Received: 22 December 2022 | Revised: 19 May 2023 | Accepted: 23 May 2023

DOI: 10.1111/epi.17665

Epilepsia®

BRIEF COMMUNICATION

Efficacy of cannabidiol in convulsive and nonconvulsive seizure types associated with treatment-resistant epilepsies in the Expanded Access Program

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Funding information
Epilepsy Therapy Project of the Epilepsy Foundation; GW Research Ltd (now part of Jazz Pharmaceuticals, Inc); New York State Department of Health; State of Alabama General Funds (Carly's Law)

Abstract

The cannabidiol (CBD) Expanded Access Program (EAP), initiated in 2014, provided CBD (Epidiolex) to patients with treatment-resistant epilepsy (TRE). In the final pooled analysis of 892 patients treated through January 2019 (median exposure = 694 days), CBD treatment was associated with a 46%–66% reduction in median monthly total (convulsive plus nonconvulsive) seizure frequency. CBD was well tolerated, and adverse events were consistent with previous findings. We used pooled EAP data to investigate the effectiveness of add-on CBD therapy for individual convulsive seizure types (clonic, tonic, tonic–clonic, atonic, focal to bilateral tonic–clonic), nonconvulsive seizure types (focal with and without impaired consciousness, absence [typical and atypical], myoclonic, myoclonic

absence), and epileptic spasms. CBD treatment was associated with a reduction in the frequency of convulsive seizure types (median percentage reduction = 47%–100%), and nonconvulsive seizure types and epileptic spasms (median percentage reduction = 50%–100%) across visit intervals through 144 weeks of treatment. Approximately 50% of patients had ≥50% reduction in convulsive and nonconvulsive seizure types and epileptic spasms at nearly all intervals. These results show a favorable effect of long-term CBD use in patients with TRE, who may experience various convulsive and nonconvulsive seizure types. Future controlled trials are needed to confirm these findings.

KEYWORDS

absence seizures, antiseizure medications, clonic seizures, epileptic spasms, seizure frequency

1 | INTRODUCTION

Treatment-resistant epilepsy (TRE) is associated with increased risks of prolonged seizures, epilepsy-related injury, and sudden unexpected death in epilepsy.[1] Patients with TRE frequently have significant neuropsychological, psychiatric, and social comorbidities that negatively impact quality of life.[1] These patients receive only partial relief from seizures with antiseizure medications (ASMs).[2]

Plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD; Epidiolex in the USA and Epidyolex in the EU and the UK) is approved for the treatment of seizures associated with Lennox–Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) based on the results from five randomized, placebo-controlled trials (RCTs).[3–7]

The CBD Expanded Access Program (EAP), initiated in January 2014, provided CBD to patients with TRE. All reports from the EAP so far have shown a reduction in the frequency of seizures, including convulsive and total seizures, following treatment with add-on CBD.[8–12] In the final pooled analysis of 892 patients treated through January 2019 (median treatment duration = 694 days [range = 10–1793]), CBD treatment was associated with 50%–67% and 46%–66% reductions in median monthly convulsive and total seizure frequency, respectively.[13] CBD was generally well tolerated in the EAP, and treatment-emergent adverse events (AEs) were similar to those reported in the RCTs.[3–12]

Previous EAP analyses have largely focused on a general assessment of seizures in TRE or seizures associated with LGS, DS, or TSC, rather than individual seizure types.[9–13] However, CBD (Epidiolex) is frequently used off-label for seizures other than those associated with the approved conditions. Such use is partially supported by results from a systematic review and an earlier smaller EAP analysis, which suggested efficacy in a broad range of seizure types, including treatment-resistant absence seizures and epileptic spasms.[12,14] To expand on these findings, we used pooled data from the EAP to investigate the effectiveness of CBD on convulsive seizure types (clonic, tonic, tonic–clonic, atonic, focal to bilateral tonic–clonic), nonconvulsive seizure types (focal with and without impaired consciousness, absence [typical and atypical seizures], myoclonic, myoclonic absence), and epileptic spasms.

2 | MATERIALS AND METHODS

Study design and patient eligibility criteria have been published previously.[9] The EAP was conducted at 35 US-based epilepsy centers. Although eligibility criteria varied by site, all patients had TRE (failure of adequate trials of two tolerated and appropriate ASMs)[2] and were receiving stable ASM doses for ≥4 weeks before enrollment. An institutional review board (IRB) at each site approved the study protocol. Patients or parents/caregivers provided written informed consent. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and local standard operating procedures.

Parents/caregivers recorded all countable seizure types in a diary during a 4-week baseline period. Patients then received CBD (100 mg/mL oral solution; Epidiolex in the USA and Epidyolex in the UK and EU, GW Research, now part of Jazz Pharmaceuticals) starting at 2–10 mg/kg/day and gradually increasing until tolerability limit or maximum of 25–50 mg/kg/day, depending on study site and IRB approval. Patients were seen every 2–4 weeks for the first 16 weeks, and every 2–12 weeks thereafter.

Each site provided seizure frequency per week, based on patient/caregiver diaries. Weekly seizure frequency was converted to frequency per 28 days.

Percentage change from baseline in seizure frequency for each patient was calculated as ([(seizure frequency/28 days) − (seizure frequency at baseline)]/[seizure frequency at baseline]) × 100. Median percentage changes in seizure frequency at 24-week visit intervals through 144 weeks of treatment are reported. The ≥50% responder rate was calculated as the percentage of patients with ≥50% reduction in monthly seizure frequency from baseline at 24-week visit intervals through 144 weeks. Patients with >0 of the specific seizure type at baseline and seizure data for ≥1 postbaseline visit were included in the efficacy analysis. Efficacy data were analyzed descriptively. Safety data were assessed for the full duration of the follow-up (up to 252 weeks) and are reported separately[13]; a brief overview is presented here.

3 | RESULTS

3.1 | Patients

Between January 15, 2014, and January 31, 2019, 892 patients were prospectively enrolled in the EAP. Baseline characteristics had been reported previously.[13] Briefly, median age was 12 years (range = 0–75), and patients were taking a median of 3 (range = 0–10) concurrent ASMs. The most commonly used ASMs were clobazam (48%), levetiracetam (34%), and valproate (28%). At baseline, the median (Q1, Q3) seizure frequency per 28 days was 40 (12, 112) for convulsive and 38 (9, 140) for nonconvulsive seizures among patients with available data ($n = 645$ and $n = 557$, respectively). Median (Q1, Q3) top CBD dose was 25 mg/kg/day (24, 30), and the median exposure duration was 694 days (range = 10–1793).

3.2 | Efficacy

Patients taking add-on CBD experienced fewer convulsive and nonconvulsive seizure types and epileptic spasms through 144 weeks of treatment versus the baseline (Figure 1). Median percentage reduction for convulsive seizure types ranged from 58% to 100% for clonic seizures, 54%–73% for tonic seizures, 47%–72% for tonic–clonic seizures, 77%–96% for atonic seizures, and 61%–77% for focal to bilateral tonic–clonic seizures at 24-week intervals (Figure 1A). Reduction for nonconvulsive seizure types and epileptic spasms ranged from 60% to 76% for focal seizures, 95%–100% for absence (typical and atypical) seizures, 63%–89% for myoclonic seizures, 50%–100% for myoclonic absence seizures, and 80%–95% for epileptic spasms (Figure 1B). At least 49% of patients had a ≥50% reduction in convulsive and nonconvulsive seizure types and epileptic spasms at nearly all 24-week intervals (Figure 2).

3.3 | Safety

Safety was assessed for up to 252 weeks, and results have been reported previously.[13] AEs were reported in 88% of patients (788/892) and led to CBD discontinuation in 7% of patients (65/892). AEs reported in >20% of patients included diarrhea (33%, 298/892), seizure (24%, 210/892), and somnolence (23%, 202/892). Serious AEs were reported in 41% of patients (369/892); the most frequent serious AEs were seizure (14%, 123/892) and status epilepticus (7%, 60/892). The most frequent liver-related AEs were abnormal liver function test (4%, 37/892), elevated aspartate aminotransferase (3%, 29/892), and elevated alanine aminotransferase (3%, 25/892). Twenty deaths were reported during the study (2%), all deemed unrelated to treatment by the investigator.

4 | DISCUSSION

In this analysis of pooled CBD EAP data, add-on CBD treatment was associated with a reduction in seizure frequency across multiple convulsive and nonconvulsive seizure types, including epileptic spasms for up to 144 weeks of treatment. Approximately half of patients had ≥50% reduction in convulsive and nonconvulsive seizure types and epileptic spasms. As reported previously,[9,13] CBD had an acceptable safety profile that was consistent with previous EAP reports and RCT results.[3–12]

We observed a substantial reduction in seizure frequency across the seizure types investigated. Although the study was not designed to make comparisons between seizure types, reductions in convulsive seizure type frequency ranged from 47% to 100%, which included median reductions of 58%–100% in clonic seizures and 77%–96% in atonic seizures. Reductions in nonconvulsive seizure types ranged from 50% to 100%, which included median reductions of 95%–100% in absence (typical and atypical) seizures; reductions in epileptic spasms ranged from 80% to 95%. In a previously published analysis of 54 patients from one EAP site, investigators found that CBD was associated with a reduction in the frequency of epileptic spasms and absence seizures.[12] Although the sample size was small (<20 patients for each seizure type), a >50% response was seen in most patients with epileptic spasms, absence seizures, tonic–clonic seizures, atonic seizures, and focal seizures with evolving components. Responses were observed less commonly in patients with focal seizures with

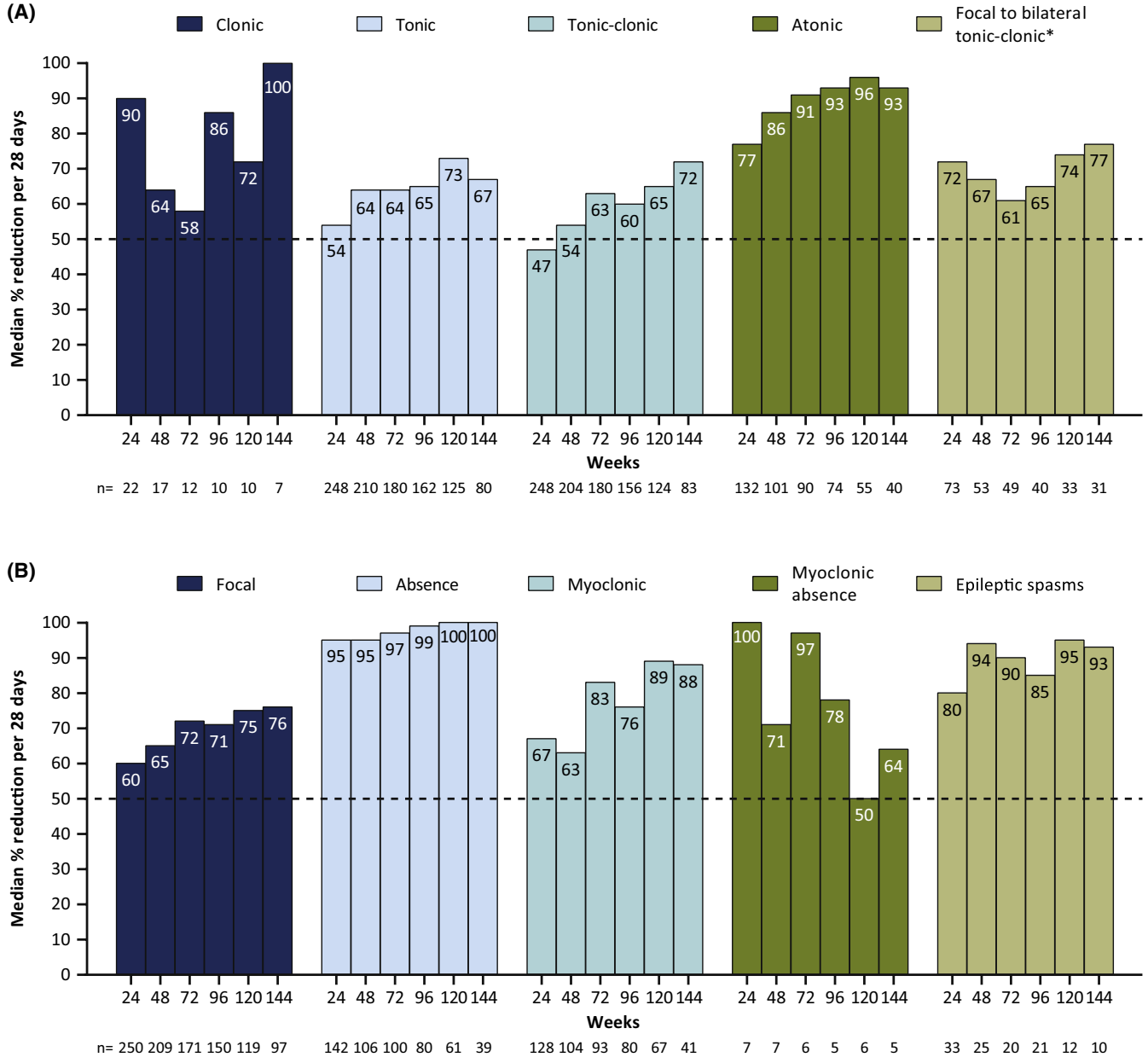

FIGURE 1 Median percentage reduction from baseline in the frequency of (A) convulsive seizure types and (B) nonconvulsive seizure types and epileptic spasms. Values within bars show the percentage reduction at each visit interval. Values below the axis are the number of patients with data for the seizure type at each visit interval. *Focal to bilateral tonic–clonic seizures were previously known as focal secondarily generalized seizures.

impaired consciousness and tonic seizures. Analysis of patients with focal seizures without impaired consciousness, myoclonic absence seizures, and atypical absence seizures was limited because of low patient numbers; nevertheless, seizure reductions were observed in these seizure types. Our current analysis, based on pooled data from the EAP, provides a robust extension of those earlier data from a single EAP site, which were likely limited by low sample size.

Results from the final pooled analysis of the EAP show, based on >3 years of data, that CBD treatment was generally well tolerated.[13] The safety profile was similar to that reported in prior EAP analyses and RCTs.[3–12]

At least 30% of patients with epilepsy have treatment-resistant seizures.[15] Mechanisms of pharmacoresistance are complex and not clearly understood, but the type of epilepsy syndrome and seizure type are considered, as they influence the choice of medication or alternative therapies.[1,16] An ASM should be appropriate for a patient's seizure type and tolerable at therapeutic dose levels.[16] In this analysis, which included patients with highly treatment-resistant epilepsy (median = 3 ASMs at baseline), add-on

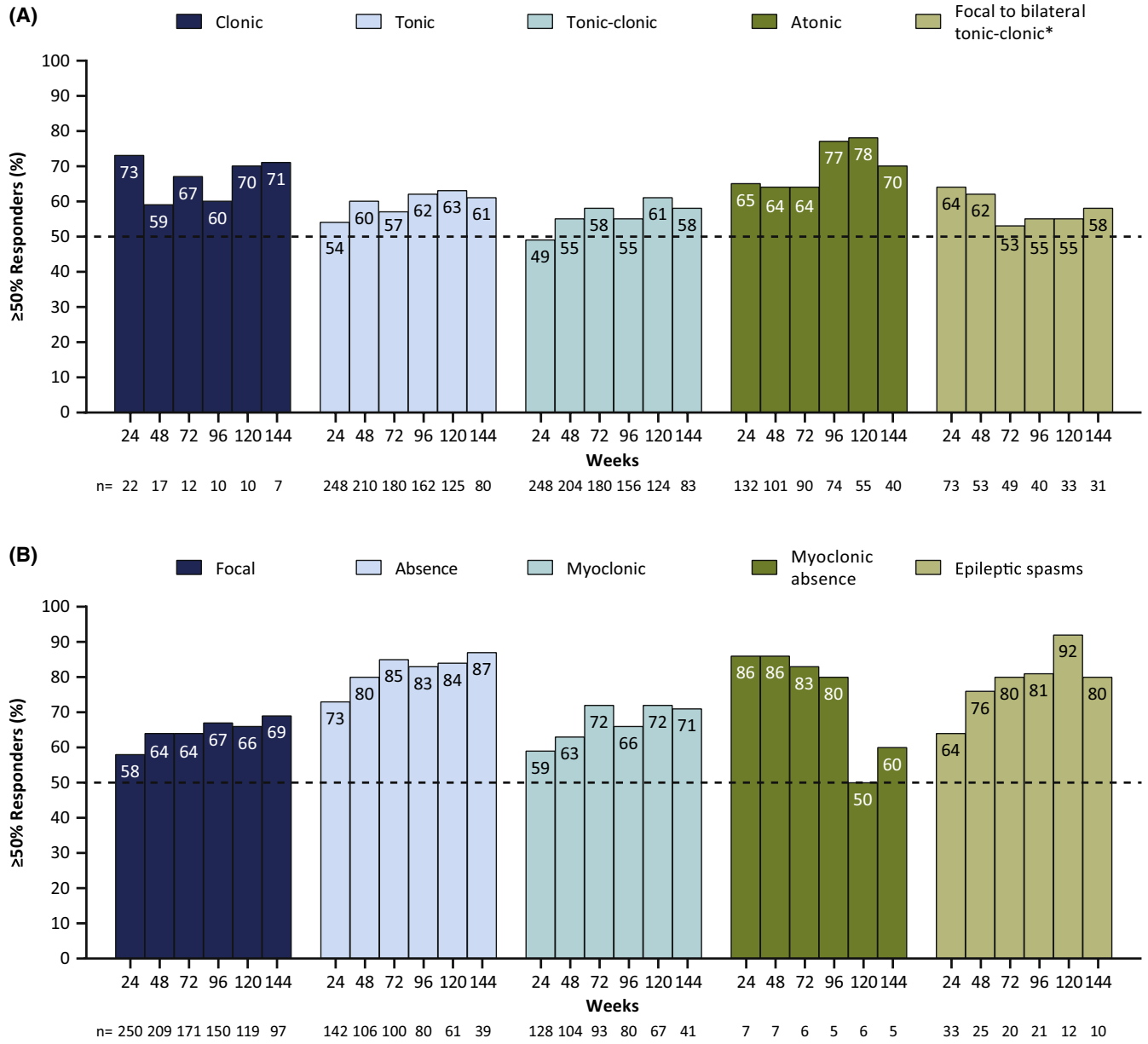

FIGURE 2 Proportion of patients with ≥50% reduction from baseline in (A) convulsive seizure types and (B) nonconvulsive seizures and epileptic spasms. Values within bars show the percentage reduction at each visit interval. Values below the axis are the number of patients with data for the seizure type at each visit interval. *Focal to bilateral tonic–clonic seizures were previously known as focal secondarily generalized seizures.

CBD was associated with a reduction in the frequency of multiple seizure types across 144 weeks of treatment and had an acceptable safety profile. These results suggest that CBD can be a treatment option for multiple seizure types in patients with TRE, even in cases where the underlying etiology or syndrome has not been identified.

Our analysis has a few limitations. This study was not designed to investigate efficacy by individual seizure type, and there was no specific verification of seizure types, which were identified by individual investigators. The reduction in treatment-resistant absence seizures was particularly notable; however, it should be noted that the frequency of absence and myoclonic seizures, which can be difficult to assess by observation only,[17,18] was not confirmed using electroencephalography. Nevertheless, these results warrant further studies to evaluate CBD in absence seizures. Additionally, details regarding the underlying syndromes and etiologies were not available for the current analysis because of the method used for data collection in the EAP. Etiologies were collected in standard reporting spreadsheets as free text, which were not always completed. Despite additional efforts to obtain categorized diagnosis for all patients, discrepancies remained, resulting in unclear specific etiologies. As described

previously,[9] the EAP was not a blinded, randomized, placebo-controlled study. Eligibility criteria and methods for reporting seizures varied by site, and not all information was uniformly collected. Sample sizes for some seizure types were low and decreased over time in all seizure types. Accordingly, results should be interpreted with caution. Further, although drug–drug interactions could have impacted efficacy and safety outcomes, this was not evaluated in the EAP.

Our results build on findings from the final pooled analysis of EAP data[13] to provide additional insight into the long-term safety and efficacy that may be expected in clinical practice. The data support CBD as an important treatment option for patients with TRE who may experience various seizure types, including generalized onset and focal onset seizures. Although the currently approved indications of LGS, DS, and TSC include multiple generalized and focal onset seizure types, future RCTs are needed to further evaluate CBD as a treatment for specific seizure types that occur outside of these diagnoses.

5 | CONCLUSIONS

Among patients with TRE in the EAP, add-on CBD was associated with a reduction in the frequency of convulsive seizure types, nonconvulsive seizure types, and epileptic spasms. At least 50% reduction was reported in ≥49% of patients across all evaluated seizure types and at nearly all intervals for up to 144 weeks of treatment.

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. All authors met the International Consortium of Medical Journal Editors authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

ACKNOWLEDGMENTS

The EAP was supported by grants from GW Research (now part of Jazz Pharmaceuticals) and the Epilepsy Therapy Project of the Epilepsy Foundation. The EAP in Alabama was supported by the State of Alabama General Funds (Carly's Law). Funding for the EAP in New York was provided by the New York State Department of Health. GW Research (now part of Jazz Pharmaceuticals) provided CBD free of charge and administrative support across all sites, and provided some sites with funds to support the study. At some sites, funds were provided for salary support for staff time spent on activities required for the EAP. GW Research (now part of Jazz Pharmaceuticals) collected data from the sites and conducted the statistical analyses. The authors would like to thank the patients, their families, and the sites that provided data for this analysis. Medical writing support for the development of the manuscript, under the direction of the authors, was provided by Meredith Kalish, MD, Ashfield MedComms US, an Inizio company, and funded by Jazz Pharmaceuticals.

FUNDING INFORMATION

The EAP was supported by grants from GW Research (now part of Jazz Pharmaceuticals) and the Epilepsy Therapy Project of the Epilepsy Foundation. The EAP in Alabama was supported by the State of Alabama General Funds (Carly's Law). Funding for the EAP in New York was provided by the New York State Department of Health. GW Research (now part of Jazz Pharmaceuticals) provided CBD free of charge and administrative support across all sites, and provided some sites with funds to support the study. At some sites, funds were provided for salary support for staff time spent on activities required for the EAP. Medical writing support for the development of the manuscript, under the direction of the authors, was provided by Meredith Kalish, MD, Ashfield MedComms US, an Inizio company, and funded by Jazz Pharmaceuticals.

CONFLICT OF INTEREST STATEMENT

R.J.F. was a principal investigator at an EAP trial site; has served on consulting/advisory boards for Greenwich Biosciences (now part of Jazz Pharmaceuticals), UCB Pharma, and Marinus Pharma; and is part of the speaker's bureaus for these companies. A.M.C. has received research funding and study drug from Greenwich Biosciences (now part of Jazz Pharmaceuticals) and previously served as a speaker for Greenwich Biosciences (now part of Jazz Pharmaceuticals). She has also received research funding from the National Institutes of Health and study drug from Pfizer. E.M.B. has served as a consultant for Greenwich Biosciences (now part of Jazz Pharmaceuticals) and Biocodex. M.G.C. has served as a speaker and consultant for Greenwich Biosciences (now part of Jazz Pharmaceuticals), Eisai, Zogenix (now UCB Pharma), and Marinus. O.D. has equity interests in Q-state Biosciences, Tevard Biosciences, Regel Therapeutics, Script Biosciences, Privateer Holdings, Tilray, Receptor Life Sciences, Empatica, Engage, Egg Rock/Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises and receives grant support from the NINDS, National Institute of Mental Health, Multidisciplinary University Research Initiative, US Centers for Disease Control and Prevention, and National Science Foundation. He is an investigator for PTC Therapeutics, Stoke Therapeutics, Marinus, Ovid, and

GW Pharmaceuticals (now part of Jazz Pharmaceuticals). S.A.H. has received research support from the Epilepsy Therapy Project, the Milken Family Foundation, the Hughes Family Foundation, the Elsie and Isaac Fogelman Endowment, the Mohammed F. AlIbrahim Endowment, the John C. Hench Foundation, the CJDA Foundation, BioPharm Solutions, Eisai, GW Pharmaceuticals (now part of Jazz Pharmaceuticals), Insys, Lundbeck, MGC Pharma, UCB Biopharma, Zogenix, and the National Institutes of Health; has received honoraria for service on the scientific advisory boards of Mallinckrodt, Insys, UCB Biopharma, Upsher-Smith, and Zogenix; has received honoraria for service as a consultant to Aquestive, Amzell, Eisai, Equilibre, GW Pharmaceuticals (now part of Jazz Pharmaceuticals), Insys, Mallinckrodt, Marinus, MGC Pharma, Radius, Shennox, UCB Biopharma, Upsher-Smith, and West Therapeutic Development; and has received honoraria for service on the speakers' bureaus of GW Pharmaceuticals (now part of Jazz Pharmaceuticals) and Mallinckrodt. P.D.L. is an investigator for Janssen, LivaNova, Syntrillo, and GW Pharmaceuticals (now part of Jazz Pharmaceuticals). A.D.P. has research funding from the National Institutes of Health, PERF, and PCORI. He has institutional research funding from Stoke and Encoded. J.P.S. has received funding from the National Institutes of Health, National Science Foundation, US Department of Defense, State of Alabama, Shor Foundation for Epilepsy Research, UCB Pharma, NeuroPace, Greenwich Biosciences (now part of Jazz Pharmaceuticals), Biogen, Xenon Pharmaceuticals, and Serina Therapeutics; has served on consulting/advisory boards for Greenwich Biosciences (now part of Jazz Pharmaceuticals), NeuroPace, Serina Therapeutics, LivaNova, UCB Pharma, iFovea, AdCel Biopharma, and Elite Medical Experts; and serves as an editorial board member for *Epilepsy & Behavior*, *Journal of Epileptology* (associate editor), *Epilepsy & Behavior Report* (associate editor), *Journal of Medical Science*, *Epilepsy Currents* (contributing editor), and *Folia Medica Copernicana*. F.S. is an employee of Jazz Pharmaceuticals and holds stock and/or stock options in Jazz Pharmaceuticals. The remaining authors have no conflicts of interest.

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How to cite this article: Flamini RJ, Comi AM, Bebin EM, Chez MG, Clark G, Devinsky O, et al. Efficacy of cannabidiol in convulsive and nonconvulsive seizure types associated with treatment-resistant epilepsies in the Expanded Access Program. Epilepsia. 2023;00:1–8. https://doi.org/10.1111/epi.17665