and for patients on clobazam. Some have previously questioned whether CBD has an antiseizure effect independent of clobazam, or whether its efficacy is due to a bidirectional drug–drug interaction with clobazam leading to increased levels of active metabolites of both drugs.[29-34] A recent trial in healthy volunteers found that active metabolites of both clobazam (*N*-desmethylclobazam [N-CLB]) and CBD (7-hydroxy-cannabidiol [7-OH-CBD]) were increased when clobazam and CBD were co-administered.[34] The increase in N-CLB has also been demonstrated in other trials in patients with treatment-resistant epilepsy treated with clobazam and CBD.[35,36] Increases in N-CLB levels are thought to be due to inhibition of cytochrome P450 (CYP) 2C19 by CBD.[37,38] As both N-CLB and 7-OH-CBD metabolites are active, an increase in either or both could contribute to treatment efficacy.

However, preclinical studies have indicated that CBD and clobazam also have independent antiseizure effects.[39,40] Anderson et al studied the pharmacokinetic and pharmacodynamic interactions between CBD and clobazam in the DS *Scn1a*$^{+/-}$ mouse model of epilepsy. Although subanticonvulsive doses of CBD increased plasma clobazam concentrations in the mice, they did not result in a greater anticonvulsive efficacy. A greater efficacy was only achieved when an anticonvulsive dose of CBD was administered in combination with clobazam.[39] Similarly, using the maximal electroshock seizure (MES) mouse model of generalized seizures, Rana et al showed that both CBD and clobazam caused brain exposure-dependent anticonvulsive effects compared with vehicle. The group demonstrated synergism between CBD and clobazam in MES mice at all fixed-ratio combinations tested (3:1, 1:1, 1:3).[40]

The analysis of phase 3 trial data described here indicates that CBD showed antiseizure efficacy in an overall population that included patients with LGS and DS who were and were not taking clobazam. In addition, an independent retrospective analysis of patients taking CBD for refractory epilepsy found that CBD was effective in reducing seizure frequency, with or without concomitant clobazam.[41] The analysis also showed that changes in N-CLB and clobazam levels did not have a clinically significant correlation with changes in weekly seizure frequency.[41]

The importance of N-CLB level elevation for the antiseizure efficacy of CBD was also questioned in two separate papers evaluating the efficacy of CBD in patients on stiripentol. Stiripentol is a potent CYP2C19 inhibitor; thus, the effect of CBD on N-CLB levels was less marked in patients on stiripentol. Nevertheless, these patients derived efficacy from CBD.[28,31]

Importantly, the increase in exposure to active metabolites of CBD and clobazam may also lead to an increased risk of some adverse events. Some TEAEs, particularly somnolence and increased transaminases, appeared to occur more frequently in patients on clobazam; other common TEAEs, such as decreased appetite and diarrhea, did not seem to be reported more often in patients on clobazam.

Somnolence and sedation are common adverse events in patients on clobazam.[42] The majority of patients who experienced somnolence in both the CBD and placebo groups were on clobazam. Other trials assessing CBD in patients with treatment-resistant epilepsy reported a high incidence of somnolence or similar adverse events, such as sedation, in patients on clobazam.[28,35,36,41] Sedation was less commonly reported than somnolence in this meta-analysis; however, the majority of patients who reported sedation were also on clobazam. Consideration of a reduction in the dose of clobazam is recommended for patients who experience somnolence or sedation when clobazam is co-administered with CBD.[27]

The most common causes of treatment discontinuation in patients with LGS and DS were increased AST and ALT. Although many of the cases were in patients on clobazam, a greater proportion of patients with increased ALT and AST were taking concomitant valproate. It is recommended that if clinically significant increases of transaminases occur, CBD and/or concomitant valproate or clobazam should be reduced or discontinued in all patients until transaminase levels return to within normal limits.[27] Valproate and other concomitant AEDs may also influence other aspects of the efficacy

and/or safety of CBD, but it is beyond the scope of this manuscript to evaluate this.

The subgroup analysis of patients on clobazam will aid clinicians in making informed decisions regarding the efficacy and safety of CBD when prescribed in conjunction with clobazam. However, there are several limitations to the analysis. First, the sample sizes of trials feeding into the meta-analysis are limited, as the trials were not designed for analysis of the on-clobazam patient group. Second, patients were not randomized by clobazam status, which may confound interpretation of the results; patients in the on-clobazam group may have different characteristics, including altered seizure response. Similarly, the analysis does not take into consideration that some patients in the off-clobazam group may have previously tried and discontinued clobazam. Whether or not a patient was taking clobazam may have influenced the physician's decision regarding whether to enter them into the trial, thus introducing further bias.

It was not feasible to assess the impact of individual clobazam levels on efficacy and safety due to wide variation in clobazam formulation, dose, and plasma levels, which were only assessed in a small number of patients before and during the treatment period. The dose of clobazam could be adjusted in patients experiencing adverse events, which would also confound any analysis of the impact of clobazam dose on the efficacy and safety of CBD. Patients with LGS and DS commonly receive polypharmacy and take a variety of medications including AEDs, which were selected based on individual response and tolerability prior to participation in the trials. The analyses presented here did not account for the influence of these concomitant medications on efficacy and safety of CBD, nor did they take into consideration the effect of pharmacogenetics and the impact of polymorphisms in genes coding for cytochrome P450 enzymes.

5 | CONCLUSION

Add-on CBD was effective in reducing seizures in patients with LGS and DS, both in the overall trial populations and in conjunction with clobazam. The safety profile appeared similar between the overall population and those on clobazam, with the exception of certain adverse events. Somnolence and sedation were more frequently reported in those patients who had concomitant administration of CBD and clobazam.

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CONFLICT OF INTEREST

B. Gunning has received consultancy fees from GW Pharmaceuticals companies, Ovid/Takeda, and Zogenix, and has been a principal investigator for GW Research Ltd and Zogenix; M. Mazurkiewicz-Bełdzińska has been a principal investigator for Biogen, GW Research Ltd, Ovid/Takeda, and Roche; R.F.M. Chin has received consultancy fees from Eisai, GW Pharmaceuticals companies, and Zogenix, and has been a principal investigator for GW Research Ltd; H. Bhathal has received consultancy fees from BIAL and GW Pharmaceuticals, and has been a principal investigator for Eisai and GW Research; C. Nortvedt is employed by GW Pharmaceuticals Ltd and owns shares in GW Pharmaceuticals plc; E. Dunayevich is employed by Greenwich Biosciences Inc. and owns shares in GW Pharmaceuticals plc; and D. Checketts is employed by GW Research Ltd and owns shares in GW Pharmaceuticals plc.

DATA AVAILABILITY STATEMENT

The sponsor is adhering to current US and EU requirements so will not make individual deidentified participant data available; however, protocols and statistical analysis plans will be made available upon request to corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Material

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