Received: 13 October 2021 | Revised: 2 December 2021 | Accepted: 6 December 2021

DOI: 10.1111/epi.17150

Epilepsia®

RESEARCH ARTICLE

Long-term cannabidiol treatment for seizures in patients with tuberous sclerosis complex: An open-label extension trial

Elizabeth A. Thiele[1] | **E. Martina Bebin**[2] | **Francis Filloux**[3] | **Patrick Kwan**[4] | **Rachael Loftus**[5] | **Farhad Sahebkar**[6] | **Steven Sparagana**[7] | **James Wheless**[8]

[1]Massachusetts General Hospital, Boston, Massachusetts, USA

[2]University of Alabama School of Medicine, Birmingham, Alabama, USA

[3]University of Utah School of Medicine, Salt Lake City, Utah, USA

[4]Monash University and the University of Melbourne, Melbourne, Victoria, Australia

[5]GW Research Ltd, Cambridge, UK

[6]Greenwich Biosciences, Inc., Carlsbad, California, USA

[7]Scottish Rite for Children and the University of Texas Southwestern Medical Center, Dallas, Texas, USA

[8]Le Bonheur Children's Hospital and the University of Tennessee Health Science Center, Memphis, Tennessee, USA

Correspondence
Elizabeth A. Thiele, Pediatric Epilepsy Program, 175 Cambridge St, Suite 340, Boston, MA 02114, USA.
Email: ethiele@mgh.harvard.edu

Funding information
This study was sponsored by GW Research Ltd., Cambridge, UK.

Abstract

Objective: To evaluate the long-term safety and efficacy of add-on cannabidiol (CBD) in patients with seizures associated with tuberous sclerosis complex (TSC) in the open-label extension (OLE) of the randomized, placebo-controlled phase 3 trial GWPCARE6 (NCT02544763). Results of an interim (February 2019 data cut) analysis are reported.

Methods: Patients who completed the randomized trial enrolled to receive CBD (Epidiolex® in the United States; Epidyolex® in the EU; 100 mg/mL oral solution). The initial target dose was 25 mg/kg/day, which, based on response and tolerability, could be decreased or increased up to 50 mg/kg/day. The primary end point was safety. Key secondary end points included percentage reduction in TSC-associated (countable focal and generalized) seizures, responder rates, and Subject/Caregiver Global Impression of Change (S/CGIC).

Results: Of 201 patients who completed the randomized phase, 199 (99%) entered the OLE. Mean age was 13 years (range, 1–57). At the time of analysis, 5% of patients had completed treatment, 20% had withdrawn, and 75% were ongoing. One-year retention rate was 79%. Median treatment time was 267 days (range, 18–910) at a 27 mg/kg/day mean modal dose. Most patients (92%) had an adverse event (AE). Most common AEs were diarrhea (42%), seizure (22%), and decreased appetite (20%). AEs led to permanent discontinuation in 6% of patients. There was one death that was deemed treatment unrelated by the investigator. Elevated liver transaminases occurred in 17 patients (9%) patients; 12 were taking valproate. Median percentage reductions in seizure frequency (12-week windows across 48 weeks) were 54%–68%. Seizure responder rates (≥50%, ≥75%, 100% reduction) were 53%–61%, 29%–45%, and 6%–11% across 12-week windows for 48 weeks. Improvement on the S/CGIC scale was reported by 87% of patients/caregivers at 26 weeks.

Significance: In patients with TSC, long-term add-on CBD treatment was well tolerated and sustainably reduced seizures through 48 weeks, with most patients/caregivers reporting global improvement.

KEYWORDS

antiseizure medication, cannabidiol, epilepsy, focal seizures, treatment-resistant epilepsy, tuberous sclerosis complex

1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is a highly variable genetic disorder characterized by benign hamartomas in multiple organ systems, most notably in brain, skin, kidneys, lungs, heart, and eyes.[1–4] It is caused primarily by mutations in tumor suppressor genes *TSC1* or *TSC2*, resulting in an increased mechanistic target of rapamycin (mTOR) activation with subsequent excessive cell growth and proliferation.[1–3,5] The incidence of TSC is estimated at 1 in 6000 live births, affecting 40 000–80 000 people in the United States and 1–2 million people worldwide.[6,7] Approximately ~85% of patients with TSC experience epilepsy, with onset usually during the first 2 years of life; it can persist lifelong with multiple seizure types.[6,8–11] Patients with TSC experience infantile spasms and focal seizures as infants and various other seizure types as the disease progresses.[9,12]

Current treatments for seizures associated with TSC include antiseizure medications (ASMs), commonly referred to as antiepileptic drugs; the mTOR pathway inhibitor everolimus; surgical procedures; vagus nerve stimulation; and dietary therapy.[6,13–17] Despite these treatment options, more than 60% of patients have treatment-resistant epilepsy,[12] which can be associated with various neurodevelopmental disorders.[10,18]

Highly purified pharmaceutical formulation of cannabidiol (CBD; Epidiolex® in the United States and Epidyolex® in the United Kingdom, European Union, and Australia) has demonstrated efficacy, with an acceptable safety profile against seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in four randomized, placebo-controlled phase 3 trials.[19–22] Results from an expanded-access program demonstrated that CBD may also be an effective and well-tolerated treatment for TSC-associated seizures.[23] The effect of CBD on seizures associated with TSC was further evaluated in a 16-week, randomized, double-blind, placebo-controlled, multicenter phase 3 trial (GWPCARE6). In this trial, add-on CBD produced almost 50% reduction in TSC-associated seizures compared with an ≈30% reduction with placebo, and had an acceptable safety profile.[24] Based on these results, CBD was approved for treatment of seizures associated with TSC in patients aged 1 year and older in the United States[25] and at least 2 years of age in the United Kingdom and in the European Union.[26]

Key Points

- This was an open-label extension (OLE) of a phase 3 trial (GWPCARE6), evaluating the long-term safety and efficacy of cannabidiol (CBD) in patients with tuberous sclerosis complex (TSC)–associated seizures
- One hundred ninety-nine patients were treated with CBD at a mean modal dose of 27 mg/kg/day for a median of 267 days (range, 18–910) of treatment
- Most patients (92%) had an adverse event (AE); the most common AEs were diarrhea, seizure, and decreased appetite, and they were mostly mild or moderate in severity
- The median percentage reduction of 54% in TSC-associated seizures was observed at week 12 and sustained through 48 weeks of treatment
- More than 80% of patients/caregivers and physicians reported an improvement in the patient's overall condition at 26 weeks

Patients who completed treatment in the placebo-controlled, double-blind phase of GWPCARE6 were eligible to enroll in the open-label extension (OLE) phase under the same protocol for evaluation of the long-term safety and efficacy of CBD. Herein we present results of an interim analysis (data cutoff, February 26, 2019) of safety, efficacy, and patient/caregiver- and physician-reported outcomes in patients with TSC enrolled in the OLE phase of GWPCARE6.

2 | METHODS

This study was an OLE of the 16-week randomized, double-blind, placebo-controlled, multinational phase 3 trial GWPCARE6 (NCT02544763) and enrolled patients

who completed treatment in the randomized, controlled, blinded phase. Patients with a definite clinical diagnosis of TSC[1] and treatment-resistant epilepsy were eligible if they were 1–65 years of age; had at least eight TSC-associated seizures during the 4-week baseline period, with at least one seizure occurring in at least 3 of the 4 weeks; and were taking at least one ASM at baseline of the randomized, controlled phase. Key exclusion criteria were a history of nonepileptic seizures, clinically significant illness other than epilepsy, surgery for epilepsy in the 6 months before screening, felbamate use for less than 1 year before screening, and a history of alcohol or substance abuse or recreational or medicinal use of cannabis or cannabinoid-based medications. Although not allowed during the randomized phase, on-label use of mTOR inhibitors for the treatment of seizures and tumors was permitted during the OLE. The trial protocol was approved by the relevant institutional review board or ethics committee at each participating site and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice. All patients or their caregivers provided written informed consent before any trial procedure was carried out. Patients who were developmentally mature enough to understand the trial provided written assent.

All patients received a pharmaceutical formulation of highly purified CBD derived from *Cannabis sativa* L. plant (100 mg/ml oral solution; Epidiolex® in the United States and Epidyolex® in the United Kingdom, European Union, and Australia; GW Research Ltd, Cambridge, United Kingdom). After completing treatment in the randomized phase, patients started a 2-week blinded transition period, during which the blinded medication (CBD 25 mg/kg/day, CBD 50 mg/kg/day, or placebo) from the randomized, controlled phase was tapered down to zero while simultaneously CBD was titrated up to 25 mg/kg/day (Table S1). The dose could then be titrated up to 50 mg/kg/day during a 3-week titration period in increments of 2.5 mg/kg/day every 2 days. The daily dose of CBD was maintained throughout the trial; however, the investigator could decrease the dose if a patient experienced intolerance or could increase it up to the maximum dose of 50 mg/kg/day if required for better seizure control, until the optimal dose was found. CBD was taken twice daily in equally divided doses in addition to the patient's current ASM. The dose for concomitant ASMs could also be adjusted to manage side effects associated with their use. Patients could receive treatment for up to 1 year, except in the United States and Poland, where they could continue treatment beyond 1 year. At the end of treatment, patients (outside the United States and Poland) could continue using CBD outside the study. For patients who did not immediately continue using CBD outside the trial or upon decision to withdraw, CBD dose was tapered down by 10% per day for 10 days, unless continued dosing was not possible because of an adverse event (AE). A follow-up visit was performed 4 weeks after the last dose of CBD (including the final taper period dose) in patients completing or withdrawing from the trial. The study design is shown in Figure S1.

The primary objective of this OLE study was to evaluate the long-term safety and tolerability of add-on CBD based on the incidence, type, and severity of treatment-emergent AEs in patients with uncontrolled seizures associated with TSC. Patients used paper diaries for daily recording of any AEs, CBD intake, and the use of concomitant ASMs and rescue medications throughout the study. Blood and urine samples for clinical laboratory assessments were collected at all clinic visits (when possible).

The secondary objective was evaluation of efficacy through assessment of percentage change in the frequency of TSC-associated seizures; the number of patients considered treatment responders with ≥25%, ≥50%, ≥75%, and 100% reduction in TSC-associated seizures; change in overall condition of patients on the Subject/Caregiver Global Impression of Change (S/CGIC) scale and Physician Global Impression of Change (PGIC) scale; and percentage change in the frequency of total seizures. All changes were assessed relative to the pre-randomization baseline of the trial's blinded phase. TSC-associated seizures included countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures (tonic–clonic, tonic, clonic, or atonic); they excluded absence, myoclonic, focal sensory, and infantile/epileptic spasms. This functional definition of TSC-associated seizures was approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Epilepsy Study Consortium's independent committee of experts. Total seizures included TSC-associated seizures, infantile/epileptic spasms, and absence, myoclonic, and focal sensory seizures. Patients or their caregivers used an interactive voice-response system to record the number and type of seizures, severity of focal seizures, and the number of status epilepticus episodes. The S/CGIC and PGIC scales are both 7-point scales that include three categories for improvement (slightly improved, much improved, and very much improved), three for worsening (slightly worse, much worse, and very much worse), and an option to indicate no change.

No formal sample size was calculated for this open-label trial, and all patients who completed the blinded, placebo-controlled phase were eligible to enroll. All

patients who received at least one dose of CBD during the OLE were included in the safety evaluation data set. Safety data for the complete OLE phase are reported here. Seizure frequency (average per 28 days) was calculated for each 12-week treatment window and expressed as median percentage reduction from pre-randomization baseline. Seizure outcomes for up to 48 weeks of treatment are presented here. Analyses of seizure frequency and treatment responder rates were repeated using the last observation carried forward (LOCF) imputation step, which is described in the Appendix S1. Seizure outcomes analyses were conducted for patients who completed weeks 37–48 of the treatment period. In addition, we conducted a post hoc analysis to evaluate the safety and efficacy of CBD by modal dose categories ≤25 and >25 mg/kg/day. The S/CGIC and PGIC results at the 26-week visit are reported. There was no formal hypothesis testing and results are presented descriptively.

3 | RESULTS

3.1 | Patients

Of the 201 patients who completed treatment in the placebo-controlled, double-blind phase of the trial, 199 enrolled in the OLE phase (Figure 1) conducted at 43 sites across six countries (Australia, The Netherlands, Poland, Spain, United Kingdom, and the United States). At the time of this analysis, 10 patients (5%) had completed treatment, 39 (20%) had withdrawn, and 150 (75%) had treatment ongoing. The reasons for withdrawal from the OLE were AEs (11 patients [6%]) and decision to withdraw by the patient (8 [4%]), parent/guardian (5 [3%]), or investigator (3 [2%]); 1 patient (0.5%) met the withdrawal criteria, and 11 patients (6%) had other reasons for withdrawal. The 1-year retention rate (calculated as the number of patients who reached the treatment window at weeks 37–48 divided by the total number of patients who could have reached it at the time of this analysis) was 79%, with 104 patients reaching weeks 37–48 of the 131 patients who could have reached the treatment window (Table S2).

The median patient age was 10.8 years; 46 (23%) were age 18 and older (Table 1). Patients had previously tried and discontinued a median of four ASMs and were taking a median of three ASMs at the start of the placebo-controlled phase. Valproate (41%), vigabatrin (36%), clobazam (32%), and levetiracetam (29%) were the most commonly used medications during the OLE. Although mTOR inhibitors were not allowed during the randomized phase, 9 patients received everolimus and 25 sirolimus during the OLE. Five patients (3%) were on concomitant ketogenic diet therapy, and 23 (12%) were using vagus nerve stimulation. The median number of TSC-associated seizures during the 4-week pre-randomization baseline was 56.9.

Overall median treatment duration was 267 days (range, 18–910 days) and patient-years on treatment was 152.9, and the mean modal (standard deviation [SD]) dose was 27 mg/kg/day (7.3). The mean modal (SD) dose was 26 mg/kg/day (6.1) for weeks 1–12 and 28 mg/kg/day (7.7–8.8) for the remaining 12-week treatment windows through week 48. Of the total 199 patients, 156 (78%) had a CBD modal dose ≤25 mg/kg/day with a mean (SD) of 24 mg/kg/day (3.3) and 43 (22%) had modal dose >25 mg/kg/day with a mean (SD) of 38 mg/kg/day (7.4). The median treatment duration was 232 days (range, 18–876 days) and patient-years on treatment was 110.5 for patients with a modal dose ≤25 mg/kg/day. For patients with a modal dose >25 mg/kg/day, the median treatment duration was 318 days (range, 40–910 days) and patient-years on treatment was 42.4.

3.2 | Safety

Treatment-emergent AEs were reported in 92% of all patients, 91% of patients with modal dose ≤25 mg/kg/day, and 98% of patients with modal dose >25 mg/kg/day (Table 2). Most AEs were of mild or moderate severity, with 36% of patients reporting the severity as mild, 47% as moderate, and 9% as severe. Diarrhea, seizures, and decreased appetite were the most frequently reported AEs, and most of these were of mild or moderate severity (Table 2 and Table S3). Somnolence was reported more frequently in patients taking concomitant clobazam (16 of 66 patients [24%]) than in patients not on clobazam (15 of 133 patients [11%]); the overall incidence of AEs was similar between the two subgroups (94% of patients taking clobazam vs 92% of those not taking clobazam). An AE was listed as one of the reasons for permanent treatment discontinuation in 12 patients (6%). The most common AE leading to permanent treatment discontinuation in >1% of patients was seizures (four patients [2%]; Table S3). Fifty patients (25%) had permanent dose reduction because of an AE, primarily diarrhea (21 patients [11%]; Table S3). Serious AEs were reported by 15% of all patients, with seizures and status epilepticus as the most frequently reported serious AEs in >1% of patients (Table 2). There was one death due to cardiopulmonary failure during the study, which was deemed not treatment related by the investigator.

Laboratory testing showed elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of more than 3 times the upper limit of normal (ULN) in 17 patients (9%), 12 of whom (71%)

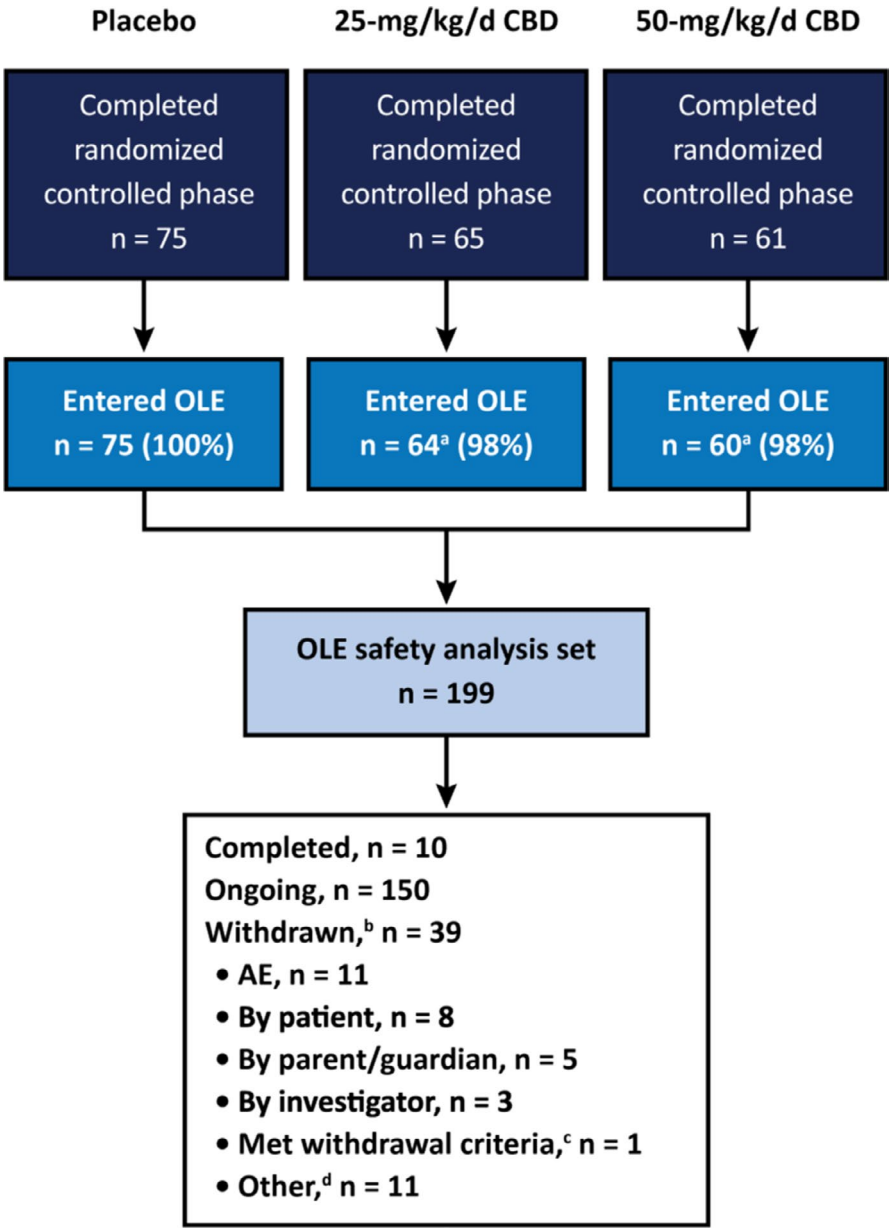

FIGURE 1 Patient disposition. [a]One patient taking cannabidiol (CBD) 25 mg/kg/day in the randomized phase was withdrawn after completing the treatment because of vomiting and did not enter the open label extension (OLE); another patient taking CBD 50 mg/kg/day did not enter the OLE after completing treatment in the randomized phase because of logistical problems and on psychiatrist's recommendation. [b]Withdrawals are reported by the primary reason reported for each patient. [c]One patient met the withdrawal criterion of elevation in ALT/AST levels. [d]Of patients who had other reasons, nine withdrew due to lack of efficacy, one withdrew because of difficulty maintaining compliance, and one switched to a commercial product. Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, cannabidiol; OLE, open-label extension

were taking concomitant valproate. No patient met the standard criteria for severe drug-induced liver injury (Hy's Law) with concurrent bilirubin levels more than 2 times ULN. One patient discontinued treatment because of elevated transaminase levels. Elevations occurred within 1 month of starting treatment in 9 of the 17 patients and between 1 and 3 months of starting treatment in 6 patients; 2 patients had elevations more than 3 months (100 days) after starting treatment. At the time of this analysis, increased ALT or AST levels had resolved in 14 of 17 patients—spontaneously in 6 patients, following treatment discontinuation in 1, and after CBD or ASM dose reduction in 7 (4 patients reduced valproate dose); transaminase levels had not resolved in 3 patients.

3.3 | Efficacy

During the first 12 weeks of the OLE, CBD treatment produced a median reduction of 54% from the randomized phase baseline in the monthly TSC-associated seizure frequency (Figure 2A). The effect was maintained throughout the treatment windows at weeks 13–24, 25–36, and 37–48, with 54%–68% reduction from baseline. Median reduction of 52%–73% was observed in patients with modal dose ≤25 mg/kg/day and 49%–61% in those with modal dose >25 mg/kg/day across the 12-week treatment windows up to 48 weeks (Figure S2A). In the LOCF analysis, a 54%–56% reduction from baseline in TSC-associated seizures was observed across the 12-week windows (Figure S3A); reduction was 61%–68%

TABLE 1 Demographics and characteristics of patients in the OLE

Parameter	CBD modal dose ≤25 mg/kg/day (*n* = 156)	CBD modal dose >25 mg/kg/day (*n* = 43)	Total CBD (*N* = 199)
Age at entry to randomized, controlled phase, years			
Mean (SD)	13.5 (10.5)	12.0 (8.0)	13.2 (10.0)
Median (range)	11.0 (1.1–56.8)	10.1 (1.7–32.7)	10.8 (1.1–56.8)
Age group, years, *n* (%)			
<2	3 (2)	5 (12)	8 (4)
2–5	37 (24)	5 (12)	42 (21)
6–11	44 (28)	15 (35)	59 (30)
12–17	36 (23)	8 (19)	44 (22)
18–65	36 (23)	10 (23)	46 (23)
Sex, *n* (%)			
Male	94 (60)	24 (56)	118 (59)
Race, *n* (%)			
White	138 (88)	39 (91)	177 (89)
Other	18 (12)	4 (9)	22 (11)
Geographic region, *n* (%)			
United States	77 (49)	26 (60)	103 (52)
Rest of the world	79 (51)	17 (40)	96 (48)
Number of ASMs at the start of randomized, controlled phase, median (range)			
Previous	4 (0–15)	4 (0–13)	4 (0–15)
Current	3 (0–5)	3 (1–5)	3 (0–5)
ASMs at start of randomized, controlled phase (>20% of patients in any group), *n* (%)			
Valproate	63 (40)	17 (40)	80 (40)
Vigabatrin	54 (35)	15 (35)	69 (35)
Levetiracetam	41 (26)	15 (35)	56 (28)
Clobazam	43 (28)	11 (26)	54 (27)
Most common ASMs during the OLE (>20% of patients in any group), *n* (%)			
Valproate	65 (42)	17 (40)	82 (41)
Vigabatrin	56 (36)	15 (35)	71 (36)
Clobazam	50 (32)	14 (33)	64 (32)
Levetiracetam	42 (27)	15 (35)	57 (29)
Lamotrigine	30 (19)	15 (35)	45 (23)
Lacosamide	32 (21)	12 (28)	44 (22)
Oxcarbazepine	25 (16)	9 (21)	34 (17)
Number of seizures per 28 days, median (Q1, Q3)			
TSC-associated	54.7 (27.5, 111.0)	66.0 (38.0, 106.0)	56.9 (28.0, 109.0)
Total	57.0 (29.0, 116.9)	66.0 (38.0, 131.0)	58.9 (29.8, 117.0)
Seizure subtypes, *n* (%)			
Focal seizures without impaired awareness	69 (44)	21 (49)	90 (45)
Focal seizures with impaired awareness	108 (69)	26 (60)	134 (67)
Focal to bilateral motor seizures	51 (33)	8 (19)	59 (30)

TABLE 1 (Continued)

Parameter	CBD modal dose		
	≤25 mg/kg/day ($n = 156$)	>25 mg/kg/day ($n = 43$)	Total CBD ($N = 199$)
Tonic–clonic	31 (20)	11 (26)	42 (21)
Tonic	43 (28)	14 (33)	57 (29)
Clonic	7 (4)	0	7 (4)
Atonic	21 (13)	4 (9)	25 (13)
Absence	18 (12)	4 (9)	22 (11)
Myoclonic	10 (6)	2 (5)	12 (6)
Partial sensory	3 (2)	2 (5)	5 (3)
Infantile or epileptic spasms	11 (7)	2 (5)	13 (7)

Abbreviations: ASM, antiseizure medication; CBD, cannabidiol; OLE, open-label extension; Q1, first quartile; Q3, third quartile; SD, standard deviation; TSC, tuberous sclerosis complex.

among patients who completed the weeks 37–48 treatment window (Figure S4A).

More than 50% of patients had ≥50% reduction in TSC-associated seizure frequency across the 12-week treatment windows; ≥75% reduction in seizures was observed in >25% of patients (Figure 3A). More than 5% of patients were seizure-free during each 12-week treatment window, with seven patients (4%) remaining seizure-free the entire treatment period. The proportion of patients who had ≥25%, ≥50%, ≥75%, and 100% reduction in TSC-associated seizures remained consistent across the treatment windows when LOCF was used to calculate responder rates (Figure S5A), as well as among patients who completed the weeks 37–48 treatment window (Figure S6A).

A median reduction from baseline of 51% in the monthly total seizure frequency was observed at the weeks 1–12 treatment window; reduction in seizures was maintained across the 12-week treatment windows through week 48 (54%–67% reduction from baseline; Figure 2B). Reduction in total seizures ranged from 53%–70% in patients with a modal dose ≤25 mg/kg/day and 48%–55% in those with modal dose >25 mg/kg/day (Figure S2B). In the LOCF analysis, 50%–53% reduction in total seizure frequency was observed (Figure S3B). Among patients who completed weeks 37–48 of treatment, 61%–67% reduction from baseline was observed (Figure S4B). Overall, a ≥50% reduction in total seizure frequency was observed in 51%–60% of patients across the 12-week treatment windows for up to 48 weeks (Figure 3B). Patients reporting ≥25%, ≥50%, ≥75%, and 100% reduction in seizures were consistent across the treatment windows in the LOCF analysis of responder rates (Figure S5B), as well as among patients who completed the treatment window at weeks 37–48 (Figure S6B).

At the 26-week visit, 87% of the 124 patients or caregivers who completed the S/CGIC evaluations reported an improvement from baseline in the overall condition of patients (Figure 4). Improvements were reported by 80% of physicians on the PGIC scale.

4 | DISCUSSION

In this interim analysis of the OLE phase of trial GWPCARE6, add-on CBD treatment had an acceptable safety profile and resulted in a sustained reduction in seizures associated with TSC through 48 weeks of treatment. The safety profile of CBD in the OLE was consistent with that in the randomized, placebo-controlled phase of the trial, with more than 90% of patients on CBD reporting a treatment-emergent AE; most AEs were of mild or moderate severity. The safety profile was also consistent with that observed in the trials for Dravet and Lennox-Gastaut syndromes, and no new safety concerns were identified.[19,21,22,27–29] The most frequently reported AEs were similar in the OLE and the randomized, controlled phase, with diarrhea being most common. Although the etiology is not known, diarrhea has been reported as the most frequent AE in other clinical trials of CBD; in most cases, however, the severity was mild or moderate and resolved before the end of treatment.[30,31] Permanent treatment discontinuation because of an AE was low (6%) despite some patients being on treatment for up to 130 weeks, supporting a favorable safety profile of CBD for long-term use in patients with TSC-associated seizures.

Elevations in serum ALT/AST levels (>3 times ULN) were more frequently reported in patients on concomitant valproate. This possible interaction between CBD and valproate leading to elevation in liver enzyme levels was also observed in the randomized phase of this trial, as well as in trials of patients with Dravet and Lennox-Gastaut syndromes.[19,21,22,24,27–29] Therefore, it is recommended

TABLE 2 Treatment-emergent adverse events during the OLE

	CBD modal dose		
	≤25 mg/kg/day (*n* = 156)	>25 mg/kg/day (*n* = 43)	Total CBD (*N* = 199)
Adverse event	**Patients, *n* (%)**		
Any AE	142 (91)	42 (98)	184 (92)
AEs leading to permanent discontinuation[a]	12 (8)	0	12 (6)
Serious AEs	19 (12)	10 (23)	29 (15)
Deaths	1 (0.6)	0	1 (0.5)
AEs reported in >10% of patients in any group			
Diarrhea	63 (40)	20 (47)	83 (42)
Seizure	30 (19)	14 (33)	44 (22)
Decreased appetite	26 (17)	13 (30)	39 (20)
Pyrexia	21 (13)	11 (26)	32 (16)
Vomiting	20 (13)	12 (28)	32 (16)
Somnolence	19 (12)	12 (28)	31 (16)
Nasopharyngitis	22 (14)	6 (14)	28 (14)
Upper respiratory tract infection	19 (12)	7 (16)	26 (13)
Alanine aminotransferase increased[b]	7 (4)	6 (14)	13 (7)
Fall	8 (5)	6 (14)	14 (7)
Cough	7 (4)	5 (12)	12 (6)
Aspartate aminotransferase increased[b]	5 (3)	5 (12)	10 (5)
Weight decreased	5 (3)	5 (12)	10 (5)
Serious AEs reported in >1% of patients in any group			
Seizure	3 (2)	3 (7)	6 (3)
Status epilepticus	4 (3)	1 (2)	5 (3)
Influenza	2 (1.3)	0	2 (1)
Alanine aminotransferase increased[b]	1 (0.6)	1 (2)	2 (1)
Aspartate aminotransferase increased[b]	1 (0.6)	1 (2)	2 (1)
Dehydration	1 (0.6)	1 (2)	2 (1)
Mental status changes	0	2 (5)	2 (1)
Platelet count decreased	1 (0.6)	1 (2)	2 (1)
Transaminase increased	1 (0.6)	1 (2)	2 (1)
Blood bilirubin increased	0	1 (2)	1 (0.5)
Diarrhea	0	1 (2)	1 (0.5)
Gastroenteritis	0	1 (2)	1 (0.5)
Gastroenteritis astroviral	0	1 (2)	1 (0.5)
Lethargy	0	1 (2)	1 (0.5)
Respiratory tract infection	0	1 (2)	1 (0.5)
Seizure cluster	0	1 (2)	1 (0.5)
Soft tissue inflammation	0	1 (2)	1 (0.5)

Abbreviations: AE, adverse event; CBD, cannabidiol; OLE, open-label extension.

[a]Includes patients who listed an AE as one of the reasons for permanent treatment discontinuation and one patient who died during the study.

[b]Liver enzyme elevations include only those reported as an adverse event.

that transaminase levels be monitored regularly in all patients taking CBD, especially those taking concomitant valproate.[25] In 53% of patients with ALT/AST elevations, onset occurred within 1 month of starting treatment, which is also consistent with the controlled phase. In most patients, elevations resolved spontaneously, after

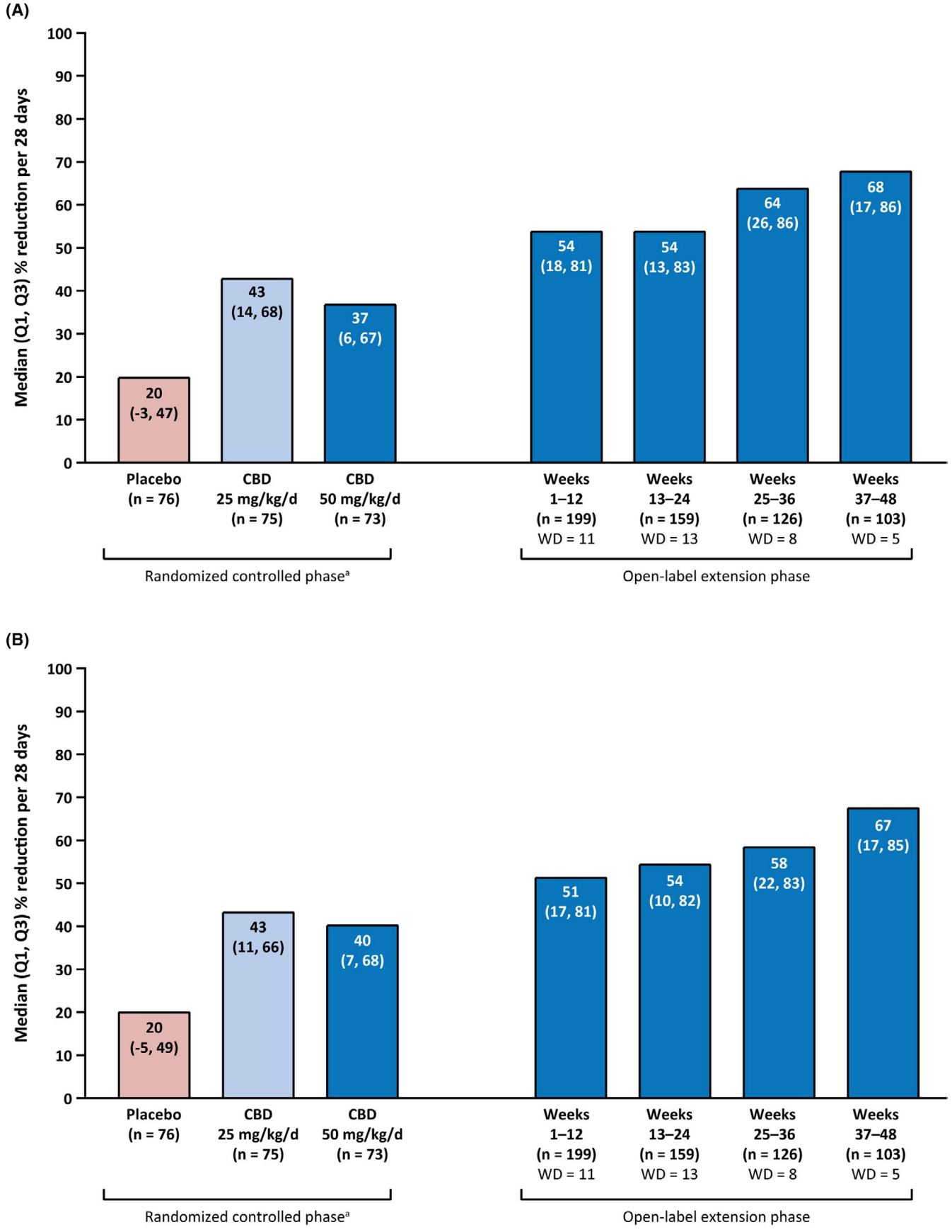

FIGURE 2 Reduction in (A) TSC-associated seizure frequency and (B) total seizure frequency. (A) Data from the randomized, controlled phase of the trial are presented here for comparison. Abbreviations: CBD, cannabidiol; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex; WD, number of patients who withdrew during a treatment window

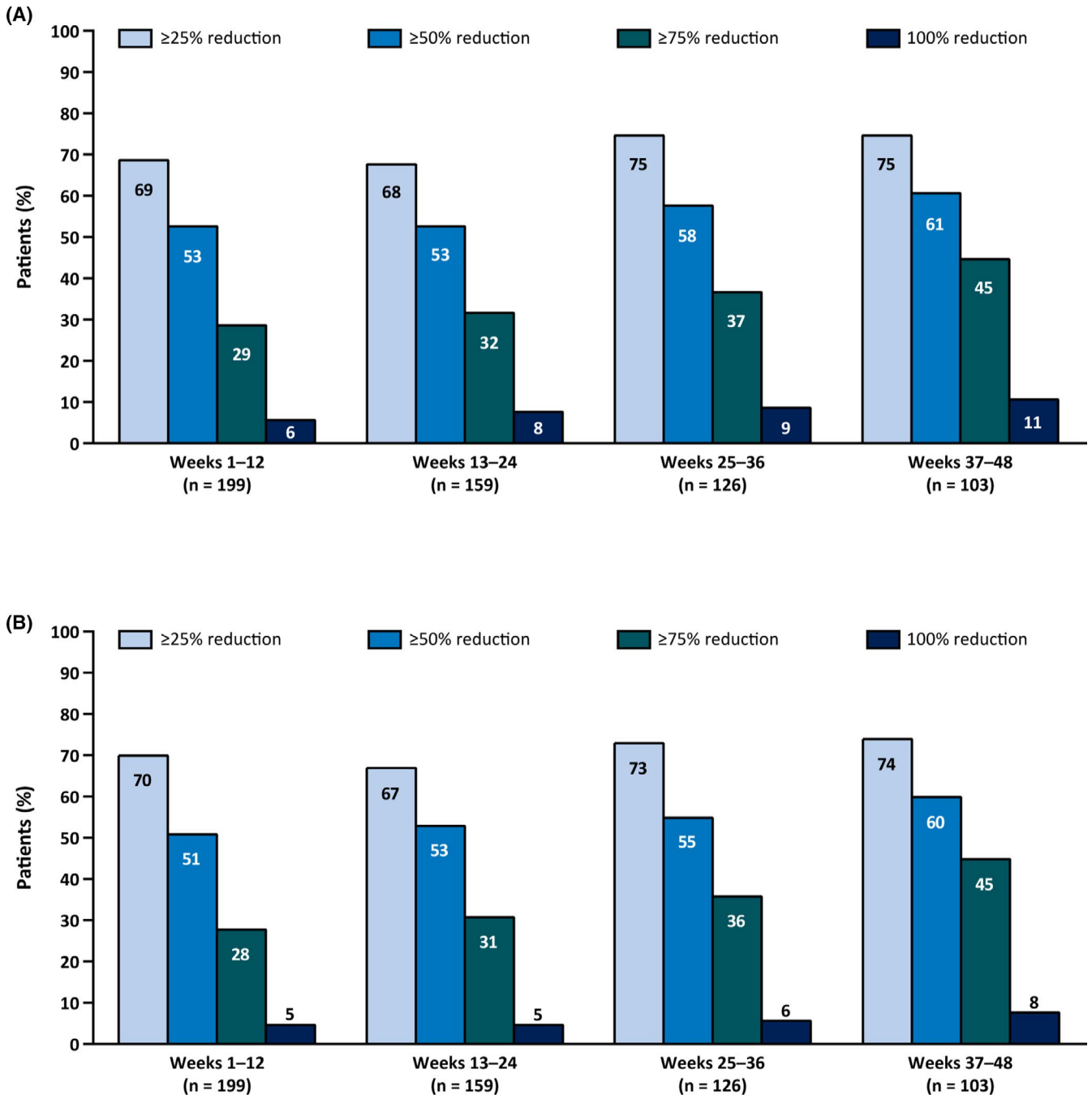

FIGURE 3 Responder rates for (A) TSC-associated seizures and (B) total seizures. Abbreviation: TSC, tuberous sclerosis complex

treatment discontinuation, or following CBD/ASM dose reductions. Thus discontinuation or reduction of CBD and/or concomitant valproate dose may be considered for management of liver enzyme elevations. Although the potential for interaction between CBD and the mTOR inhibitors everolimus and sirolimus was not evaluated in this study, CBD treatment has been shown to produce a clinically significant increase in the levels of mTOR inhibitors in some patients with TSC.[32] Therefore, in patients taking CBD in addition to everolimus or sirolimus, the doses of these mTOR inhibitors may need to be adjusted to avoid potentially significant toxicity.

Treatment with CBD produced a sustained reduction in TSC-associated seizures, including countable focal and generalized seizures but excluding absence, myoclonic, focal sensory, and infantile/epileptic spasms, as well as in total seizures, which included all of the above-mentioned seizures types. In the randomized, placebo-controlled phase of the trial, CBD produced an ~40% reduction in the frequency of seizures associated with

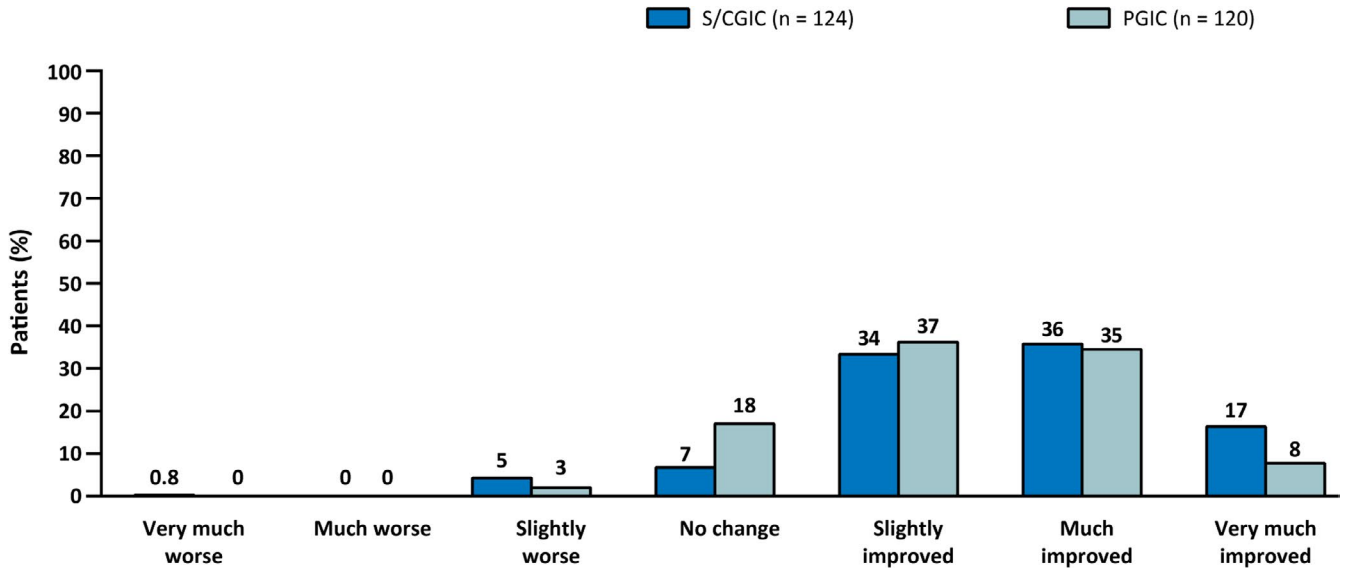

FIGURE 4 Global impression of change in patients' overall condition on the S/CGIC and PGIC scales at the 26-week visit. Abbreviations: PGIC, Physician Global Impression of Change; S/CGIC, Subject/Caregiver Global Impression of Change

TSC. Improvements during the OLE were higher and were sustained through 48 weeks of treatment. More than 50% reductions in TSC-associated and total seizures were observed during the 12-week treatment windows. Seizure responder rates (≥25%, ≥50%, and ≥75% reduction in seizures) were sustained throughout the study, with 29%–45% of patients experiencing ≥75% reduction in seizures and at least 5% of patients becoming seizure-free during each 12-week treatment window reported here. This effect on seizure reduction and responder rates over time was not due to patient withdrawal, as consistently robust response was also observed with LOCF analyses conducted to assess the effect of patient withdrawals on seizure reduction end points.

In addition to the substantial reduction from baseline in seizure frequency, more than 80% of patients or their caregivers and physicians reported improvements in the overall condition of patients, assessed using S/CGIC and PGIC scales, indicating that CBD treatment provided meaningful improvement in patient quality of life.

In an analysis by modal dose, >90% of patients with modal dose ≤25 mg/kg/day and those with modal dose >25 mg/kg/day had an AE. A similar reduction in monthly seizure frequency was observed in patients with modal dose ≤25 mg/kg/day and those with modal dose >25 mg/kg/day. However, both the safety and efficacy results by modal dose must be interpreted with caution because the dose categories were based on patients' modal or most frequent dose, which could vary between the treatment windows; in addition, the dose could be titrated up or down, depending on tolerability and response, throughout the follow-up.

Retention rate in OLE studies has been suggested as a measure of long-term benefit of antiseizure medications.[33] The 1-year retention rate in the GWPCARE6 OLE was 79%, suggesting that most patients were receiving clinically meaningful benefit from CBD treatment. In addition, the mean modal dose did not vary considerably between the 12-week treatment windows, suggesting that patients did not develop tolerance to CBD, necessitating a dose increase to control seizure frequency.

The goal of an epilepsy treatment for patients with TSC is to prevent or control seizures as soon as possible after the diagnosis and with a minimum number of ASMs and AEs.[13] ASMs are frequently prescribed treatment for seizures associated with TSC[13]; in a study of patients enrolled in the TSC Natural History Database, >99% of patients had received an ASM therapy.[34] TSC-associated seizures are difficult to manage and ~60% of patients taking ASMs have usually tried three or more distinct ASMs.[34] Currently, vigabatrin is recommended as the first-line monotherapy for infantile spasms and/or focal seizures associated with TSC in the first year of life[13,35]; however, the risk of a visual field constriction associated with prolonged use of vigabatrin remains a concern.[13,36] Adrenocorticotropic hormone is recommended as the second-line treatment for infantile spasms.[13,36] Topiramate, carbamazepine, and oxcarbazepine are also used as second-line therapies for focal seizures.[37] The mTOR inhibitor everolimus has also shown efficacy as adjunctive treatment of TSC-associated focal-onset seizures.[38] Standard treatment guidelines are recommended for other TSC-associated seizures.[39] The results of our study show that add-on CBD can be an efficacious long-term treatment for TSC-associated seizures

with manageable side effects and has been approved in patients as young as 1 year of age in the United States.[25]

Our study does have some limitations. As an OLE, it did not include a placebo comparator. Efficacy measures and patient-reported outcomes were evaluated relative to the pre-randomization baseline of the trial; therefore, CBD exposure varied among patients depending on whether they were randomized to placebo or CBD group. Efficacy outcomes could have been affected by a change in the patient's concomitant medications, especially by addition of a new ASM. Patient/caregiver's impression of the improvement in patient's overall condition could have been affected by close monitoring and the perception of increased attention and care associated with participating in a trial. Because this was an interim analysis of the OLE, not all patients had completed later treatment windows. Although classification of seizures in this trial was confirmed by the Epilepsy Study Consortium, video-electroencephalographic confirmation of the individual seizure subtypes was not done.

Despite certain limitations, the results of this OLE of GWPCARE6 trial demonstrated that CBD had an acceptable safety profile as a long-term add-on treatment for seizures associated with TSC. Reduction in the seizure frequency observed during the randomized, placebo-controlled phase of the trial was sustained during long-term CBD treatment. Patients and their caregivers reported meaningful improvements in the patient's overall condition on the S/CGIC scale; improvements were also reported by most physicians on the PGIC scale. Thus our results support the long-term benefit of add-on CBD therapy for patients with treatment-resistant epilepsy associated with TSC. This trial was conducted with Epidiolex®/Epidyolex® and results do not apply to other CBD-containing products.

ACKNOWLEDGMENTS

The authors would like to thank the patients, their families, and the staff at sites that participated in this study. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Ritu Pathak, PhD, and editing support by Dena McWain, both of Ashfield MedComms, an Ashfield Health company, and funded by Greenwich Biosciences, Inc.

CONFLICT OF INTEREST

Elizabeth A. Thiele received support from GW Research Ltd as an investigator during the conduct of the trial; outside of the current work, she serves as a principal investigator on clinical trials for GW Research Ltd and Zogenix and serves as a consultant for Aquestive Therapeutics, Biocodex, West Therapeutics, Greenwich Biosciences, and Zogenix. E. Martina Bebin received support from GW Research Ltd as a site principal investigator during the conduct of the trial and serves as a consultant for Greenwich Biosciences and Biocodex. Francis Filloux and Patrick Kwan have nothing to disclose. Rachael Loftus is a full-time employee of GW Research Ltd. Farhad Sahebkar is a full-time employee of Greenwich Biosciences. Steven Sparagana has received personal compensation for serving as a consultant for Greenwich Biosciences and Nobelpharma. His institution has received research support from Greenwich Biosciences, Tuberous Sclerosis Complex Alliance, and Novartis. He has a noncompensated relationship as a professional advisory board member or committee member with Tuberous Sclerosis Complex Alliance. James Wheless has received personal compensation for serving as a consultant for Eisai, Supernus, Aquestive, GW Pharmaceuticals companies, and Neurelis. He has served on a speakers bureau for LivaNova, Eisai, Supernus, GW Pharmaceuticals companies, UCB, BioMarin, and Zogenix. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

All authors provided substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; and provided final approval of the version to be published.

ORCID

Elizabeth A. Thiele https://orcid.org/0000-0003-3431-4713
E. Martina Bebin https://orcid.org/0000-0003-1264-3428
Patrick Kwan https://orcid.org/0000-0001-7310-276X
James Wheless https://orcid.org/0000-0002-4735-3431

REFERENCES

1. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2012;2013(49):243–54.
2. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372:657–68.
3. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355:1345–56.
4. Wang S, Fallah A. Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. Neuropsychiatr Dis Treat. 2014;10:2021–30.
5. Chan JA, Zhang H, Roberts PS, Jozwiak S, Wieslawa G, Lewin-Kowalik J, et al. Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: biallelic inactivation of TSC1 or TSC2 leads to mTOR activation. J Neuropathol Exp Neurol. 2004;63:1236–42.
6. Tuberous Sclerosis Complex Alliance. Diagnosis, surveillance, and management for healthcare professionals. https://www.

tscalliance.org/healthcare-professionals/diagnosis/ Accessed September 21, 2021.
7. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125–7.
8. Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. TuberOus SClerosis registry to increase disease Awareness (TOSCA) – baseline data on 2093 patients. Orphanet J Rare Dis. 2017;12:2.
9. Jeong A, Wong M. Systemic disease manifestations associated with epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57:1443–9.
10. de Vries PJ, Wilde L, de Vries MC, Moavero R, Pearson DA, Curatolo P. A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). Am J Med Genet C Semin Med Genet. 2018;178:309–20.
11. de Vries PJ, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOSCA natural history study. Orphanet J Rare Dis. 2018;13:157.
12. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010;51:1236–41.
13. Curatolo P, Nabbout R, Lagae L, Aronica E, Ferreira JC, Feucht M, et al. Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations. Eur J Paediatr Neurol. 2018;22:738–48.
14. Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. Pediatr Neurol. 2001;25:213–6.
15. Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. Epilepsy Behav. 2008;13:357–60.
16. Zamponi N, Petrelli C, Passamonti C, Moavero R, Curatolo P. Vagus nerve stimulation for refractory epilepsy in tuberous sclerosis. Pediatr Neurol. 2010;43:29–34.
17. Elliott RE, Carlson C, Kalhorn SP, Moshel YA, Weiner HL, Devinsky O, et al. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery. Epilepsy Behav. 2009;16:454–60.
18. Amin S, Lux A, Calder N, Laugharne M, Osborne J, O'Callaghan F. Causes of mortality in individuals with tuberous sclerosis complex. Dev Med Child Neurol. 2017;59:612–7.
19. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376:2011–20.
20. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90:e1204–e11.
21. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378:1888–97.
22. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391:1085–96.
23. Hess EJ, Moody KA, Geffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016;57:1617–24.
24. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2021;78:285–92.
25. EPIDIOLEX® (cannabidiol) oral solution [prescribing information]. Carlsbad, CA; Greenwich Biosciences, Inc.; 09/2021. Available at: https://www.epidiolex.com/ Accessed October 13, 2021
26. Epidyolex (cannabidiol) oral solution [summary of product characteristics]. Amersfoort, The Netherlands; GW Pharma (International) B.V.; 04/2021. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex#product-information-section Accessed April 29, 2021
27. Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, Halford JJ, Gunning B, Devinsky O, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study. Epilepsia. 2019;60:419–28.
28. Devinsky O, Nabbout R, Miller I, Laux L, Zolnowska M, Wright S, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: an open-label extension trial. Epilepsia. 2019;60:294–302.
29. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. JAMA Neurol. 2020;77:613–21.
30. Madan Cohen J, Checketts D, Dunayevich E, Gunning B, Hyslop A, Madhavan D, et al. Time to onset of cannabidiol (CBD) treatment effect and resolution of adverse events in patients with Dravet syndrome: pooled analysis of 2 randomized controlled trials. AES 2019 Annual Meeting Abstract Database. 2019; AESnet.org Accessed June 25, 2020
31. Wu J, Cock H, Devinsky O, Joshi C, Miller I, Roberts C, et al. Time to onset of cannabidiol (CBD) treatment effect and resolution of adverse events (AEs) in the tuberous sclerosis complex (TSC) phase 3 randomized controlled trial (GWPCARE6) (674). Neurology. 2020;94:674.
32. Ebrahimi-Fakhari D, Agricola KD, Tudor C, Krueger D, Franz DN. Cannabidiol elevates mechanistic target of rapamycin inhibitor levels in patients with tuberous sclerosis complex. Pediatr Neurol. 2020;105:59–61.
33. Toledo M, Beale R, Evans JS, Steeves S, Elmoufti S, Townsend R, et al. Long-term retention rates for antiepileptic drugs: a review of long-term extension studies and comparison with brivaracetam. Epilepsy Res. 2017;138:53–61.
34. Song J, Swallow E, Said Q, Peeples M, Meiselbach M, Signorovitch J, et al. Epilepsy treatment patterns among patients with tuberous sclerosis complex. J Neurol Sci. 2018;391:104–8.
35. Curatolo P, Jozwiak S, Nabbout R, SEGA TSCCMf, Epilepsy M. Management of epilepsy associated with tuberous sclerosis complex (TSC): clinical recommendations. Eur J Paediatr Neurol. 2012;16:582–6.
36. Riikonen R, Rener-Primec Z, Carmant L, Dorofeeva M, Hollody K, Szabo I, et al. Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study. Dev Med Child Neurol. 2015;57:60–7.
37. Overwater IE, Bindels-de Heus K, Rietman AB, Ten Hoopen LW, Vergouwe Y, Moll HA, et al. Epilepsy in children with tuberous sclerosis complex: chance of remission and response to antiepileptic drugs. Epilepsia. 2015;56:1239–45.
38. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3):

a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016;388:2153–63.
39. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015;14:733–45.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Thiele EA, Bebin EM, Filloux F, Kwan P, Loftus R, Sahebkar F, et al. Long-term cannabidiol treatment for seizures in patients with tuberous sclerosis complex: An open-label extension trial. Epilepsia. 2022;63:426–439. https://doi.org/10.1111/epi.17150