Received: 30 March 2021 | Revised: 22 November 2021 | Accepted: 29 November 2021

DOI: 10.1002/epi4.12575

Epilepsia Open® Open Access

ORIGINAL ARTICLE

PROVE: Retrospective, non-interventional, Phase IV study of perampanel in real-world clinical care of patients with epilepsy

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Abstract

Objective: To assess retention, dosing, efficacy, and safety of perampanel in a large cohort of patients with epilepsy during routine clinical care.

Methods: PROVE was a retrospective, non-interventional Phase IV study (NCT03208660). Data were obtained retrospectively from the medical records of patients in the United States initiating perampanel after January 1, 2014, according to treating clinicians' recommendation. Retention rate was the primary efficacy endpoint. Secondary efficacy endpoints included median percent changes in seizure frequency per 28 days from baseline, seizure-freedom rate, and overall investigator impression of seizure effect. Safety endpoints included incidence of treatment-emergent adverse events (TEAEs). Efficacy and safety were also assessed according to baseline use of enzyme-inducing antiseizure medications (EIASMs).

Results: Overall, 1703 patients were enrolled and included in the Safety Analysis Set (SAS; ≥1 baseline EIASMs, n = 358 [21.0%]; no baseline EIASMs, n = 1345 [79.0%]). Mean (standard deviation [SD]) cumulative duration of exposure to perampanel was 17.4 (15.7) months; mean (SD) daily perampanel dose was 5.6 (2.7) mg. The most frequent perampanel titration intervals were weekly (23.4%) and every 2 weeks (24.7%). Across the SAS, 24-month retention rate was 48.1% (n = 501/1042). Based on overall investigator impression at the end of treatment, 51.9%, 35.8%, and 12.3% of patients in the SAS experienced improvement, no change, or worsening of seizures, respectively. TEAEs occurred in 704 (41.3%) patients; 79 (4.6%) had serious TEAEs. The most common TEAE was dizziness (7.3%). There was some variation in efficacy according to EIASM use, while retention rates and safety were generally consistent.

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Significance: In this final analysis of >1700 patients with epilepsy receiving perampanel in routine clinical care, favorable retention and sustained efficacy were demonstrated for ≥12 months.

KEYWORDS
antiseizure medication, dosing, long-term observational, postmarketing, seizure

1 | INTRODUCTION

Retrospective postmarketing studies offer advantages that complement clinical efficacy trials and allow the evaluation of the effectiveness and safety of a drug as experienced by patients and clinicians during real-world clinical care.[1] Advantages may include more heterogeneous patient populations, increased flexibility around dosing and titration schedules, and the potential for longer treatment durations. Such advantages mean that continuous evaluation of therapies during postmarketing studies can be valuable to support clinicians in making informed treatment decisions, thereby potentially improving patient outcomes.[2] In addition, the Food and Drug Administration (FDA) sometimes requires postmarketing studies to support regulatory approvals of new drugs and biologics and has established a framework to evaluate real-world evidence for use in regulatory decisions.[2–5]

Previous real-world studies in patients with epilepsy have reported retention, effectiveness, and safety data for antiseizure medications (ASMs) including brivaracetam, levetiracetam, and lacosamide.[6–10] These data may contribute to better-informed approaches to the treatment of epilepsy and provide valuable insights into patient populations that are under-represented in traditional clinical efficacy trials.

Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a once-daily oral ASM approved for focal-onset seizures (FOS) and generalized tonic-clonic seizures (GTCS).[11,12] In the United States, perampanel is approved for the treatment of FOS (adjunctive and monotherapy) in patients aged ≥4 years, and as adjunctive treatment of GTCS in patients aged ≥12 years.[11] Initial approvals were based on results from Phase III studies in patients with FOS (Studies 304 [NCT00699972], 305 [NCT00699582], and 306 [NCT00700310]) and patients with GTCS (Study 332 [NCT01393743]).[13–16] Later, several observational studies were conducted to evaluate real-world outcomes of perampanel for the treatment of epilepsy in Europe for up to 1 year.[17–19] However, limited information is available on the real-world use of perampanel in the United States, or over longer (≥12 months) treatment durations.

Key Points

- PROVE was a Phase IV real-world outcomes study of patients with epilepsy treated with perampanel in routine clinical care.
- This final analysis of 1703 patients initiating perampanel due to clinician decision found 48.1% were receiving perampanel at 24 months.
- Efficacy and safety of perampanel were generally consistent regardless of baseline use of enzyme-inducing antiseizure medications.
- Treatment-emergent adverse events were consistent with the known safety profile and did not vary by modal dose or titration schedule.

PROVE (Perampanel Real-world Evidence) was a retrospective, noninterventional Phase IV study to assess the retention, dosing, efficacy, and safety of perampanel when administered to patients with epilepsy during routine clinical care at centers across the United States. An interim analysis of PROVE has been reported as well as interim data from pediatric and adolescent subgroups[20–22]; off-label use of perampanel was described in some patients, as is often observed in observational, real-world studies. Here, we report the retention, dosing, efficacy, and safety of perampanel in the real-world clinical care of patients with epilepsy based on the final analyses of the full PROVE study population. Any off-label use of perampanel reported here was based on the clinicians' own treatment decisions and is reflective of the real-world use of perampanel captured during the study.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

The PROVE study protocol was approved by institutional review boards or independent ethics committees at each

site. Due to the retrospective design, PROVE was conducted under a waiver of consent that was approved by the ethics committees for every site. No sites requiring consent were included in the study.

2.2 | Study design

The full methods of PROVE (ClinicalTrials.gov identifier: NCT03208660) have been published.[20] In brief, PROVE was a retrospective, noninterventional, observational Phase IV study conducted between April 10, 2017, and April 1, 2019. Patient enrollment closed on March 15, 2019; key study milestones are presented alongside the dates of US regulatory approvals for perampanel in Table S1. Data were obtained retrospectively from medical and pharmacy records at sites across the United States.

2.3 | Patients

Patients were eligible for inclusion if they had a diagnosis of epilepsy, had been prescribed perampanel after January 1, 2014, based on their treating clinician's recommendation, and had attended their usual epilepsy clinic. The decision to prescribe perampanel was made independently of study participation and no maximum target enrollment was specified. There were no exclusion criteria.

2.4 | Data collection

Data were collected from all eligible patients by review of historical patient medical records and entered into an electronic case report form. Where available, patient demographics, medical history, seizure type, and treatment details (including prior/concomitant ASMs) were recorded as baseline clinical characteristics. Seizure counts for evaluation of efficacy were based on seizure-frequency data from patient notes/seizure diaries and/or investigator assessment of therapeutic response. Details of treatment-emergent adverse events (TEAEs) were collected for evaluation of safety.

2.5 | Assessments

Assessments were made based on the Safety Analysis Set (SAS; patients who received perampanel and had safety data recorded) or the Full Analysis Set (FAS; patients who received perampanel and had seizure-frequency data recorded). For patients who stopped and subsequently restarted perampanel treatment, analyses were based on the total time on treatment, calculated by summing the durations of separate periods on treatment.

The primary efficacy endpoint was the retention rate following 3, 6, 12, 18, and 24 months on perampanel. Retention rates were also measured up to 36 months. Retention rate was calculated as the number of patients in the SAS who remained on treatment for x number of months as a percentage of the total number of patients who could have remained on treatment for x number of months, based on when they initiated perampanel (eg, only patients who initiated perampanel ≥24 months prior to the cutoff date were included in the calculation for retention rate at 24 months).

Secondary efficacy endpoints, assessed in the FAS, included median percent change in seizure frequency per 28 days from baseline, and 50% responder, 75% responder, and seizure-freedom rates (defined as the proportion of patients with a ≥50%, ≥75%, or 100% reduction in seizure frequency per 28 days from baseline, respectively). Baseline included all data up to 3 months before the first dose of perampanel. Patients who had no seizures during baseline were excluded from the seizure-related analyses since a percent change from baseline could not be derived. An exception to this was the analysis of seizure worsening since this was considered as any increase in seizure frequency, and as such, could be assessed for patients with no seizures at baseline given that any seizures on treatment would be classed as worsening. Proportions of patients in the SAS with improvement, no change, or a worsening in seizures, based on the investigator impression of seizure effect, were also assessed at the end of treatment.

Maximum and average perampanel doses, and safety endpoints, were assessed in the SAS. Safety endpoints included incidences of TEAEs, serious TEAEs, and TEAEs leading to perampanel discontinuation. Searches for broad and narrow standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) terms were used to identify TEAEs related to hostility and/or aggression.

In post hoc analyses, efficacy and safety endpoints were assessed according to the use of concomitant ASMs. Patients receiving enzyme-inducing ASMs (EIASMs) were defined as all those who received perampanel with ≥1 concomitant EIASM (oxcarbazepine, carbamazepine, phenytoin, or eslicarbazepine) at baseline, while patients receiving non-EIASMs were defined as all those who received perampanel with concomitant non-EIASMs or no concomitant ASMs at baseline. Patients were also categorized according to whether they received perampanel as adjunctive therapy,

primary monotherapy (administration of perampanel in the absence of any concomitant ASMs), or secondary monotherapy (conversion from adjunctive perampanel to monotherapy by withdrawal of concomitant ASMs). Patients who received both adjunctive perampanel and perampanel monotherapy were included in each respective group.

3 | RESULTS

3.1 | Patients

There were 1703 patients enrolled at 38 study sites across the United States; 1703 patients were included in the SAS and 329 patients in the FAS. At the time of data collection, 51.0% of patients in the SAS were ongoing on perampanel, 47.7% had discontinued perampanel, and disposition was unknown for 1.4% (Figure 1). The most common primary reasons for discontinuation of perampanel were adverse events (AEs) (22.9%; n = 390) and inadequate therapeutic effect (13.3%; n = 226). Other reasons for discontinuation included cost in a small number of patients (1.1%; n = 18) and unknown reasons in 6.2% (n = 105) of patients.

Across the SAS, 98.4% (n = 1676) of patients received perampanel as adjunctive therapy, 1.9% (n = 33) as primary monotherapy, and 0.8% (n = 14) as secondary monotherapy.

Based on all patients in the SAS with nonmissing age-related data (n = 1695), the mean (standard deviation [SD]) age at baseline was 28.5 (16.5) years (Table 1). Most patients were female (52.7%) and White (72.3%). The most common seizure types based on epilepsy-specific medical history were focal impaired awareness (59.2%; n = 1006), primary generalized convulsions (51.0%; n = 867), and focal to bilateral convulsions (36.4%; n = 619).

Overall, 77.6% (n = 1321) of patients received 1–3 concomitant ASMs at baseline (taken at the date of first dose of perampanel). Of 1676 patients who received adjunctive perampanel during the study, the most common concomitant ASMs at baseline were levetiracetam (34.6%; n = 580), lacosamide (27.9%; n = 467), and clobazam (24.3%;

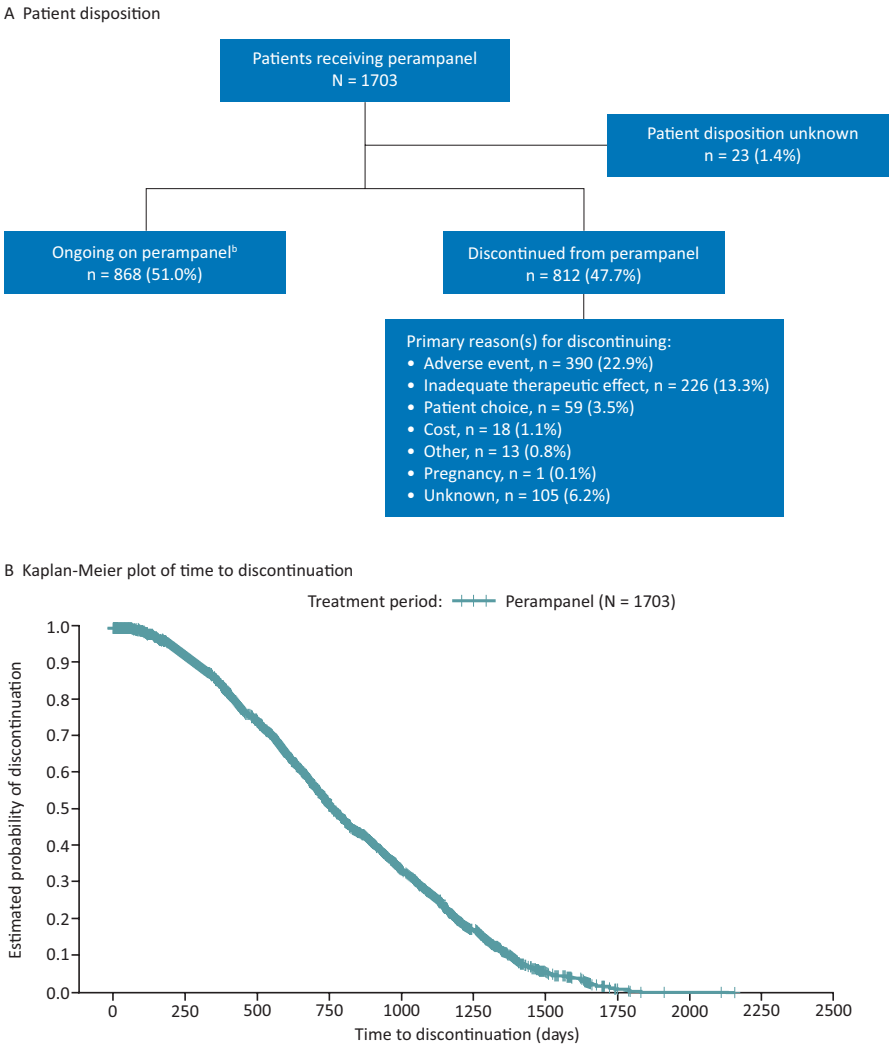

FIGURE 1 (A) Patient disposition[a] and (B) Kaplan-Meier plot of time to discontinuation (Safety Analysis Set). [a]All enrolled and treated patients. [b]At time of date of data collection. This will occur at different time points on treatment for different patients

n = 407). In the SAS, 21.0% (n = 358) of patients received perampanel with ≥1 concomitant EIASM at baseline (oxcarbazepine [45.8%; n = 164], carbamazepine [25.1%; n = 90], phenytoin [19.0%; n = 68], and eslicarbazepine [14.2%; n = 51]), and 79.0% (n = 1345) received perampanel with non-EIASMs at baseline. Of these subgroups, the FAS

TABLE 1 Demographics and clinical characteristics during baseline for overall patients, patients receiving EIASMs at baseline, and patients receiving non-EIASMs at baseline

	Safety analysis set			Full analysis set		
	Overall (N = 1703)	EIASMs (n = 358)	Non-EIASMs (n = 1345)	Overall (N = 329)	EIASMs (n = 66)	Non-EIASMs (n = 263)
Age,[a] years						
Mean (SD)	28.5 (16.5)	33.6 (16.1)	27.1 (16.4)	29.1 (16.6)	33.2 (13.8)	28.1 (17.1)
Median (min, max)	26.0 (1, 84)	33.0 (1, 84)	24.0 (1, 84)	26.0 (1, 77)	32.5 (8, 60)	24.0 (1, 77)
Female, n (%)	898 (52.7)	175 (48.9)	723 (53.8)	173 (52.6)	32 (48.5)	141 (53.6)
Race,[b] n (%)						
White	1231 (72.3)	256 (71.5)	975 (72.5)	233 (70.8)	43 (65.2)	190 (72.2)
Black	176 (10.3)	38 (10.6)	138 (10.3)	46 (14.0)	11 (16.7)	35 (13.3)
Asian	41 (2.4)	9 (2.5)	32 (2.4)	8 (2.4)	1 (1.5)	7 (2.7)
Other[c]	255 (15.0)	55 (15.4)	200 (14.9)	42 (12.8)	11 (16.7)	31 (11.8)
Mean (SD) age at epilepsy diagnosis,[d] years	13.8 (15.4)	15.3 (14.9)	13.4 (15.5)	13.8 (16.6)	13.9 (12.6)	13.8 (17.5)
Time since diagnosis,[e] years						
Mean (SD)	15.7 (13.2)	18.8 (14.6)	14.8 (12.6)	17.2 (14.1)	19.9 (14.3)	16.6 (14.0)
Median (min, max)	12.0 (0.0, 65.0)	14.0 (0, 65)	11.0 (0, 65)	12.2 (0, 65)	14.5 (0.35, 57)	12.0 (0, 65)
Seizure type,[f] n (%)						
Focal aware without motor signs	235 (13.8)	85 (23.7)	150 (11.2)	42 (12.8)	19 (28.8)	23 (8.7)
Focal aware with motor signs	322 (18.9)	82 (22.9)	240 (17.9)	44 (13.4)	11 (16.7)	33 (12.5)
Focal impaired awareness	1006 (59.2)	279 (77.9)	727 (54.2)	194 (59.0)	53 (80.3)	141 (53.6)
Focal to bilateral tonic-clonic	619 (36.4)	175 (48.9)	444 (33.1)	134 (40.7)	41 (62.1)	93 (35.4)
GTC	867 (51.0)	144 (40.2)	723 (53.9)	162 (49.2)	23 (34.8)	139 (52.9)
Myoclonic	328 (19.3)	23 (6.4)	305 (22.7)	61 (18.5)	3 (4.5)	58 (22.1)
Absence	301 (17.7)	36 (10.1)	265 (19.7)	44 (13.4)	3 (4.5)	41 (15.6)
Atypical absence	88 (5.2)	9 (2.5)	79 (5.9)	11 (3.3)	2 (3.0)	9 (3.4)
Clonic	161 (9.5)	30 (8.4)	131 (9.8)	13 (4.0)	2 (3.0)	11 (4.2)
Tonic	343 (20.2)	53 (14.8)	290 (21.6)	48 (14.6)	5 (7.6)	43 (16.3)
Atonic	178 (10.5)	17 (4.7)	161 (12.0)	26 (7.9)	3 (4.5)	23 (8.7)
Other[g]	187 (11.0)	29 (8.1)	158 (11.8)	18 (5.5)	2 (3.0)	16 (6.1)
Missing	3	0	3	0	0	0
ILAE classification, n (%)						
Focal-onset	849 (49.9)	236 (65.9)	613 (45.6)	179 (54.4)	52 (78.8)	127 (48.3)
Idiopathic generalized epilepsy	290 (17.0)	23 (6.4)	267 (19.9)	54 (16.4)	3 (4.5)	51 (19.4)
Other	275 (16.1)	36 (10.1)	239 (17.8)	60 (18.2)	2 (3.0)	58 (22.1)
Unknown	289 (17.0)	63 (17.6)	226 (16.8)	36 (10.9)	9 (13.6)	27 (10.3)
Number of concomitant ASMs[h]						
0	166 (9.7)[i]	2 (0.6)[j]	164 (12.2)	11 (3.3)	0 (0.0)	11 (4.2)
1	332 (19.5)	60 (16.8)	272 (20.2)	54 (16.4)	7 (10.6)	47 (17.9)

(Continues)

TABLE 1 (Continued)

	Safety analysis set			Full analysis set		
	Overall (N = 1703)	EIASMs (n = 358)	Non-EIASMs (n = 1345)	Overall (N = 329)	EIASMs (n = 66)	Non-EIASMs (n = 263)
2	591 (34.7)	115 (32.1)	476 (35.4)	135 (41.0)	22 (33.3)	113 (43.0)
3	398 (23.4)	107 (29.9)	291 (21.6)	88 (26.7)	25 (37.9)	63 (24.0)
>3	216 (12.7)	74 (20.7)	142 (10.6)	41 (12.5)	12 (18.2)	29 (11.0)

Abbreviations: ASM, antiseizure medication; EIASM, enzyme-inducing antiseizure medication; GTC, generalized tonic-clonic; ILAE, International League Against Epilepsy; max, maximum; min, minimum; SD, standard deviation.

[a]Age at perampanel treatment initiation; based on the total number of patients included in the Safety Analysis Set with nonmissing data (overall, n = 1695; EIASMs, n = 356; non-EIASMs, n = 1339).

[b]Percentages are based on the total number of patients included in the Safety Analysis Set with nonmissing data (overall, n = 1702; EIASMs, n = 358; non-EIASMs, n = 1344).

[c]Includes Arabic, Hispanic, Indian, Kuwaiti, Latino, Middle Eastern, Native American, and unknown.

[d]Based on the total number of patients with nonmissing data in the Safety Analysis Set (overall, n = 1609; EIASMs, n = 339; non-EIASMs, n = 1270) or Full Analysis Set (overall, n = 309; EIASMs, n = 61; non-EIASMs, n = 248) due to incorrect recording of date of birth; 14 patients had an incorrect derived age at diagnosis.

[e]Based on the total number of patients included in the Safety Analysis Set with nonmissing data (overall, n = 1630; EIASMs, n = 343; non-EIASMs, n = 1287).

[f]Based on the total number of patients included in the Safety Analysis Set with seizure type data (overall, n = 1703; EIASMs, n = 355; non-EIASMs, n = 1348).

[g]Other seizure types include, but are not limited to: drop attacks, grand mal, infantile spasms, Lennox-Gastaut syndrome, nonepileptic seizures, and pseudoseizures.

[h]ASMs being administered during baseline (taken at date of first dose of perampanel; rescue medications not included).

[i]There were 139 patients who received perampanel but had no baseline ASMs recorded.

[j]There were two patients who received EIASMs (oxcarbazepine, n = 1; phenytoin, n = 1), but were recorded as having received no baseline ASMs due to missing date information.

included 66 patients receiving EIASMs and 263 patients receiving non-EIASMs. Baseline demographics and clinical characteristics for the FAS are shown in Table 1.

3.2 | Dosage and exposure

The overall mean (SD, range) cumulative duration of perampanel exposure was 17.4 (15.7, 0.0–77.1) months; 51.4% and 29.4% of patients achieved ≥12 and ≥24 months' cumulative durations of perampanel exposure, respectively (Figure 2A). The overall mean (SD) daily perampanel dose was 5.6 (2.7) mg; for patients receiving EIASMs and non-EIASMs, mean (SD) daily perampanel doses were 5.8 (2.8) mg and 5.6 (2.7) mg, respectively. The overall mean (SD) maximum daily perampanel dose achieved was 6.6 (3.2) mg, with more than half of patients (55.4% [n = 943/1703]) receiving maximum daily perampanel doses of 6 mg or lower; the most common (≥15.0% of patients) maximum daily perampanel doses were 8 mg (22.8%; n = 388), 4 mg (20.7%; n = 352), and 6 mg (20.6%; n = 350; Figure 2B). A minority of patients received maximum doses above 12 mg (3.6% [13/358] of patients receiving EIASMs and, off-label, 0.6% [8/1345] of patients receiving non-EIASMs).

The top three most common modal daily perampanel doses overall were 4 mg (19.5%; n = 332), 6 mg (17.6%; n = 299), and 8 mg (16.0%; n = 272). Overall mean (SD) modal daily perampanel dose was 5.9 (3.0) mg; when split by age groups, mean (SD) modal daily perampanel doses were 2.8 (2.1) mg for infant patients (aged <4 years), 4.7 (2.7) mg for pediatric patients (aged 4 to <12 years), 5.8 (2.9) mg for adolescent patients (aged 12 to <18 years), and 6.1 (3.0) mg for adult patients (aged ≥18 years).

Perampanel titration occurred weekly in 23.4% (n = 399) of patients, every 2 weeks in 24.7% (n = 420) of patients, and every 3 weeks in 1.1% (n = 19) of patients. Other reported titration rates included: more frequently than weekly in 0.6% (n = 11) of patients, no titration in 9.6% (n = 164) of patients, as per investigator's discretion/irregular in 8.2% (n = 139) of patients, monthly/every 4 weeks in 1.8% (n = 30) of patients, less frequently than every 4 weeks in 2.1% (n = 36) of patients, and unknown in 28.5% (n = 485) of patients.

3.3 | Efficacy

Following 12 and 24 months on perampanel treatment during routine clinical care, 58.5% (n = 876/1498) and 48.1% (n = 501/1042) of eligible patients in the SAS remained on perampanel treatment, respectively

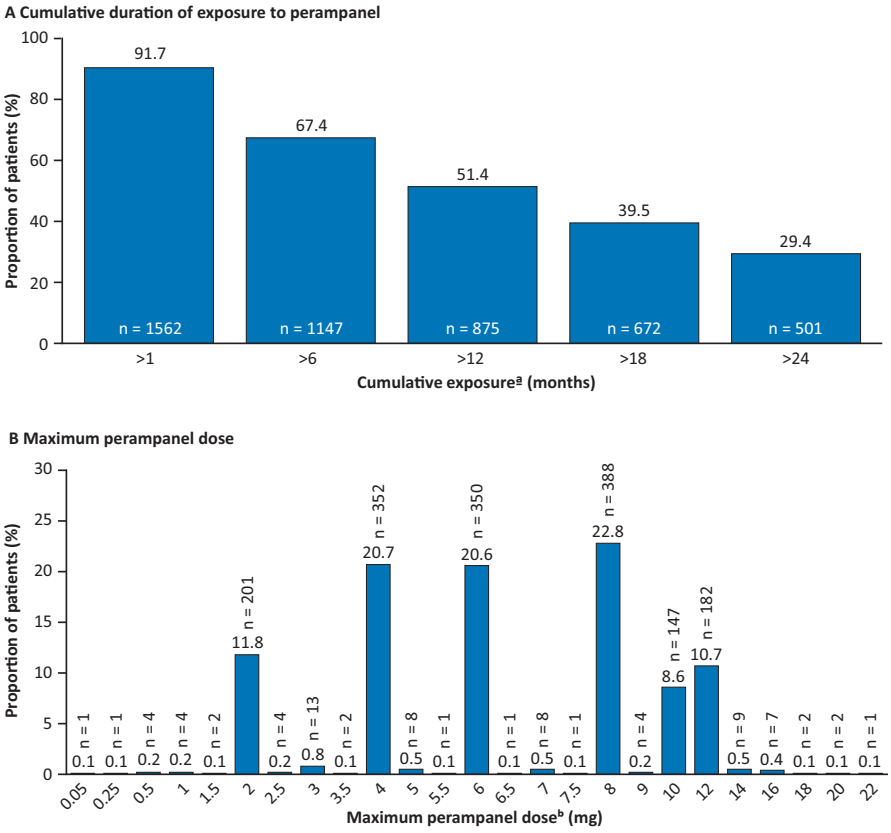

FIGURE 2 (A) Cumulative duration of exposure to perampanel and (B) maximum perampanel dose (Safety Analysis Set). [a]Patients were counted in each applicable category. [b]Data for maximum perampanel dose were missing for eight patients

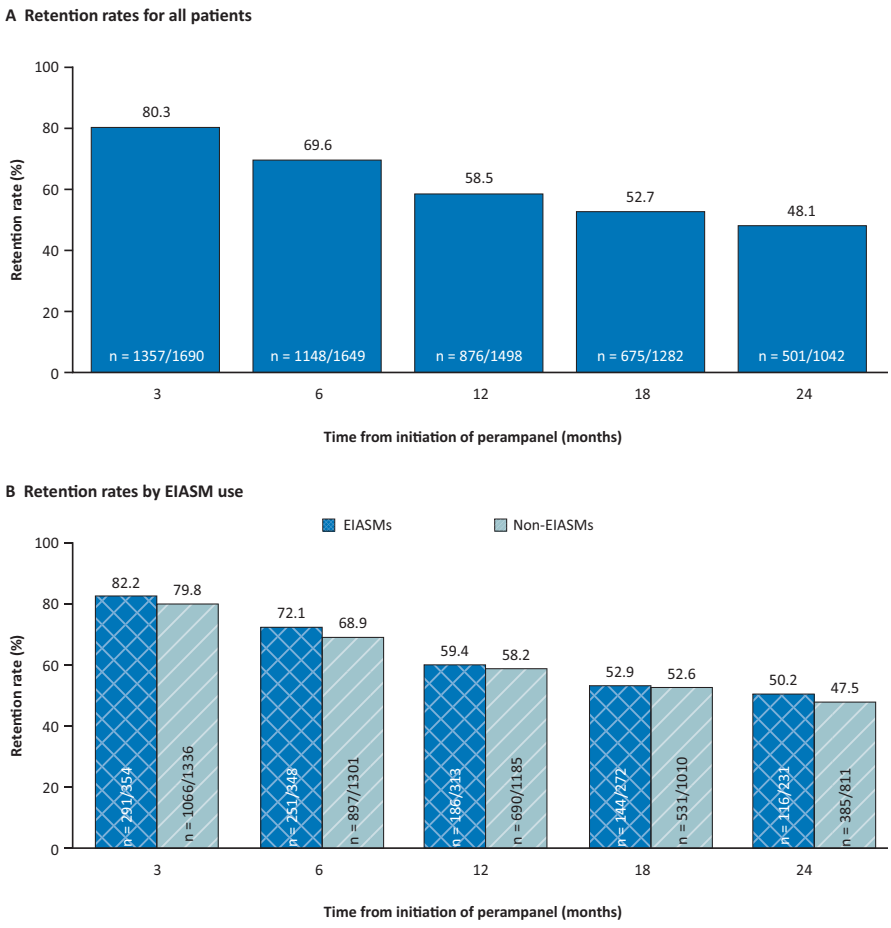

FIGURE 3 Retention rates over 24 months following initiation of perampanel treatment[a] (A) for all patients and (B) for patients receiving EIASMs or non-EIASMs at baseline (Safety Analysis Set)[a]. Abbreviation: EIASM, enzyme-inducing antiseizure medication. Retention rate = number of patients on treatment for at least *x* months/number of patients who could have been on treatment for at least *x* months. [a]As patients initiated treatment on perampanel at different times, changes in the denominator over time correspond with the decreasing number of patients who could have been on perampanel treatment at each successive time point, due to reaching study cutoff

(Figure 3A); at 36 months, 43.4% (n = 267/615) of eligible patients in the SAS remained on perampanel treatment. For patients receiving EIASMs and non-EIASMs, respectively, 24-month retention rates on perampanel were 50.2% (n = 116/231) and 47.5% (n = 385/811; Figure 3B). Retention rates for patients receiving perampanel as monotherapy or adjunctive therapy are shown in Figure S1A.

Secondary efficacy endpoints were assessed in the FAS, which included a relatively small number of patients, particularly at later time points (n = 306 at months 1–3, reducing to n = 51 at months 22–24), due to the limited availability of seizure-frequency data documented in medical records. Nonetheless, these efficacy endpoints are shown in Figure S2. During months 22–24 of perampanel treatment, median reduction in seizure frequency per 28 days from baseline was 89.4% (n = 51; Figure S2A), 50% responder rate was 76.5% (n = 39/51; Figure S2B), 75% responder rate was 64.7% (n = 33/51; Figure S2C), and seizure freedom was achieved by 39.2% of patients (n = 20/51; Figure S2D).

The efficacy endpoints are reported according to perampanel use as monotherapy or adjunctive therapy in Figure S1B–E and by EIASM use in Figure S3A–D. During months 10–12 of perampanel treatment, in patients receiving EIASMs and non-EIASMs, respectively, median reductions in seizure frequency were 75.0% (n = 25) and 72.1% (n = 98), 50% responder rates were 68.0% (n = 17/25) and 61.2% (n = 60/98), 75% responder rates were 56.0% (n = 14/25) and 49.0% (n = 48/98), and seizure-freedom rates were 24.0% (n = 6/25) and 32.7% (n = 32/98). During months 22–24, the equivalent median reductions in seizure frequency were 59.5% (n = 10) and 96.7% (n = 41), 50% responder rates were 60.0% (n = 6/10) and 80.5% (n = 33/41), 75% responder rates were 40.0% (n = 4/10) and 70.7% (n = 29/41), and seizure-freedom rates were 20.0% (n = 2/10) and 43.9% (n = 18/41). However, at these later time points, patient numbers were low, particularly for patients receiving EIASMs (n = 10 at months 22–24).

Of 1427 patients in the SAS for whom seizure-effect data were recorded, an improvement of seizures was reported in 51.9% of patients, no change was reported in 35.8%, and worsening of seizures was reported in 12.3%, based on overall investigator impression of seizure effect (Figure S4A). When split by concomitant EIASM use, improvement, no change, and worsening of seizures were reported in 50.9%, 36.4%, and 12.7% of patients receiving EIASMs (n = 291), respectively, and in 52.2%, 35.7%, and 12.1% of patients receiving non-EIASMs (n = 1136), respectively (Figure S4B). Investigator impression of seizure effect by epilepsy syndrome is shown in Figure S5.

3.4 | Safety

TEAEs were reported in 41.3% (n = 704) of patients (Table 2): 42.7% (n = 153) of patients receiving EIASMs and 41.0% (n = 551) of patients receiving non-EIASMs. The most common TEAEs overall were dizziness (7.3%; n = 125), aggression (5.3%; n = 90), and irritability (4.1%; n = 69). Overall, serious TEAEs occurred in 4.6% (n = 79) of patients and included 15 deaths (0.9%; 6.1 per 1000 patient-years); causes of death were unknown (n = 7), neoplasm (n = 2), and cardiac arrest/respiratory failure, craniocerebral injury, drowning, respiratory distress, respiratory failure/unknown, and seizure (n = 1 each).

TEAEs leading to perampanel discontinuation were reported in 24.3% (n = 414) of patients overall, and in 24.3% (n = 87) of patients and 24.3% (n = 327) of patients receiving EIASMs and non-EIASMs, respectively. Overall, the most common TEAEs leading to perampanel discontinuation were aggression (3.1%; n = 53), irritability (3.1%; n = 52), and dizziness (2.6%; n = 45). When split by titration rate, TEAEs leading to discontinuation were reported in 45.5% (n = 5/11), 27.8% (n = 111/399), 30.0% (n = 126/420), 15.8% (n = 3/19), 13.3% (n = 4/30), and 13.9% (n = 5/36) of patients receiving dose titrations more than weekly, weekly, every 2 weeks, every 3 weeks, every 4 weeks, and less than every 4 weeks, respectively. For patients receiving irregular dose titration or according to investigator discretion, TEAEs leading to discontinuation were reported in 16.5% (n = 23/139) of patients, compared with 28.7% (n = 47/164) of patients receiving no dose titration. Discontinuations were reported in 63.6% (n = 7/11) of patients receiving dose titration more than weekly, 48.1% (n = 192/399) of patients receiving dose titration weekly, 49.0% (n = 206/420) of patients receiving dose titration every 2 weeks, 36.8% (n = 7/19) of patients receiving dose titration every 3 weeks, and 20.0% (n = 6/30) of patients receiving dose titration every 4 weeks.

Incidences of psychiatric TEAEs were similar across subgroups defined by maximum perampanel doses or perampanel modal doses (Table S2). Numbers of patients with psychiatric TEAEs at each modal dose are shown in Table S3 according to use of EIASMs and number of baseline ASMs. Searches for broad and narrow SMQ terms related to hostility and/or aggression identified such TEAEs in 15.4% (n = 263/1703) of patients: 21.9% (n = 85/389) of patients with a history of psychiatric illness and 13.5% (n = 178/1314) of patients with no history of psychiatric illness. The most common TEAEs related to hostility and/or aggression were aggression (5.3%; n = 90/1703) and irritability (4.1%; n = 69/1703). There were no clear patterns in the rates of TEAEs related to hostility and/or aggression by perampanel dose-titration regimens: aggression was reported in 2.8%–9.1% of patients receiving perampanel

TABLE 2 Summary of TEAEs and most common TEAEs (occurring in ≥3.0% of patients overall) for overall patients, patients receiving EIASMs at baseline, and patients receiving non-EIASMs at baseline (Safety Analysis Set)

	Overall (N = 1703)	EIASMs (n = 358)	Non-EIASMs (n = 1345)
TEAEs	704 (41.3)	153 (42.7)	551 (41.0)
Serious TEAEs	79 (4.6)	19 (5.3)	60 (4.5)
Deaths	15 (0.9)	1 (0.3)	14 (1.0)
TEAEs leading to perampanel dose adjustment, n (%)	571 (33.5)	116 (32.4)	455 (33.8)
Withdrawal	414 (24.3)	87 (24.3)	327 (24.3)
Dose reduction	163 (9.6)	33 (9.2)	130 (9.7)
Dose interruption	15 (0.9)	0 (0.0)	15 (1.1)
Dose increase	12 (0.7)	0 (0.0)	12 (0.9)
Most common (≥3.0% of patients overall) TEAEs,[a] n (%)			
Dizziness	125 (7.3)	27 (7.5)	98 (7.3)
Aggression	90 (5.3)	19 (5.3)	71 (5.3)
Irritability	69 (4.1)	13 (3.6)	56 (4.2)
Fatigue	54 (3.2)	14 (3.9)	40 (3.0)
Somnolence	54 (3.2)	6 (1.7)	48 (3.6)

Note: For each row category, a patient with ≥2 TEAEs in that category is counted only once; a TEAE is defined as an adverse event that (1) emerges during treatment, having been absent at Pretreatment; or (2) re-emerges during perampanel treatment, having been present at Pretreatment, but ceased prior to treatment initiation.

Abbreviations: EIASM, enzyme-inducing antiseizure medication; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

[a]Preferred term based on MedDRA version 21.1.

titration (more than weekly: 9.1% [n = 1/11], weekly: 4.5% [n = 18/399], every 2 weeks: 6.2% [n = 26/420], every 3 weeks: 5.3% [n = 1/19], every 4 weeks: 6.7% [n = 2/30], less than every 4 weeks: 2.8% [n = 1/36], per investigator discretion/irregular: 5.0% [n = 7/139], no titration: 3.7% [n = 6/164]), irritability was reported in 0.0%–18.2% of patients receiving perampanel titration (more than weekly: 18.2% [n = 2/11], weekly: 6.0% [n = 24/399], every 2 weeks: 4.5% [n = 19/420], every 3 weeks: 5.3% [n = 1/19], every 4 weeks: 6.7% [n = 2/30], less than every 4 weeks: 0.0%, per investigator discretion/irregular: 1.4% [n = 2/139], no titration: 1.8% [n = 3/164]), and anger was reported in 0.0%-9.1% of patients receiving perampanel titration (more than weekly: 9.1% [n = 1/11], weekly: 1.3% [n = 5/399], every 2 weeks: 4.3% [n = 18/420], every 3 weeks/every 4 weeks/less than every 4 weeks: all 0.0%, per investigator discretion/irregular: 2.9% [n = 4/139], no titration: 1.2% [n = 2/164]). There was a low incidence of hostility, regardless of dose-titration regimen (more than weekly/weekly/every 3 weeks/every 4 weeks/less than every 4 weeks/no titration: all 0.0%, every 2 weeks: 0.7% [n = 3/420], per investigator discretion/irregular: 0.7% [n = 1/139]).

TEAEs in patients receiving perampanel as primary or secondary monotherapy, or as adjunctive therapy, are shown in Table S4.

4 | DISCUSSION

PROVE recorded perampanel use in the real-world clinical care of patients with epilepsy over a time period when several extensions were made to the approved indications. These included approvals for adjunctive treatment of GTCS in patients aged ≥12 years, monotherapy treatment for FOS in patients aged ≥12 years, and treatment for FOS in patients aged ≥4 years. This final analysis of PROVE demonstrates favorable retention and sustained efficacy for ≥12 months following perampanel initiation. This is despite the fact that 55.4% of patients received relatively low perampanel doses (maximum daily doses: ≤6 mg), which were lower than FDA–recommended maintenance doses of 8–12 mg for the treatment of FOS or 8 mg for the treatment of GTCS.[11] Furthermore, most patients in PROVE (77.6%) were receiving 1-3 concomitant ASMs during baseline suggesting they had refractory seizures. As such, the efficacy and safety data reported here are particularly encouraging, especially given that a high number of previous ASMs has been associated with an unfavorable prognosis.[23]

Retention rate is considered a surrogate marker for effectiveness, since only patients who achieve adequate efficacy and tolerability would continue treatment in the real-world setting. The final 12- and 24-month retention

rates of PROVE (58.5% and 48.1%, respectively) were consistent with rates previously reported at an interim analysis (59.1% and 49.5%, respectively),[20] with 12-month retention rates also within the range of those reported in previous observational studies of perampanel in real-world clinical care in Europe (analysis of pooled data from European centers, 48%[17]; FYDATA study, 61%[18]; GENERAL study, 83%[19]). This final analysis also indicated that 39.2% of patients were seizure-free during months 22–24 and daily perampanel doses were generally well tolerated, with TEAEs consistent with the known safety profile.[11,12] As in interim reports of PROVE, the most common reasons for discontinuations were AEs and inadequate therapeutic effect; in addition, a minority of patients recorded cost as the reason for discontinuation.

It has previously been reported that TEAEs related to hostility and/or aggression increase in a perampanel dose-dependent manner: In a pooled analysis of Phase III studies, the incidence of hostility and/or aggression leading to discontinuation was 5.0%, 5.2%, 12.3%, and 20.4% in patients receiving perampanel 2, 4, 8, and 12 mg/day, respectively.[24] However, in this final analysis of PROVE, there were few clear associations between psychiatric TEAEs and perampanel modal dose, maximum dose, or dose-titration regimen. This may be attributable to differences in study designs, particularly the fact that patients in the Phase III studies were randomized to target dose groups, whereas dosing in PROVE was at the discretion of treating clinicians and so perhaps more likely to reflect how well perampanel was tolerated in each patient. Notably, the incidence of TEAEs related to hostility and/or aggression was slightly higher in patients with prior history of psychiatric illness vs those with no prior history, suggesting that caution may be needed in these patients. The incidence of psychiatric TEAEs was generally similar across perampanel modal dose groups (range: 18.3% to 28.6%), although patient numbers varied across subgroups, which may limit comparisons. However, the incidences reported here are broadly aligned with rates reported at 1 year in previous observational perampanel studies (analysis of pooled data from European centers, 26%[17]; GENERAL study, 27.5%)[19] and in the pooled analysis of Phase III studies (15.3%).[24]

While retention rates and seizure outcomes were generally consistent irrespective of EIASM use, 50% responses and seizure freedom across months 22–24 were achieved by greater proportions of patients receiving non-EIASMs than patients receiving EIASMs (80.5% vs 60.0% and 43.9% vs 20.0%, respectively). Retention rates were generally greater with adjunctive perampanel compared with primary monotherapy (24-month retention rates: 47.6% [n = 491/1031] vs 31.3% [n = 5/16]; Figure S1A). However, these results should be interpreted with caution due to the low patient numbers in the EIASM subgroups at later time points, and in the monotherapy subgroups.

Perampanel use varied, with a number of patients receiving perampanel as a primary (n = 33) or secondary (n = 14) monotherapy rather than as adjunctive therapy. In many patients, perampanel was titrated more slowly than the weekly 2-mg increments specified as a maximum frequency in the US Prescribing Information,[11] which may reflect clinicians optimizing treatment schedules for individual patients. Similar to findings during the interim analyses of PROVE,[20] off-label perampanel use was recorded, including daily doses above 12 mg and administration to patients aged <4 years. However, perampanel use in the treatment of off-label indications was not recorded since only patients with epilepsy were included in PROVE. As a retrospective, observational study, these reports provide valuable information representative of real-world decisions made by clinicians. Off-label perampanel use has been reported previously: e.g., perampanel has been used in EU countries for the treatment of status epilepticus (via nasogastric delivery in patients unable to swallow[25] and at doses >12 mg),[26] despite such use being off-label in the EU.

This study does have limitations. As is common with real-world, observational studies, there was no randomization, blinding, or placebo arm. There are also limitations inherent to retrospective studies that utilize medical record data, such as incomplete records and variable approaches toward record-keeping at different sites. For example, not all baseline ASMs were captured, there may have been variations in the way that TEAEs were recorded, and some sites recorded improvements or worsening of seizures without systematically documenting seizure counts. Furthermore, since seizure counts were obtained from patient notes and/or diary data, there was a lack of complete and detailed seizure-frequency data available for the vast majority of patients (FAS, N = 329 vs SAS, N = 1703); therefore, interpretation of efficacy data may be limited, particularly in subgroups with low patient numbers at later time points (eg, months 22–24, n = 10). In addition, inaccuracies may have been recorded in patients' notes/diaries regarding seizure classifications, which limit interpretation of the efficacy outcomes in terms of the benefits for specific seizure types. Finally, increased responder and seizure-freedom rates at later time points may reflect a selection bias, with patients who do not respond well to perampanel more likely to discontinue earlier.

Nonetheless, PROVE provides important information on the real–world use of perampanel. Although real-world outcomes have been reported for patients receiving perampanel for up to 1 year in retrospective observational studies in Europe,[17–19] limited data have been

available on real-world use in the United States, or over longer treatment durations. Here, we report outcomes at US centers for up to 2 years, providing important information on the long-term efficacy and safety of perampanel in a more heterogeneous patient population than is commonly included in Phase III clinical trials, which is more reflective of patients routinely seen in clinical practice.

Other noninterventional studies of ASMs have supported the advantages of real-world data in offering insights into patient populations that are underrepresented in traditional clinical efficacy trials, such as older patients or patients with difficult-to-treat epilepsy.[10,27] For example, an observational study demonstrated the utility of levetiracetam in patients aged ≥65 years with uncontrolled focal epilepsy,[10] while clinical outcomes of lacosamide in patients aged ≥65 years have been evaluated in a noninterventional study enrolling a greater proportion of elderly patients than included in pivotal trials.[27] Moreover, modest benefits of brivaracetam have been demonstrated in patients with difficult-to-treat epilepsy (median number of previous ASMs: 10),[28] while perampanel improved 12-month seizure outcomes in patients with idiopathic generalized epilepsy across various seizure types including GTCS and myoclonic and absence seizures.[19]

In conclusion, in this final analysis of >1700 patients with epilepsy receiving perampanel in routine clinical care, favorable retention and sustained efficacy were demonstrated for ≥12 months, with no new safety signals detected. Further analyses of the PROVE study will be published separately, including data in infant and pediatric patients aged <12 years and adolescent and adult patients aged ≥12 years.

ACKNOWLEDGMENTS

The authors would like to thank the study participants. The PROVE study (NCT03208660) was funded by Eisai Inc. Medical writing support, under the direction of the authors, was provided by David Pertab, and Daniela DiBiase, of CMC AFFINITY, McCann Health Medical Communications, funded by Eisai Inc., in accordance with Good Publication Practice (GPP3) guidelines. The data reported in this paper have previously been presented at the 73rd Annual Meeting of the American Epilepsy Society, Baltimore, MD, USA, December 6-10, 2019.

CONFLICT OF INTEREST

Robert T. Wechsler has been a clinical trial investigator for Aquestive, Biogen, Cavion, Cerevel, Eisai, Engage Pharma, Greenwich Biosciences, Lundbeck, Otsuka, Pfizer, SK Life Science, Sunovion, UCB Pharma, Xenon, and Zogenix; has served on advisory boards and/or carried out consulting work for Brain Sentinel, Cerevel, Eisai, Engage Pharma, Greenwich Biosciences, Lundbeck, Otsuka, SK Life Science, Sunovion, and UCB Pharma; has received speaker bureau honoraria from Aquestive, Eisai, Greenwich Biosciences, LivaNova, Neurelis, SK Life Science, Sunovion, and UCB Pharma; and is a member of the Epilepsy Study Consortium. James Wheless has received grant support from Aquestive, Eisai, Greenwich, INSYS Inc, LivaNova, Mallinckrodt, Neurelis, NeuroPace, the Shainberg Foundation, and West; has served as a consultant for Aquestive, BioMarin, Eisai, Greenwich, Mallinckrodt, Neurelis, NeuroPace, Shire, Supernus, and Zogenix; and has received speaker bureau honoraria from BioMarin, Eisai, Greenwich, LivaNova, Mallinckrodt, and Supernus. Muhammad Zafar has received research support from and has been a consultant for Eisai, LivaNova, and Marinus Pharmaceuticals; has received research support from Stoke Therapeutics and UCB Pharma; and has been a consultant for Mallinckrodt. Graham R. Huesmann has no disclosures to make in relation to this work. Marcelo Lancman has received research grant support from Eisai. Eric Segal has received honoraria from Eisai, GW Pharma, Lundbeck, and Zogenix. Michael Chez has served as a consultant for, and has received grant support and/or speaker or advisory honoraria from, Aquestive, Eisai, GW Pharma, Mallinckrodt Zogenix, Marinus, and UCB Pharma. Sami Aboumatar has served on advisory boards and/or has carried out consulting work for Eisai and Sunovion. Anna Patten is an employee of Eisai Europe Ltd. Alejandro Salah is a former employee of Eisai Inc. Manoj Malhotra is an employee of Eisai Inc. 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 contributed to the interpretation of the data and reviewed each draft of the manuscript; Robert T. Wechsler, Anna Patten, Alejandro Salah, and Manoj Malhotra contributed to the conception and design of the study; Robert T. Wechsler, James Wheless, Muhammad Zafar, Graham R. Huesmann, Marcelo Lancman, Eric Segal, Michael Chez, and Sami Aboumatar contributed to the acquisition of the data; Anna Patten conducted the analysis of the data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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: Wechsler RT, Wheless J, Zafar M, et al. PROVE: Retrospective, non-interventional, Phase IV study of perampanel in real-world clinical care of patients with epilepsy. Epilepsia Open. 2022;7:293–305. https://doi.org/10.1002/epi4.12575