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FULL-LENGTH ORIGINAL RESEARCH

Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial

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Abstract

Objective: Add-on cannabidiol (CBD) reduced seizures associated with Dravet syndrome (DS) in two randomized, double-blind, placebo-controlled trials: GWPCARE1 Part B (NCT02091375) and GWPCARE2 (NCT02224703). Patients who completed GWPCARE1 Part A (NCT02091206) or Part B, or GWPCARE2, were enrolled in a long-term open-label extension trial, GWPCARE5 (NCT02224573). We present an interim analysis of the safety, efficacy, and patient-reported outcomes from GWPCARE5.

Methods: Patients received a pharmaceutical formulation of highly purified CBD in oral solution (100 mg/ml), titrated from 2.5 to 20 mg/kg/day over a 2-week period, added to their existing medications. Based on response and tolerance, CBD could be reduced or increased to 30 mg/kg/day.

Results: Of the 330 patients who completed the original randomized trials, 315 (95%) enrolled in this open-label extension. Median treatment duration was 444 days (range = 18–1535), with a mean modal dose of 22 mg/kg/day; patients received a median of three concomitant antiseizure medications. Adverse events (AEs) occurred in 97% patients (mild, 23%; moderate, 50%; severe, 25%). Commonly reported AEs were diarrhea (43%), pyrexia (39%), decreased appetite (31%), and somnolence (28%). Twenty-eight (9%) patients discontinued due to AEs. Sixty-nine (22%) patients had liver transaminase elevations >3 × upper limit of normal; 84% were on concomitant valproic acid. In patients from GWPCARE1 Part B and GWPCARE2, the median reduction from baseline in monthly seizure frequency assessed in 12-week periods up to Week 156 was 45%–74% for convulsive seizures and 49%–84% for total seizures. Across all visit windows, ≥83% patients/caregivers completing a Subject/Caregiver Global Impression of Change scale reported improvement in overall condition.

Significance: We show that long-term CBD treatment had an acceptable safety profile and led to sustained, clinically meaningful reductions in seizure frequency in patients with treatment-resistant DS.

KEYWORDS
antiseizure medication, cannabinoid, childhood onset epilepsy, convulsive seizures, Dravet syndrome

1 | INTRODUCTION

Dravet syndrome (DS) is a developmental and epileptic encephalopathy that is often treatment-resistant, with onset at around 6 months of age.[1] It is typically refractory to standard antiseizure medications (ASMs) and leads to cognitive, motor, and often behavioral impairment from the second year of life.[2,3] Early mortality is high, around 17% by 20 years of age, with sudden unexpected death in epilepsy (SUDEP) and status epilepticus the leading causes of death.[4]

Highly purified cannabidiol (CBD) is approved in the United States as Epidiolex (Greenwich Biosciences) for the treatment of seizures associated with Lennox–Gastaut syndrome (LGS), DS, or tuberous sclerosis complex (TSC) in patients ≥1 years of age; it is approved in the United Kingdom and European Union as Epidyolex (GW Pharma [International] B.V.) for LGS or DS in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in Northern Ireland and the European Union for TSC in patients ≥2 years of age.[5–8] In patients with DS, in two Phase 3 randomized controlled trials (RCTs; GWPCARE1 [Part B] and GWPCARE2), add-on CBD treatment significantly reduced convulsive seizure frequency, and had an acceptable safety profile.[5,8]

GWPCARE5 is an open-label extension (OLE) trial of add-on CBD treatment in patients with DS who participated in GWPCARE1 or GWPCARE2.[5,8] The OLE trial also included patients with LGS who completed treatment in one of two Phase 3 trials (GWPCARE3[9] or GWPCARE4[7]); however, these data will be published separately.

Here, we report up to 3-year efficacy outcomes and safety data for the full duration of follow-up for patients with DS in GWPCARE5 with a data cutoff date of December 3, 2019. This analysis provides longer term safety, efficacy, and patient-reported outcome results than previously reported (median treatment duration = 39 weeks, range = .1–73, analyzed in November 2016).[10] We also include patients from the now completed GWPCARE2 trial, as they were excluded from interim data efficacy analysis because GWPCARE2 was ongoing and not yet unblinded.

Key Points

- An open-label CBD extension trial in Dravet syndrome produced sustained reductions in convulsive and total seizures observed over 156 weeks
- The CBD mean modal dose was 22 mg/kg/day, and median treatment duration was 444 days (range = 18–1535 days)
- The most common AEs were diarrhea, pyrexia, decreased appetite, and somnolence; most AEs were moderate in severity
- Eighty-three percent or more patients or caregivers reported improvement in overall condition across all visit windows up to 156 weeks of treatment

2 | MATERIALS AND METHODS

2.1 | Compliance with ethical standards

This trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and ethical principles, based on the Declaration of Helsinki. Prior to any trial procedures, written consent was obtained from patients or their parent, caregiver, or legal representative, and, when possible, written assent was obtained from the patient. The informed consent form, protocol, and amendments were approved by the institutional review board or independent ethics committee at each trial site. The trial protocol is registered on the clinicaltrials.gov website (NCT02224573).

2.2 | Patients

Patients who completed the treatment period in trials GWPCARE1 (Part A, NCT02091206; Part B, NCT02091375) or GWPCARE2 (NCT02224703) were eligible for enrollment in the OLE trial. All patients had a clinical diagnosis of DS, confirmed by the Epilepsy Study Consortium, with seizures that were inadequately

controlled by one or more current ASMs. Patients from GWPCARE1 Part B and GWPCARE2 were 2–18 years of age with four or more convulsive seizures in the 4-week baseline period, whereas patients from the dose-ranging study GWPCARE1 Part A were 4–10 years of age with less than four convulsive seizures during the 4-week baseline period. Convulsive seizures in the trials were defined as tonic–clonic, tonic, clonic, and atonic seizures.

2.3 | Trial design

Patients received plant-derived highly purified CBD (Epidiolex in the United States; Epidyolex in the United Kingdom, European Union, and Australia; 100 mg/ml oral solution). The dose was titrated from 2.5 to 20 mg/kg/day and administered in two divided doses over a 2-week period, beginning on the evening of Day 1 of the OLE trial. Patients continued to receive this dose during the maintenance period. Patients received CBD in addition to their existing ASM regimen. Investigators were permitted to decrease the dose of CBD and/or concomitant ASMs if a patient experienced intolerable adverse effects. Investigators could also increase the CBD dose to a maximum of 30 mg/kg/day if they considered it may be of benefit.

At the time of data cutoff, patients could receive treatment for up to 1 year (United Kingdom, Spain, the Netherlands, and Australia), 3 years (Israel), or 4 years (United States, France, and Poland). Upon completion of the OLE treatment period, either patients continued dosing with CBD if market authorization was granted or the dose of CBD was tapered by 10% per day for 10 days for patients not continuing treatment. Patients who withdrew early could also begin the taper period following the withdrawal visit (unless continued dosing was not possible due to an adverse event [AE]). A follow-up visit was performed 4 weeks (+3 days) after the last dose of CBD (including the last tapered dose, where applicable).

The OLE trial, conducted at 56 sites (one in Israel, two in Australia, four in the United Kingdom, seven in Spain, two in the Netherlands, 32 in the United States, four in France, and four in Poland) began on June 2015 and is ongoing at some sites. The OLE trial was conducted with Epidyolex or Epidiolex, and results do not apply to other CBD-containing products.

2.4 | Trial procedures

Patients or their caregivers completed a paper diary daily to record AEs and daily use of CBD, concomitant ASMs, and rescue medications during treatment. Information on seizure number and type was collected through an interactive voice recording system telephone diary, completed weekly until the end of treatment/withdrawal visit. Blood and urine sampling for clinical laboratory assessments was carried out at all clinic visits through end of taper. The 7-point Subject/Caregiver Global Impression of Change (S/CGIC) scale was assessed at Weeks 24, 38, 48, 76, 104, 132, and 156; if both caregiver and patient completed the S/CGIC, the caregiver score was used (see Supporting Information).

2.5 | Outcome measures

The primary objective of this OLE trial was to investigate the long-term tolerability and safety of add-on CBD in children and adults with inadequately controlled DS. The operational definition of the term "safety" in this paper includes both safety and tolerability. Safety variables included AEs, vital signs, 12-lead electrocardiograms, clinical laboratory parameters, and physical examination parameters.

Secondary objectives were to evaluate the efficacy of CBD as determined by changes in convulsive seizure (defined as tonic–clonic, tonic, clonic, and atonic seizures) and total seizure frequency, seizure reduction responder rates (proportion of patients with ≥25%, ≥50%, ≥75%, and 100% reductions in convulsive and total seizure frequency), episodes of status epilepticus, and changes in the S/CGIC scale.

Changes to trial outcomes after the trial started included the addition of the assessment of total seizures in addition to seizure subtypes. Assessment of the efficacy of CBD in total seizures was a secondary endpoint in the two DS and two LGS RCTs that led into this trial and is an important measure of the effectiveness of CBD treatment.

2.6 | Statistical analysis

2.6.1 | Sample size

Only patients who completed treatment in two previous RCTs were eligible for inclusion. Safety analyses included all enrolled patients ($n = 315$). Patients originally enrolled in GWPCARE1 Part A ($n = 24$) were excluded from efficacy analyses in GWPCARE5 because the randomization criteria were different from GWPCARE1 Part B and GWPCARE2 (<4 convulsive seizures vs. ≥4 convulsive seizures in the baseline period, respectively). Thus, the safety population included 315 patients, and the efficacy population included 291 patients.

2.6.2 | Statistical methods

Efficacy outcomes were assessed through 156 weeks (3 years) in the OLE trial; very few patients had efficacy data available past that time point. All data collected during this trial were summarized across time, using descriptive statistical methods. Seizure frequencies (per 28 days) were determined for each 12-week period of treatment. Percentage change in seizure frequency for each 12-week visit window through the 156 weeks was calculated relative to the prerandomization baseline period from the original placebo-controlled trial. For defined periods, total seizures in 12 weeks were counted, then divided by the number of days over which data were captured and multiplied by 28 to give "per 28 days" value. Analyses of seizure frequency and seizure reduction responder rates were repeated using inclusion of a last observation carried forward (LOCF) step, described in detail in Supporting Information. All analyses were descriptive, and there was no formal hypothesis testing.

3 | RESULTS

3.1 | Disposition of patients

Of the 330 patients with DS who completed the GWPCARE1 and GWPCARE2 RCTs, 315 (95%) enrolled in this OLE trial across 56 sites in the United States, Europe, Israel, and Australia. Overall, 143 patients (45%) withdrew from treatment, most commonly because of patient or parent/guardian decision (n = 61 [19%]), AEs (n = 25 [8%]), or investigator decision (n = 23 [7%]; Figure 1). Although lack of efficacy was not a prespecified option, of the 111 patients with primary reasons for withdrawal reported as withdrawn by patient/caregiver, withdrawn by investigator, or other, 91 patients had additional free-text comments from the investigator suggesting withdrawal due to lack of efficacy. Median treatment duration was 444 days (range = 18–1535). Time to withdrawal for any reason is presented in Figure S1. At the time of analysis, 157 patients (50%) had completed treatment; 15 patients (5%) had ongoing treatment and had not yet reached later treatment windows.

3.2 | Demographics

Patient demographics are outlined in Table 1. The mean age of the patients at entry into the OLE was 10 years, and 50% were male. Patients were taking a median of three concurrent ASMs at baseline; approximately 75% of patients were receiving three or more concurrent ASMs. During the OLE, 69% patients were taking valproic acid, 68% clobazam, and 38% stiripentol. At baseline of the RCTs, patients had median 12 convulsive and 36 total seizures per 28 days. One (.3%) patient had been previously treated with a ketogenic diet, and 30 (10%) received a ketogenic diet during the trial. Overall, 21 (7%) patients had been previously treated with vagus nerve stimulation, and 42 (13%) received vagus nerve stimulation during the trial.

3.3 | Drug exposure

The mean duration of CBD dosing was 626.8 days, equating to 540.6 patient-years of exposure, and the mean modal dose of CBD was 22 mg/kg/day over the treatment period for all patients. For each 12-week reporting interval, and for the duration of the trial period to the data cut, the daily dose remained generally stable; the mean modal dose per 12-week reporting interval ranged from 20 to 24 mg/kg/day over the first 156 weeks of treatment, and during the last 12 weeks of treatment, the mean modal dose was 22 mg/kg/day (n = 314). The median CBD treatment duration was 444 days (63 weeks; range = 18–1535 days); these data included patients for whom national regulations limited the period of treatment to 1 year.

3.4 | Safety

Treatment-emergent AEs were reported by 306 of 315 (97%) patients (Table 2); most were moderate in severity (156 [50%] patients), 72 (23%) experienced mild AEs, and 78 (25%) experienced severe AEs. The incidence of AEs by modal dose (≤20, >20–25, or >25 mg/kg/day) was generally similar (Table 2), although higher incidence of status epilepticus was observed with increasing CBD dose. Diarrhea, pyrexia, decreased appetite, and somnolence were the most common AEs. Serious AEs were reported in 132 patients (42%); the most common were status epilepticus (15%), convulsion (11%), pneumonia (6%), and pyrexia (5%; Table 2). Incidence of serious AEs was 30%–52% for pediatric age groups (age <2, 2–5, 6–11, or 12–17 years) and 33% for adult patients (age ≥18 years). Twenty-eight patients discontinued due to AEs (9%), most commonly (>1%) due to increased aspartate aminotransferase (AST; n = 8 [3%]) and/or alanine aminotransferase (ALT; n = 7 [2%]) levels, and convulsion (n = 8 [3%]); 16 patients discontinued due to multiple AEs. Incidence of AEs leading to discontinuation was 8%–10% for pediatric age groups and 0% for adult patients. There were five deaths during the trial, of which four were due to SUDEP and one was reported as due to convulsion (the

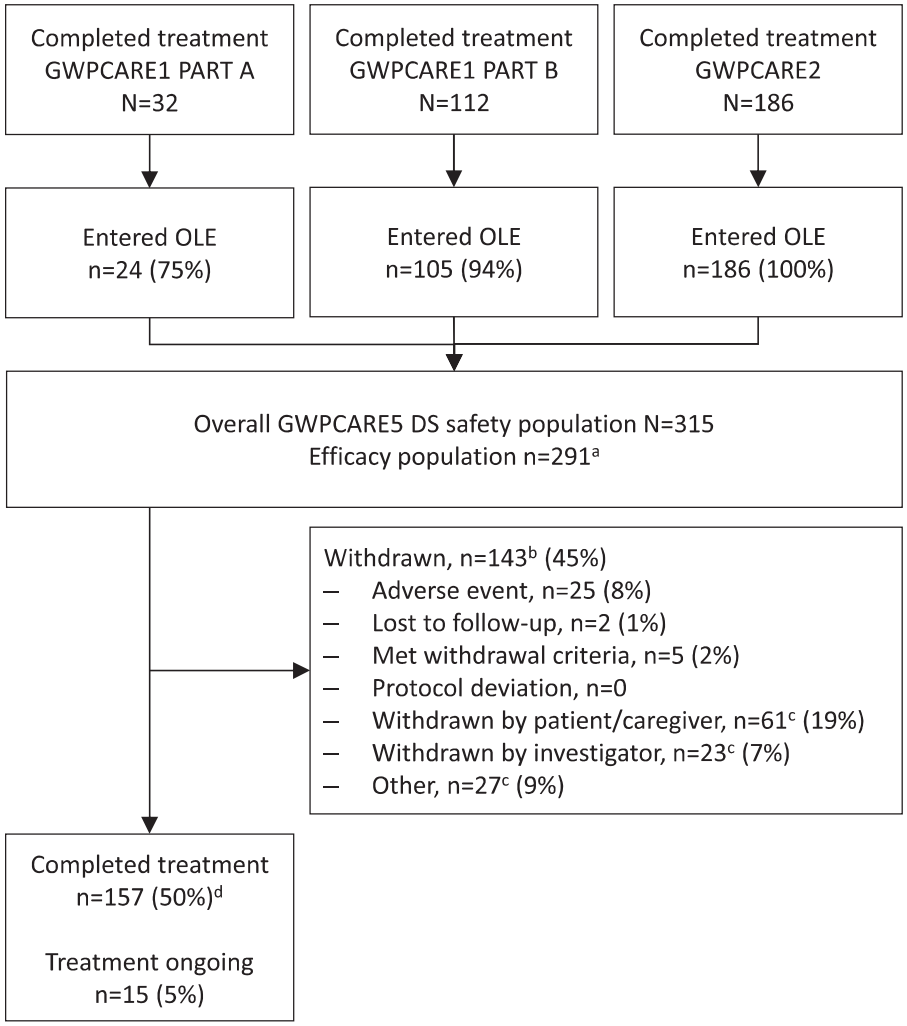


FIGURE 1 Disposition of patients. DS, Dravet syndrome; OLE, open-label extension. [a]Patients originally enrolled in GWPCARE1 Part A (different enrollment criteria) were excluded from efficacy analyses. [b]Withdrawals are shown by the primary reason reported for each patient and encompass the full follow-up period. [c]Of the 111 patients with primary reasons for withdrawal reported as withdrawn by patient/caregiver, withdrawn by investigator, or other, 91 patients had written-in comments entered by the investigator suggesting withdrawal due to lack of efficacy. [d]Patients in the United Kingdom, the Netherlands, Australia, and Spain could receive treatment for a maximum of 1 year. "Completed treatment" refers to patients who completed the maximum permitted 1 year of treatment in the United Kingdom, the Netherlands, Australia, and Spain. Patients with "Treatment ongoing" either had not reached 1 year of treatment in these countries or were enrolled in countries where there was no time limit on how long they could receive cannabidiol

patient had risk factors for SUDEP such as tonic–clonic and nocturnal seizures); none was considered related to CBD by the respective investigator.

Increases in ALT or AST >3 × upper limit of normal (ULN) occurred in 69 patients (22%); of these patients, 58 (84%) were on concomitant valproic acid. No patient met the standard criteria for severe drug-induced liver injury (Hy's law) with concurrent elevated bilirubin >2 × ULN. Thirteen (4%) patients withdrew from treatment due to elevated ALT or AST levels. After initiating CBD treatment in the OLE, of the 69 patients with ALT or AST elevations, 26 (38%) patients first had an ALT or AST elevation within 1 month (30 days), for 19 (28%) patients this was between 1 and 3 months, and for 24 (35%) patients this was after 3 months (100 days). At the time of analysis, 59 (86%) patients had resolved ALT or AST levels, either spontaneously during stable CBD dosing (n = 22 [37%]), following discontinuation from trial (n = 12 [20%]), or after CBD/ASM dose reduction (n = 25 [42%]), with 10 elevations still ongoing. Of the 25 patients who had their CBD/ASM dose reduced, 14 patients had their valproic acid dose reduced.

3.5 | Efficacy

The decrease in the number of patients included in the efficacy analyses through the later 12-week treatment periods was due to withdrawals (Figure S1) and also due to patients with ongoing treatment not having reached the

TABLE 1 Demographics and baseline characteristics for CBD OLE, $N = 315$

Parameter	Value
Age at entry to OLE, years	
Mean (SD)	9.7 (4.4)
Median (range)	9.3 (2.5–19.3)
Age group, years, *n* (%)	
2–5	82 (26)
6–11	134 (43)
12–17	90 (29)
≥18	9 (3)
Gender, *n* (%)	
Male	156 (50)
Geographical region, *n* (%)	
United States	176 (56)
Rest of world	139 (44)
Body mass index at entry to OLE, mean (SD)	19 (5)
Number of concomitant ASMs, median (range)	3 (1–8)
Baseline seizure frequency, median (lower quartile, upper quartile)	
Convulsive	12.4 (6.3, 33.4)
Total	36.0 (10.6, 194.1)
Concomitant ASMs [>20%], *n* (%)	
Valproic acid	218 (69)
Clobazam	215 (68)
Stiripentol	120 (38)
Levetiracetam	92 (29)
Topiramate	83 (26)
Time on CBD treatment, days, median (range)	444 (18–1535)
Modal CBD dose, mg/kg/day, mean (SD)	22 (5)

Abbreviations: ASM, antiseizure medication; CBD, cannabidiol; *N*, number of patients in analysis set; *n*, number of patients with data/characteristic; OLE, open-label extension.

later treatment periods at the time of this analysis (see Supporting Information).

During Weeks 1–12 of the OLE, the median reduction in monthly convulsive seizure frequency from the baseline period was 45% (a reduction from a median of 12 to a median of 7 seizures per month), and this reduction remained consistent at each 12-week interval through 156 weeks (45%–74%; Figure 2A). LOCF analysis results were generally similar; median reductions in monthly convulsive seizure frequency were 38%–47% through 156 weeks (Figure S2A). For the 143 patients who discontinued the study, median (Q1, Q3) convulsive seizure reduction during their last 12 weeks of treatment was 14% (−33%, 52%). Twenty-one of 290 (7%) patients were convulsive seizure-free in their last 12 weeks of treatment, regardless of when they withdrew from the trial. More than 45% of patients had convulsive seizure frequency reductions of ≥50% at each visit window; ≥25%, ≥50%, ≥75%, and 100% responder rates are shown in Figure 3A. Between Weeks 145 and 156, 49 (74%), 40 (61%), 30 (46%), and 11 (17%) patients experienced ≥25%, ≥50%, ≥75%, and 100% reductions in convulsive seizure frequency, respectively. Responder rates were generally similar in the LOCF analysis, and ≥44% of patients had convulsive seizure frequency reductions of ≥50% at each visit window (Figure S3A).

Median reduction in total seizure frequency from baseline to Weeks 1–12 was 49% (from a median of 36 to a median of 13 seizures per month), and reductions during the subsequent treatment windows ranged from 56% to 84% (Figure 2B). In the LOCF analysis, during Weeks 1–12, the median reduction in monthly total seizure frequency from the baseline period was 49%, and this reduction was generally sustained at each 12-week interval through 156 weeks (49%–55%; Figure S2B). Twelve of 290 (4%) patients were seizure-free in their last 12 weeks of treatment, regardless of when they withdrew from the trial. At least 49% of patients had total seizure-frequency reductions of ≥50% at each visit window, and responder rates of ≥25%, ≥50%, ≥75%, and 100% remained consistent over time (Figure 3B). Responder rates were generally similar in the LOCF analysis; ≥49% of patients had total seizure frequency reductions of ≥50% at each visit window (Figure S3B).

After 156 weeks of treatment, 85% of the 48 patients/caregivers who completed this questionnaire reported an overall improvement in the patient's condition on the S/CGIC (Figure 4). Similar proportions of patients/caregivers reported improvements at each visit.

4 | DISCUSSION

Our long-term OLE data extend previous findings, demonstrating that add-on CBD treatment in patients with DS led to sustained reductions in seizure frequency in the majority of patients with an acceptable safety profile. CBD reduced the frequency of total and convulsive seizures up to 156 weeks of treatment.

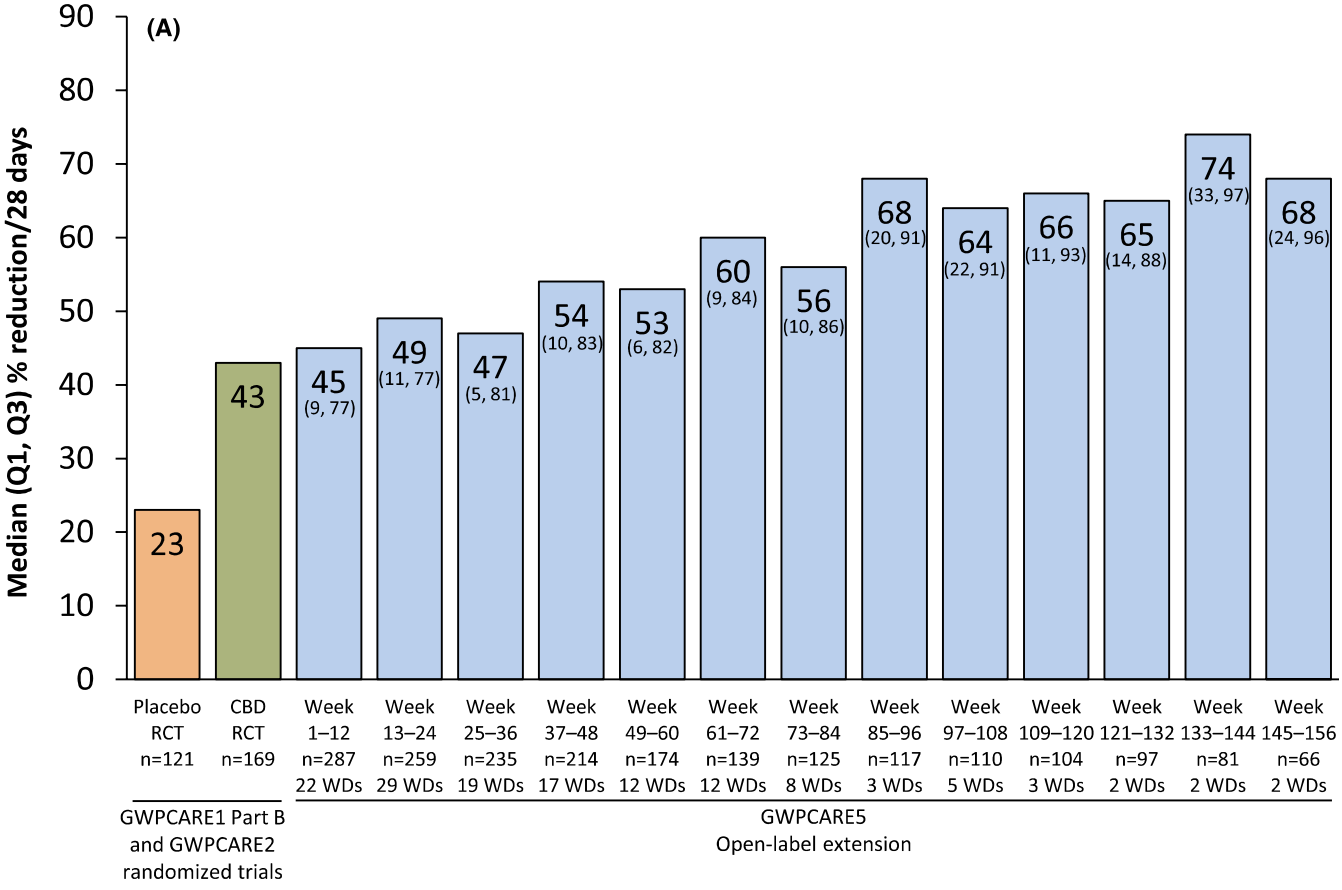
At the time of analysis, 45% patients had withdrawn, 50% had completed the OLE part of the trial, and 5% had ongoing treatment and had not yet reached later treatment windows. Considering the duration of follow-up, the withdrawal rate of 45% in the current trial is not surprising and was similar to the range of other long-term ASM studies of 20%–40% at approximately 1-year follow-up.[11,12] Study burden and the addition of new drug

TABLE 2 All-causality AEs reported in ≥10% patients overall (safety analysis set)

	CBD modal dose			
	≤20 mg/kg/day, *n* = 178	>20–25 mg/kg/day, *n* = 57	>25 mg/kg/day, *n* = 80	CBD, *N* = 315
All-causality AEs, *n* (%)	172 (97)	57 (100)	77 (96)	306 (97)
AEs leading to withdrawal, *n* (%)[a]	25 (14)	1 (2)	2 (3)	28 (9)
Serious AEs, *n* (%)	73 (41)	26 (46)	33 (41)	132 (42)
AEs reported in >10% of patients, *n* (%)				
Diarrhea	64 (36)	35 (61)	36 (45)	135 (43)
Pyrexia	61 (34)	25 (44)	38 (48)	124 (39)
Decreased appetite	53 (30)	20 (35)	26 (33)	99 (31)
Somnolence	49 (28)	17 (30)	21 (26)	87 (28)
Nasopharyngitis	38 (21)	22 (39)	18 (23)	78 (25)
Convulsion	43 (24)	15 (26)	21 (26)	79 (25)
Upper respiratory tract infection	39 (22)	17 (30)	22 (28)	78 (25)
Vomiting	27 (15)	17 (30)	19 (24)	63 (20)
Status epilepticus	20 (11)	9 (16)	18 (23)	47 (15)
Cough	16 (9)	10 (18)	15 (19)	42 (13)
Fatigue	24 (14)	6 (11)	9 (11)	39 (12)
AST increased	24 (14)	8 (14)	6 (8)	38 (12)
Influenza	17 (10)	7 (12)	13 (16)	37 (12)
Sinusitis	13 (7)	8 (14)	17 (21)	38 (12)
Pneumonia	19 (11)	9 (16)	9 (11)	35 (11)
Ear infection	13 (7)	10 (18)	12 (15)	35 (11)
ALT increased	21 (12)	8 (14)	7 (9)	36 (11)
Abnormal behavior	17 (10)	10 (18)	7 (9)	34 (11)
GGT increased	18 (10)	6 (11)	8 (10)	32 (10)
Serious AEs reported in >1% of patients, *n* (%)				
Status epilepticus	20 (11)	9 (16)	18 (23)	47 (15)
Convulsion	18 (10)	6 (11)	10 (13)	34 (11)
Pneumonia	11 (6)	4 (7)	5 (6)	20 (6)
Pyrexia	13 (7)	2 (4)	2 (3)	17 (5)
AST increased	6 (3)	2 (4)	2 (3)	10 (3)
ALT increased	3 (2)	2 (4)	2 (3)	7 (2)
Influenza	3 (2)	0	4 (5)	7 (2)
Dehydration	4 (2)	1 (2)	1 (1)	6 (2)
Diarrhea	4 (2)	0	1 (1)	5 (2)
Sudden unexplained death in epilepsy	4 (2)	0	0	4 (1)
Generalized tonic–clonic seizure	2 (1)	0	2 (3)	4 (1)
GGT increased	3 (2)	1 (2)	0	4 (1)
Gastroenteritis, viral	1 (1)	0	3 (4)	4 (1)
Respiratory syncytial virus infection	1 (1)	2 (4)	1 (1)	4 (1)
Pneumonia aspiration	2 (1)	0	2 (3)	4 (1)

Abbreviations: AE, treatment-emergent adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, cannabidiol; GGT, gamma glutamyl transferase; *N*, number of patients in analysis set; *n*, number of patients with data/characteristic.

[a]Includes all patients with an AE listed as one of the reasons for withdrawal.



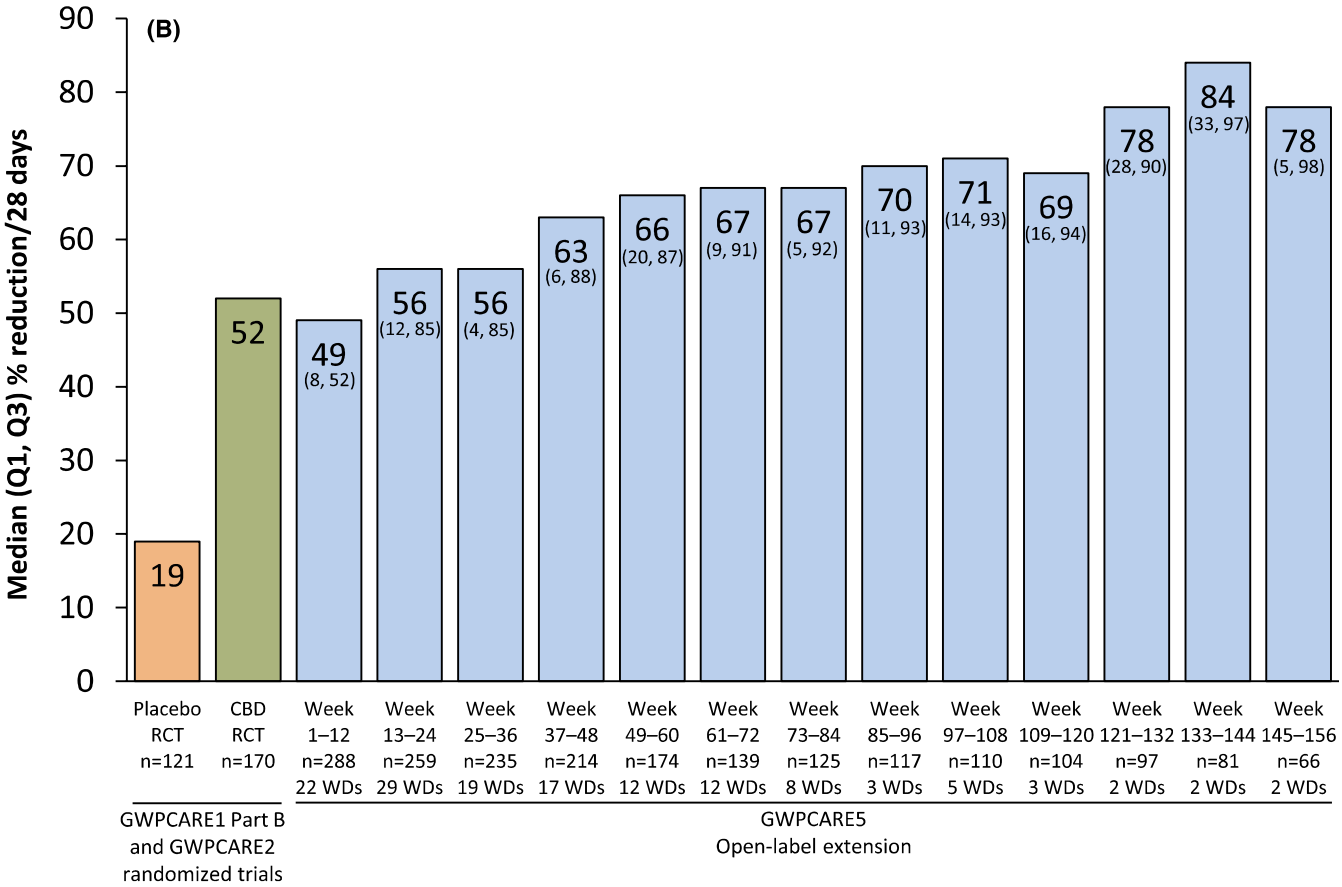


FIGURE 2 Reductions in (A) convulsive seizure frequency and (B) total seizure frequency (efficacy population). CBD, cannabidiol; Q1, quartile 1; Q3, quartile 3; RCT, randomized controlled trial; WDs, withdrawals. Due to staggered entry into the study, the decreasing *n* at the later time points reflects a combination of discontinuations and patients still in the study who had not yet reached the later time points

trials for DS (fenfluramine [NCT02826863] and ataluren [NCT02758626]) also likely contributed to the withdrawals in the current study.

Overall, the safety profile of CBD was similar to the original 14-week RCTs, GWPCARE1 Part B and GWPCARE2, with no new safety signals emerging.[5,8] The most common AEs in this trial were diarrhea, pyrexia, decreased appetite, and somnolence.

Median CBD exposure in this OLE trial was approximately 63 weeks, with patients treated for up to 219 weeks. The median CBD exposure was approximately 5 times the duration of the original RCTs,[5,8] and more than double the duration of the previously reported data from this OLE.[10]

In GWCARE1, the target CBD dose was 20 mg/kg/day,[5] and in GWPCARE2, target doses were 10 or 20 mg/kg/day.[8] In the OLE trial, patients were able to titrate to up to 30 mg/kg/day CBD, and the mean modal dose was 22 mg/kg/day. In GWPCARE2, both CBD doses led to similar clinically relevant reductions in convulsive seizure frequency, with a better safety and tolerability profile at the 10-mg/kg/day dose.[8] Withdrawal rates due to AEs were similar in the OLE trial compared with the preceding RCTs (9% in OLE vs. 13% in GWPCARE1 and 0%–7% [10- and 20-mg/kg/day dose groups, respectively] in GWPCARE2).[5,8] Only three of 137 (2%) patients taking CBD at modal doses of >20 mg/kg/day experienced AEs leading to discontinuation, compared with 25 of 178 (14%) patients taking ≤20 mg/kg/day, indicating that some patients are capable of tolerating CBD at higher doses than those evaluated in the RCTs.

Looking at AE data by CBD modal dose in the OLE trial (≤20, >20–25, or >25 mg/kg/day), patients taking higher CBD doses experienced more AEs of status epilepticus. Incidence rates were 11% for patients taking ≤20 mg/kg/day, 16% for patients taking >20–25 mg/kg/day, and 23% for patients taking >25 mg/kg/day CBD. In general, the incidence of status epilepticus as an AE was higher than observed in the preceding RCTs (15% in the OLE vs. 6% in GWPCARE1 Part B and 8%–10% in GWPCARE2).[5,8] These findings may be explained by the longer treatment exposure in the OLE trial and reflect the natural history of DS, where recurrent episodes of status epilepticus occur, particularly in younger individuals. Furthermore, a selection bias is likely to be operating, as those with more severe epilepsy would be more likely to be placed on higher doses of CBD, explaining the correlation of more episodes of status epilepticus occurring in those on higher doses of CBD. By CBD modal dose in the OLE trial (≤20, >20–25, or >25 mg/kg/day), there were no notable differences in overall AE or serious AE incidence rates.

In general, in the OLE trial, there was a higher proportion of patients with serious AEs (42% in the OLE vs. 16% in GWPCARE1 Part B and 20%–25% in GWPCARE2).[5,8] These findings may be explained by the longer treatment exposure in the OLE trial. More patients taking >20 mg/kg/day CBD experienced diarrhea (52%) than those taking ≤20 mg/kg/day (36%), which is consistent with the increased incidence rate seen with increasing CBD dose in GWPCARE2 (17% in 10-mg/kg/day group vs. 26% in 20-mg/kg/day group).[8] Despite AEs of diarrhea and decreased appetite being reported in many patients, AEs of decreased weight were reported by fewer patients (7%) and were usually mild in severity.

Most (84%) patients with liver enzyme elevations (ALT and/or AST >3 × ULN) were receiving concomitant valproic acid. An interaction between CBD and valproic acid leading to increased risk of liver enzyme elevations was reported in GWPCARE1, GWPCARE2, and a CBD expanded-access program.[5,8,13] Based on the findings of this and previous trials, patients taking valproic acid and CBD (especially 20 mg/kg/day or more) are at most risk of liver enzyme elevations; therefore, discontinuation or dose reduction of CBD and/or concomitant valproic acid should be considered.

Five deaths occurred during follow-up: four due to SUDEP and one due to convulsion; this is consistent with a rate of ≈7.4 deaths/1000 patient-years. Other studies have reported ≈16 deaths/1000 patient-years among patients with DS.[4]

The reductions in convulsive seizure frequency reported in GWPCARE1 Part B and GWPCARE2 were maintained in the OLE trial.[5,8] The reduction in seizure frequency was evident in both observed cases and LOCF analyses, which can better account for the impact of early discontinuations on estimates of treatment effect. This finding is notable considering the number of concomitant therapies received by enrolled patients (median = 3 ASMs) and the number of therapies discontinued by patients before CBD treatment (median = 4 ASMs in GWPCARE1 and GWPCARE2).[5,8] The reductions in total seizure frequency observed in GWPCARE1 Part B and GWPCARE2[5,8] were maintained in this OLE and were similar to reductions in convulsive seizure frequency.

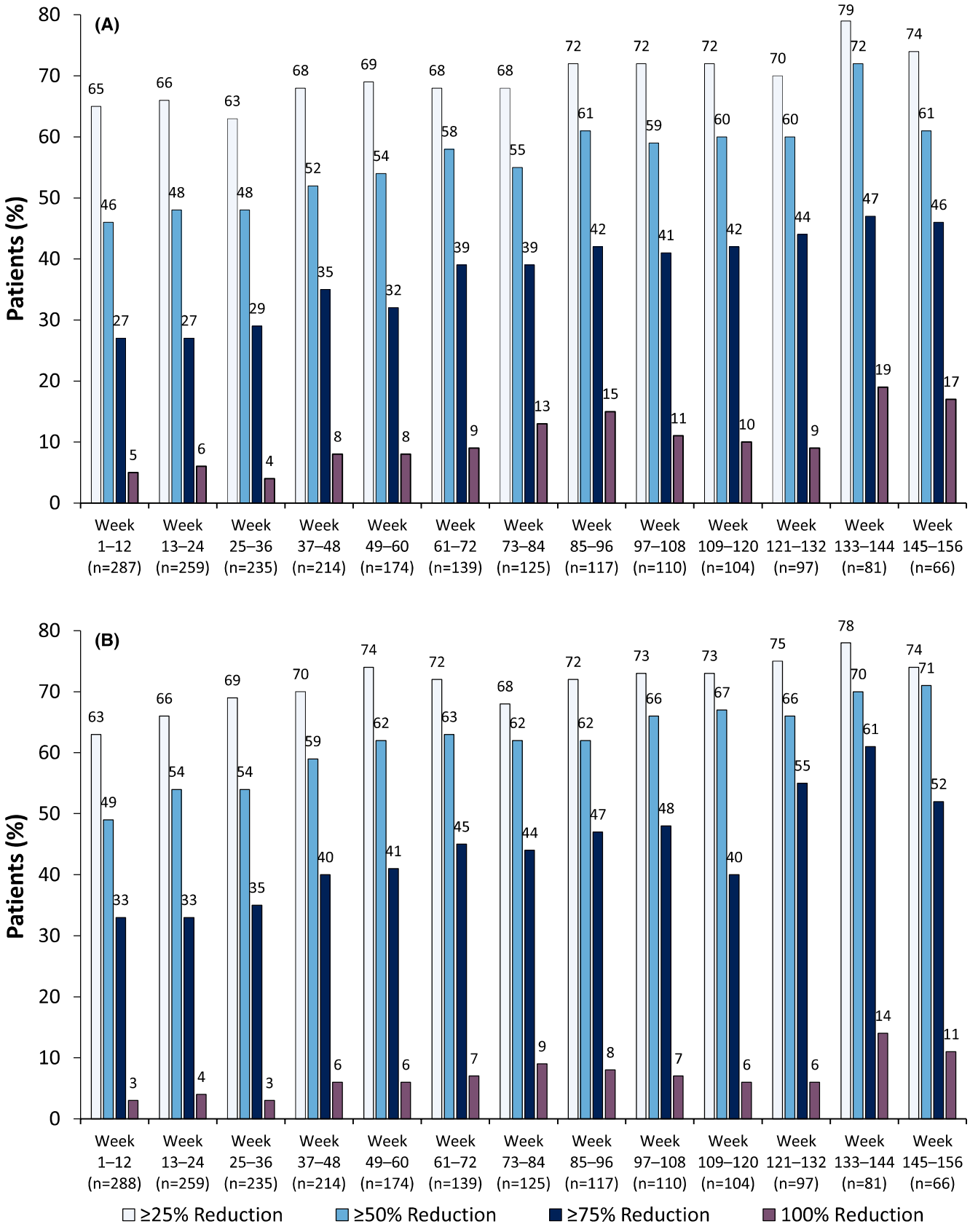


FIGURE 3 Responder rates for (A) convulsive and (B) total seizures (efficacy population)

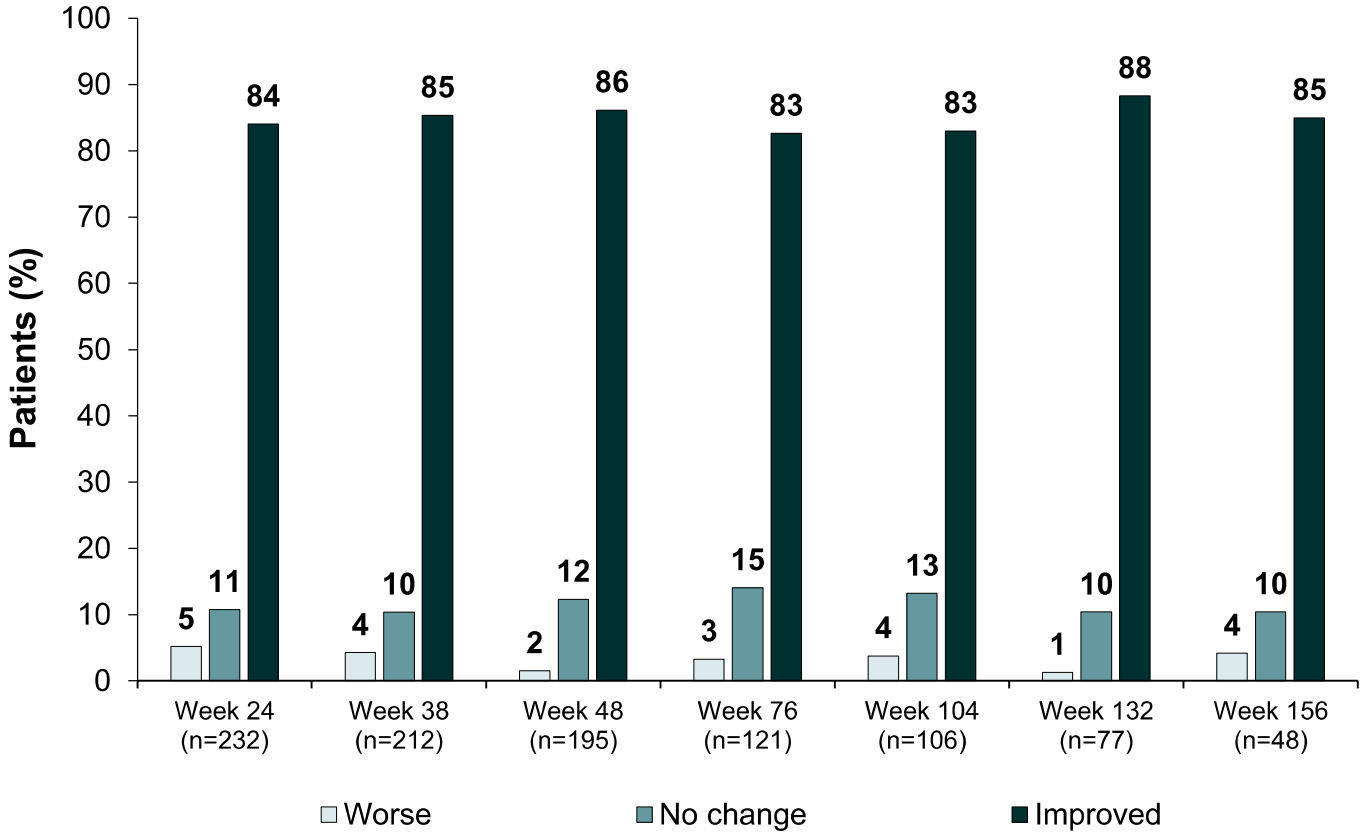


FIGURE 4 Patient/caregiver ratings of change in overall condition on the Subject/Caregiver Global Impression of Change scale

The mean modal CBD dose was generally consistent across each 12-week period as well as in the last 12 weeks of data for each patient, indicating that there was no development of tolerance to treatment and seizure frequency reductions were sustained without increased CBD dose. The proportion of patients/caregivers reporting improvement was ≥83% at all time points assessed, suggesting that the reduced seizure frequencies were clinically meaningful for most patients/caregivers.

4.1 | Limitations

There are several important limitations of this trial that warrant caution in the interpretation of our findings. Common to OLE trials was the lack of a control arm. Addition or dose reductions of ASMs (as well as diet and neuromodulation therapies such as vagus nerve stimulation) and changing CBD dose were allowed, and the analyses presented here do not investigate the potential impact of these changes on the trial outcomes. Significant attrition of the study sample over time was observed, such that the efficacy data obtained at later time points is subject to selection bias, with patients with lower efficacy or worse tolerability discontinuing the trial earlier. The same applies to fewer patients in higher CBD dose groups appearing to withdraw; it is likely that patients with poor tolerability to CBD were discontinued before the dose was increased to >20 mg/kg/day. In addition, slightly more than half of the patients participating in the OLE had been previously exposed to CBD in the parent trial, which could have lowered the rate of AEs, as patients with AEs could have discontinued in the parent trial and not participated in the OLE. Efficacy and S/CGIC data were determined as percentage changes from the pretreatment baseline from the original RCTs. This is a potential confounding factor due to the additional 14-week exposure to CBD for patients randomized to CBD compared with those originally randomized to placebo; however, the longer duration of this OLE analysis would dilute this difference over time. The high proportion of patients/caregivers reporting improvement in overall condition via the S/CGIC questionnaire may have been affected by the closer monitoring from participating in a clinical trial. Moreover, for the placebo-treated patients during the original RCT who participated in the OLE trial, seizure frequency reduction matched that of the CBD-treated patients within the first 12 weeks of OLE treatment (data not shown). There is a tendency for some DS patients to have fewer seizures as they age,[14] so the role of the natural evolution of the

disease over a 3-year follow-up, which has not been reported previously in this syndrome, may be a confounding factor.

Safety and tolerability data are reported for the OLE only. Due to this, there is the potential to underestimate AE burden, as patients who experienced AEs or dose changes due to AEs in the preceding RCTs are not reflected in this report due to withdrawal. Interpretation of safety and tolerability data should also consider the extended treatment duration, as spontaneously occurring conditions are more likely to be experienced when observations are extended over a prolonged multiyear period. For this interim analysis, patients had different durations of exposure to drug.

5 | Conclusions

Long-term, add-on CBD treatment had a reassuringly similar safety profile to that observed in the original RCTs. Sustained reductions in convulsive and total seizures were observed up to 156 weeks, with 85% of patients/caregivers reporting an improvement in overall condition. This OLE demonstrates the sustained long-term benefits of Epidiolex/Epidyolex, the regulated and highly purified formulation of plant-based CBD, for patients with DS, a critical issue for CBD in joining our ASM armamentarium.

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CONFLICT OF INTEREST

I.E.S. has served on scientific advisory boards/consulted for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Xenon Pharmaceuticals, Zynerba Pharmaceuticals, Ovid Therapeutics, Atheneum Partners, Chiesi, Encoded Therapeutics, and Knopp Biosciences; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, and Eisai; and has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharmaceuticals, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics, and Marinus. She may accrue future revenue on pending patent WO61/010176 (filed in 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics and licensed to various diagnostic companies; and has a patent for molecular diagnostic/theranostic target for benign familial infantile epilepsy (PRRT2) 2011904493, 2012900190, and PCT/AU2012/001321 (TECH ID:2012-009) with royalties paid. J.J.H. receives research support from GW Pharmaceuticals, SK Life Sciences, and Cerevel Therapeutics, and is a consultant for NCGS and SK Life Sciences. I.M. has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Insys Pharmaceuticals, GW Pharmaceuticals, TS Alliance, DS Foundation, Visualase, Neuroblate, Zogenix, and Ultragenix; and is a trial investigator for GW Research. R.N. has received research grants from the European Union (Horizons2020, FP7) and from UCB, Eisai, LivaNova, and GW Pharmaceuticals; has served as a consultant/advisor/lecturer for Novartis, Takeda, Zogenix, Supernus, Stoke, Biocodex, Nutricia, Advicenne, Eisai, and GW Pharmaceuticals; and is a study investigator for GW Research, Advicenne, UCB, Eisai, and Zogenix. R.S.-C. has received research support from GW Pharmaceuticals and Zogenix for clinical trials; has served on advisory boards for Novartis, GW Pharmaceuticals, and Zogenix; and is a trial investigator for Takeda. Y.S.-M. is a trial investigator for GW Research and for Acadia Pharmaceuticals. M.W. is a trial investigator for GW Research. M.Z. is a trial investigator for GW Research, Zogenics, and Takeda. D.C. is employed by GW Research. E.D. is employed by Greenwich Biosciences. O.D. receives grant support from the NINDS, NIMH, MURI, CDC, and NSF. He has equity and/or compensation from the following companies: Privateer Holdings, Tilray, Receptor Life Sciences, Q-State Biosciences, Tevard, Empatica, Engage, Egg Rock/Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises. He has received research support from GW Pharmaceuticals and Zogenix.

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SUPPORTING INFORMATION

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

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