

Perampanel in real-world clinical care of patients with epilepsy: Interim analysis of a phase IV study

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Abstract

Objective: To assess the retention rate, efficacy, safety, and dosing of perampanel administered to patients with epilepsy during routine clinical care in the retrospective phase IV, PROVE Study (NCT03208660).

Methods: Exposure, efficacy, and safety data were obtained from the medical records of patients initiating perampanel after January 1, 2014, across 29 US study sites. The cutoff date for this interim analysis was October 10, 2018. The primary efficacy endpoint was retention rate. Secondary efficacy endpoints included median percent changes in seizure frequency, seizure-freedom rate, and overall investigator impression of seizure effect.

Results: All enrolled patients (N = 1121) received perampanel. Mean (standard deviation [SD]) cumulative duration of exposure to perampanel was 16.6 (14.7) months; overall mean (SD) daily perampanel dose was 5.7 (2.7) mg. Perampanel uptitration occurred weekly (21.1%), biweekly (23.8%), every 3 weeks (1.5%), other (43.3%), and unknown (10.3%). Across the Safety Analysis Set (N = 1121), retention rate on perampanel at 24 months was 49.5% (n = 319/645).

At 12 months, the median reduction in seizure frequency per 28 days from baseline in the small number of patients for whom data were available was 75.0% (n = 85), and 30/85 (35.3%) patients were seizure free. Based on investigator impression at the end of treatment, improvement, no change (ie, stable), or worsening of seizures was reported in 54.3%, 33.7%, and 12.0% of patients, respectively.

Treatment-emergent adverse events occurred in 500 (44.6%) patients; the most common were dizziness (9.2%), aggression (5.4%), and irritability (4.5%). Serious treatment-emergent adverse events occurred in 32 (2.9%) patients.

Significance: Favorable retention and sustained efficacy were demonstrated for ≥12 months following initiation of perampanel during routine clinical care in patients with epilepsy.

KEYWORDS

AMPA receptor antagonist, antiseizure medication, noninterventional clinical trial, retention, retrospective

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1 | INTRODUCTION

Perampanel, a selective, noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a once-daily, oral antiseizure medication (ASM) approved for focal seizures (previously referred to as partial-onset seizures [POS]) and generalized tonic-clonic (GTC) seizures (previously primary generalized tonic-clonic seizures).^{1,2} In the United States, perampanel is approved for the treatment of focal seizures (adjunctive and monotherapy) in patients aged ≥ 4 years, and as adjunctive treatment of GTC seizures in patients aged ≥ 12 years.²

Perampanel (up to 12 mg/day) demonstrated efficacy and tolerability in randomized, double-blind, placebo-controlled phase III studies in patients aged ≥ 12 years with uncontrolled focal seizures, with or without focal to bilateral tonic-clonic (FBTC) seizures (previously secondarily generalized seizures), and in patients aged ≥ 12 years with idiopathic generalized epilepsy and GTC seizures.³⁻⁷ Perampanel oral suspension (up to 0.18 mg/kg/day) demonstrated efficacy and tolerability in a phase II study of patients aged ≥ 2 to < 12 years with epilepsy.⁸ However, there is limited information available on how data from these trials have been adapted to clinical practice in the real-world epilepsy clinic.

Real-world evidence describes information obtained outside of randomized controlled trials (RCTs) by noninterventional observations of routine clinical practice.⁹ These studies have several advantages over RCTs, allowing more heterogeneous patient populations, flexible dosing and titration, and longer drug exposures, with continued therapy most likely to be indicative of perceived benefit by the patient and the prescriber.¹⁰ Therefore, despite their limitations, these retrospective studies are more reflective of routine clinical practice, providing observations on the real-world experience of a medical product.¹⁰

Here, we report an interim analysis of PROVE (Perampanel Real-world Evidence), a retrospective, phase IV study to assess retention rate, efficacy, tolerability, and dosing of perampanel administered in the routine clinical care of patients with epilepsy.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

The study protocol was approved by institutional review boards (IRBs) or independent ethics committees (IECs) at each site. Where required by an IRB, an IEC, or regulatory authorities, written informed consent was provided

Key Points

- Real-world data for patients with epilepsy treated with perampanel are limited; we report real-world outcomes from the phase IV PROVE Study.
- Based on the 1121 patients who received perampanel in this interim analysis, the retention rate at 24 months was 49.5% ($n = 319/645$).
- At 12 months, median reduction in seizure frequency per 28 days from baseline was 75.0% ($n = 85$); 30/85 (35.3%) patients were seizure free.
- At 24 months, median reduction in seizure frequency per 28 days from baseline was 98.3% ($n = 34$); 16/34 (47.1%) patients were seizure free.
- Treatment-emergent adverse events were consistent with the known safety profile of perampanel.

by the patients, or the patient's legally authorized representative signed for the use of medical records. Patients could withdraw consent prior to the anonymization of the data. PROVE is registered with ClinicalTrials.gov (NCT03208660).

2.2 | Study design

This multicenter, noninterventional, retrospective, phase IV study was conducted between April 10, 2017, and April 1, 2019. This interim analysis is based on data recorded up to October 10, 2018. Patients were recruited at 29 sites across 16 states of the United States. Patient recruitment onto PROVE was retrospective. Cases were identified from the medical and pharmacy records of patients who had attended their usual epilepsy clinic and were prescribed perampanel after January 1, 2014, on the basis of their treating clinician's recommendation. Given that PROVE was a non-interventional study, there was no maximum target enrollment, and data were collected from as many patients as possible.

All data were collected from historical patient medical records and entered into an electronic case report form. Where available, data included demographics, medical and disease history, ASM history, seizure frequency from seizure diaries or investigator assessment of therapeutic response, perampanel titration and dosage data, and safety data including treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs that resulted in discontinuation of perampanel.

2.3 | Patients

Patients were eligible for inclusion if they had a diagnosis of epilepsy and were treated with commercially available perampanel at any time after January 1, 2014. No exclusion criteria were applied. Patients who participated in perampanel pivotal trials were not included.

2.4 | Assessments

Assessments were made based on the Safety Analysis Set (patients who received perampanel and had safety data recorded) or the Full Analysis Set (patients who received perampanel and had seizure-frequency data recorded). For patients who stopped and later restarted perampanel treatment, analyses were based on the total time on treatment as derived by summing together the different periods on treatment.

The primary efficacy endpoint was the retention rate, defined as the proportion of patients in the Safety Analysis Set who remained on perampanel treatment at 3, 6, 12, 18, and 24 months following the initiation of treatment. Retention rates were also measured up to 36 months. Given as a percentage, retention rates represent the number of patients who remained on treatment for x number of months, divided by the total number of patients who could have remained on treatment for x number of months, based on when they initiated perampanel treatment in relation to the cutoff date for the analysis; for example, only patients who initiated perampanel treatment ≥ 24 months prior to the cutoff date were included in the calculation for retention rate at 24 months.

Secondary efficacy endpoints, assessed in the Full Analysis Set, included median percent change in seizure frequency per 28 days from baseline, and 50% and 75% responder rates and seizure-freedom rates, defined as the proportion of patients with a $\geq 50\%$, $\geq 75\%$, or 100% reduction in seizure frequency per 28 days from baseline, respectively.

Maximum and average dose of perampanel was assessed in the Safety Analysis Set as a secondary endpoint. Based on investigator impression of seizure effect as assessed at the end of treatment, the proportions of patients who had an improvement, no change, or a worsening of seizures were investigated in the Safety Analysis Set. Safety endpoints assessed in the Safety Analysis Set included the incidence of TEAEs, serious TEAEs, and TEAEs leading to discontinuation of perampanel treatment.

3 | RESULTS

3.1 | Patients

The Safety Analysis Set for this analysis included 1121 patients and the Full Analysis Set included 243 patients. Based on a

total of 1121 enrolled patients, 591 (52.7%) patients remained on perampanel treatment at data cutoff and 525 (46.8%) had discontinued (Figures 1A,B); disposition was unknown for 5 (0.4%) patients. The most common primary reasons for discontinuation were adverse events ($n = 254$ [22.7%]) and inadequate therapeutic effect ($n = 143$ [12.8%]).

Of the 1121 patients included in the Safety Analysis Set, 1108 (98.8%) patients received perampanel as adjunctive therapy, 16 (1.4%) received perampanel as primary monotherapy (administration of perampanel in the absence of any concomitant ASMs), and 9 (0.8%) received perampanel as secondary monotherapy (conversion from adjunctive perampanel to monotherapy by withdrawal of concomitant ASMs); patients who received both adjunctive perampanel and perampanel monotherapy are included in each respective group.

At baseline, of the 1115 patients in the Safety Analysis Set with nonmissing data relating to age, 781 (70.0%) patients were aged ≥ 18 years, 183 (16.4%) patients were aged 12 to < 18 years, and 151 (13.5%) patients were aged < 12 years (Table 1). The mean (standard deviation [SD]) age was 29.2 (16.7) years. Slightly more patients were female (54.3%) and most were Caucasian (76.4%). The median (minimum, maximum) time since diagnosis of epilepsy was 13.0 (0.0, 65.0) years. Based on epilepsy-specific medical history, the most common seizure types reported were focal impaired awareness ($n = 674$ [60.2%]; previously complex POS), GTC ($n = 506$ [45.2%]), and focal with FBTC ($n = 434$ [38.8%]). Patient demographics and disease characteristics for the Full Analysis Set at baseline are shown in Table S1.

Overall, 77.6% ($n = 870$) of patients received 1–3 and 13.1% ($n = 147$) received > 3 concomitant ASMs during baseline, taken at the date of first dose of perampanel. Based on the 1108 patients who received treatment with adjunctive perampanel during the study, the most common concomitant ASMs at baseline were levetiracetam ($n = 403$ [36.4%]), lacosamide ($n = 319$ [28.8%]), and clobazam ($n = 276$ [24.9%]); 21.5% ($n = 238$) of patients received ≥ 1 enzyme-inducing ASM at baseline, of which oxcarbazepine ($n = 108$ [9.7%]) was the most common. For patients who had 0, 1, 2, 3, and > 3 concomitant ASMs recorded at baseline, the proportions who were ongoing on perampanel were 51.9% ($n = 54/104$), 47.5% ($n = 94/198$), 55.7% ($n = 229/411$), 47.5% ($n = 124/261$), and 61.2% ($n = 90/147$), respectively. Patients who discontinued perampanel received a mean (SD) of 2.1 (1.2) ASMs at baseline, and patients who were ongoing on perampanel received a mean (SD) of 2.2 (1.3) ASMs at baseline.

3.2 | Dosage and exposure

The overall mean (SD, range) cumulative duration of exposure to perampanel was 16.6 (14.7, 0.0–75.5) months;

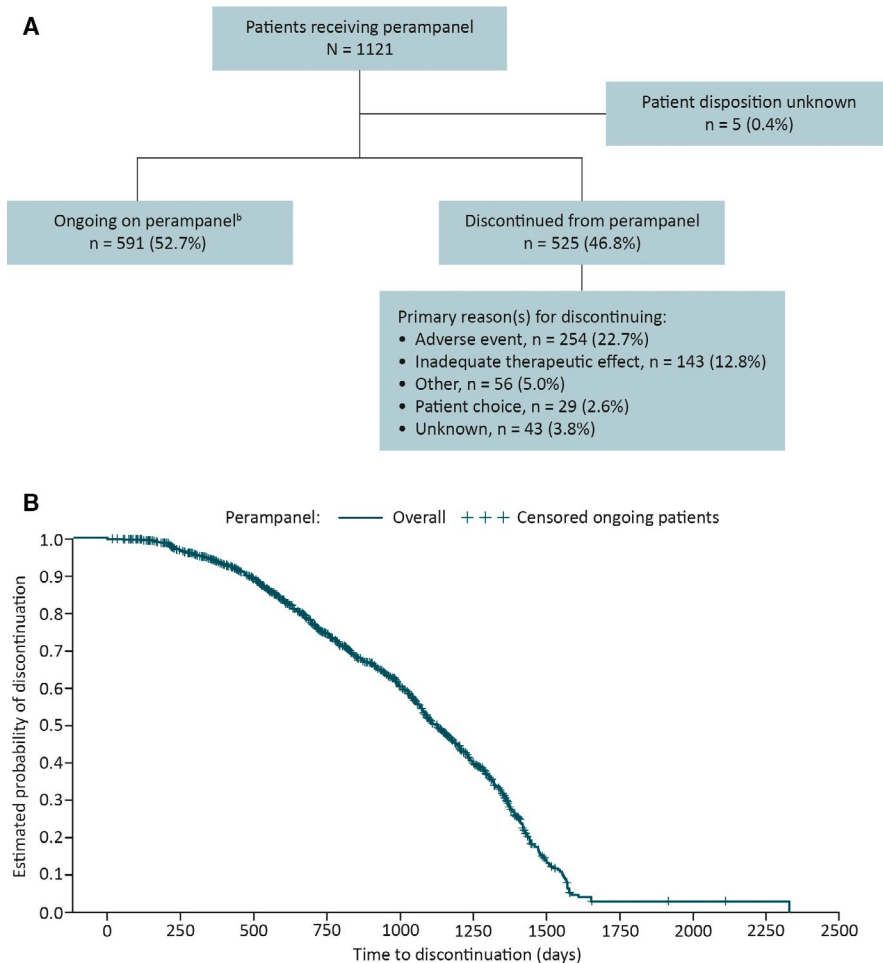


FIGURE 1 (A) Patient disposition^a and (B) Kaplan–Meier plot of time to discontinuation. ^aAll enrolled patients. ^bAt time of data collection. This will occur at different timepoints on treatment for different patients

50.2% of patients achieved ≥ 12 months' cumulative duration of exposure to perampanel and 28.5% of patients achieved ≥ 24 months' cumulative duration of exposure to perampanel (Figure 2A). Mean (SD) duration of exposure was 25.1 (13.9) months for patients who were ongoing on perampanel and 7.2 (8.6) months for patients who discontinued perampanel.

The overall mean (SD) daily perampanel dose was 5.7 (2.7) mg, the mean (SD) maximum daily perampanel dose achieved was 6.8 (3.2) mg, and the most common ($\geq 15.0\%$ of patients) maximum daily perampanel doses achieved were 8 mg ($n = 253$ [22.6%]), 4 mg ($n = 239$ [21.3%]), and 6 mg ($n = 234$ [20.9%]; Figure 2B). Mean (SD) maximum daily perampanel dose was 7.5 (3.2) mg for patients who were ongoing on perampanel and 5.9 (2.9) mg for patients who discontinued perampanel. Maximum and modal daily perampanel doses received by patients who were ongoing on perampanel and patients who discontinued perampanel are shown in Table S2.

The top three most common modal daily doses of perampanel received were 4 mg ($n = 211$ [18.8%]), 6 mg ($n = 194$ [17.3%]), and 8 mg ($n = 160$ [14.3%]). Median modal daily doses were 4 mg in pediatric patients (aged < 12 years), 6 mg in adolescent patients (aged 12 to

< 18 years), 6 mg in adult patients (aged 18 to < 65 years), and 4 mg in elderly patients (aged ≥ 65 years). For patients who were ongoing on perampanel and patients who discontinued perampanel, median modal daily doses were 6 mg and 4 mg, respectively.

Perampanel dose titration occurred weekly in 236 (21.1%) patients, every 2 weeks in 267 (23.8%) patients, every 3 weeks in 17 (1.5%) patients, "other" in 485 (43.3%) patients, and was "unknown" for 116 (10.3%) patients. "Other" titration rates included daily, no titration, variable, as needed, and monthly/every 4 weeks. Discontinuations were reported in 47.0% ($n = 111$) of patients receiving dose titration weekly, 45.7% ($n = 122$) of patients receiving dose titration every 2 weeks, 41.2% ($n = 7$) of patients receiving dose titration every 3 weeks, 49.1% ($n = 238$) of patients receiving "other" titration schedules, and 40.5% ($n = 47$) of patients receiving "unknown" titration schedules. Discontinuations due to adverse events or patient choice were reported in 30.1% ($n = 71$) and 2.5% ($n = 6$) of patients, respectively, receiving weekly dose titration, 25.8% ($n = 69$) and 1.9% ($n = 5$) of patients receiving dose titration every 2 weeks, 5.9% ($n = 1$) and 0.0% of patients receiving dose titration every 3 weeks, 20.6% ($n = 100$) and 3.1%

TABLE 1 Patient demographics and clinical characteristics during baseline (Safety Analysis Set)

	Perampanel (N = 1121)
Age, ^a years	
Mean (SD)	29.2 (16.7)
Median (min, max)	27.0 (1.0, 84.0)
Age group, ^b n (%)	
<12 years	151 (13.5)
12 to <18 years	183 (16.4)
18 to <65 years	755 (67.7)
≥65 years	26 (2.3)
Female, n (%)	609 (54.3)
Race, n (%)	
Caucasian	856 (76.4)
Black or African American	119 (10.6)
Asian	24 (2.1)
Other ^c	122 (10.9)
Mean (SD) age at epilepsy diagnosis, ^d years	13.3 (14.6)
Time since diagnosis, ^e years	
Mean (SD)	16.6 (13.6)
Median (min, max)	13.0 (0.0, 65.0)
ILAE classification, n (%)	
Focal	569 (50.8)
Idiopathic generalized epilepsy	225 (20.1)
Other	163 (14.5)
Unknown	164 (14.6)
Seizure type, n (%)	
Focal aware without motor signs	175 (15.6)
Focal aware with motor signs	213 (19.0)
Focal impaired awareness	674 (60.2)
Focal to bilateral tonic-clonic	434 (38.8)
GTC	506 (45.2)
Myoclonic	219 (19.6)
Absence	190 (17.0)
Atypical absence	53 (4.7)
Clonic	87 (7.8)
Tonic	214 (19.1)
Atonic	120 (10.7)
Other	125 (11.2)
Missing	2

Number of concomitant ASMs,^f n (%)

(n = 15) of patients receiving “other” titration schedules, and 11.2% (n = 13) and 2.6% (n = 3) of patients receiving “unknown” titration schedules. “Other” categories included “more than every week”, “every 4 weeks”, “at the investigators discretion”, and “no titration.”

	Perampanel (N = 1121)
0	104 (9.3) ^g
1	198 (17.7)
2	411 (36.7)
3	261 (23.3)
>3	147 (13.1)

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

^aAge at perampanel treatment initiation.

^bPercentages are based on the total number of patients with nonmissing data (N = 1115).

^cIncludes Hispanic, Indian, Latino, Middle Eastern, Native American, and unknown.

^dBased on the total number of patients with nonmissing data (N = 1079).

^eBased on the total number of patients with nonmissing data (N = 1093).

^fASMs being administered during baseline (taken at date of first dose of perampanel; rescue medications not included).

^gEighty-eight patients receiving adjunctive perampanel therapy had no ASMs recorded at the time of this analysis.

3.3 | Efficacy

Based on the total numbers of patients eligible for inclusion in the retention analysis at each timepoint as determined by when they initiated perampanel treatment, retention rates on perampanel at 6, 12, and 24 months after the initiation of perampanel treatment were 70.1% (n = 753/1074), 59.1% (n = 564/954), and 49.5% (n = 319/645; Figure 3A), respectively. There were 44.5% (n = 161/362) of eligible patients who remained on perampanel at 36 months after the initiation of treatment. Retention rates on perampanel broken down by maximum perampanel dose and modal perampanel dose are presented in Figures 3B,C, respectively. Retention rates by perampanel titration rate are shown in Table S3. When assessed by epilepsy syndrome, retention rates at 3, 6, 12, 24, and 36 months after the time of initiation of perampanel treatment remained high although patient numbers were low in some of the epilepsy syndrome groups (Table S4).

During Months 10–12 of perampanel treatment, the median percent reduction in seizure frequency per 28 days from baseline was 75.0% (n = 85; Figure 4A), 50% responder rate was 65.9% (n = 56/85; Figure 4B), 75% responder rate was 50.6% (n = 43/85; Figure 4C), and 35.3% (n = 30/85; Figure 4D) of patients achieved seizure freedom.

Median percent reduction in seizure frequency per 28 days from baseline during Months 22–24 was 98.3% (n = 34; Figure 4A), 50% responder rate was 76.5% (n = 26/34; Figure 4B), 75% responder rate was 61.8% (n = 21/34; Figure 4C), and 47.1% (n = 16/34; Figure 4D) of patients achieved seizure freedom.

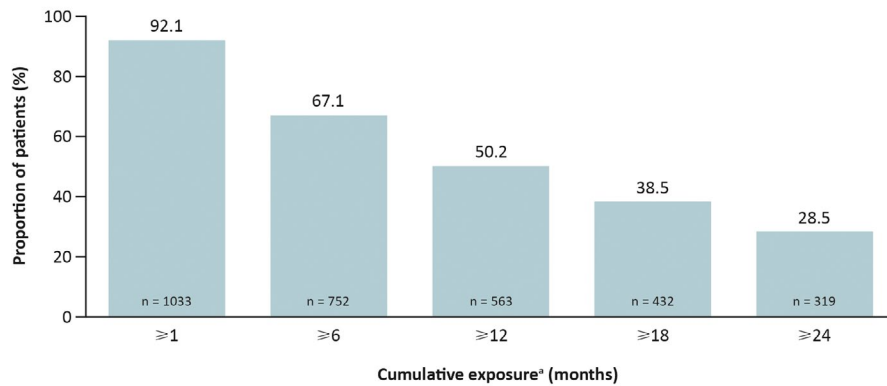
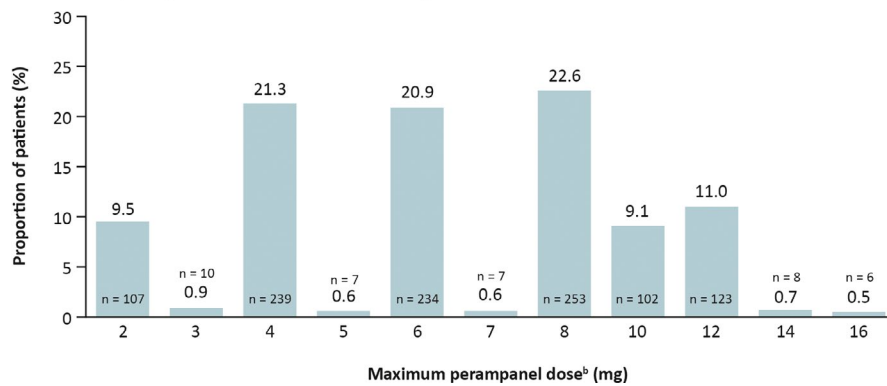
A Cumulative duration of exposure to perampanel**B** Maximum perampanel dose achieved in ≥0.5% of patients

FIGURE 2 (A) Cumulative duration of exposure to perampanel and (B) maximum perampanel dose achieved in ≥0.5% of patients (Safety Analysis Set [N = 1121]). ^aPatients were counted in each applicable exposure category. ^bMaximum perampanel doses achieved in <0.5% of patients were as follows: 1 mg (n = 4 [0.4%]); 2.5 mg (n = 3 [0.3%]); 1.5 mg and 20 mg (both n = 2 [0.2%]); and 0.05 mg, 0.25 mg, 3.5 mg, 6.5 mg, 7.5 mg, 9 mg, 18 mg, and 22 mg (each n = 1 [0.1%]).

Based on overall investigator impression of seizure effect as assessed at the end of treatment, of the 979 patients for whom seizure-effect data had been recorded, an improvement of seizures was reported in 54.3%, no change/stable in 33.7%, and a worsening of seizures in 12.0% (Figure S1). Investigator impression of seizure effect by syndrome is shown in Table S5.

3.4 | Safety

Overall, TEAEs were reported in 500 (44.6%) patients (Table 2), the most common of which were dizziness (n = 103 [9.2%]), aggression (n = 61 [5.4%]), and irritability (n = 50 [4.5%]). Serious TEAEs were experienced by 32 (2.9%) patients and included 10 deaths; causes of death were unknown (n = 5), cardiac arrest/respiratory failure (n = 1), craniocerebral injury (n = 1), drowning (n = 1), respiratory failure (n = 1), and seizure (n = 1). TEAEs related to hostility and/or aggression were reported in 186 (16.6%) patients, and the most frequent were aggression (n = 61 [5.4%]), irritability (n = 50 [4.5%]), and anger (n = 29 [2.6%]). Overall, TEAEs leading to discontinuation occurred in 279 (24.9%) patients; those occurring in >3% of patients were aggression (n = 40 [3.6%]), irritability (n = 38 [3.4%]), and dizziness (n = 36 [3.2%]).

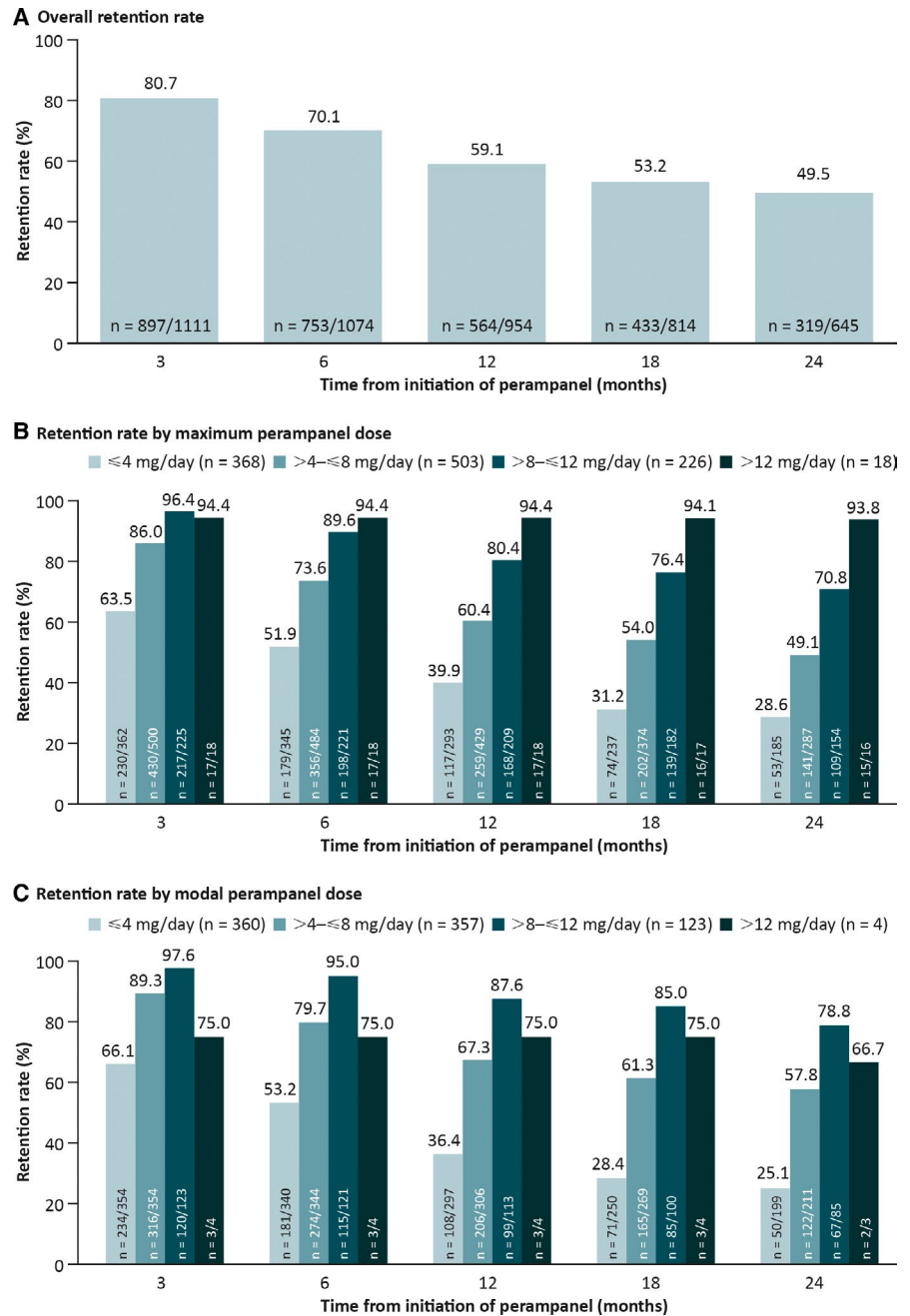
TEAEs were reported in 119 (50.4%), 139 (52.1%), 8 (47.1%), 200 (41.2%), and 34 (29.3%) patients receiving dose titration weekly, every 2 weeks, every 3 weeks, “other”, and “unknown”, respectively. Fewer TEAEs leading to perampanel discontinuation occurred with slower titration: 76 (32.2%), 79 (29.6%), 2 (11.8%), 106 (21.9%), and 16 (13.8%) patients receiving dose titration weekly, every 2 weeks, every 3 weeks, “other,” and “unknown”, respectively.

4 | DISCUSSION

This interim analysis of PROVE demonstrates favorable retention rates (approximately 50%) and sustained efficacy for up to 2 years following initiation of perampanel treatment during routine clinical care in patients with epilepsy. Notably, retention rates have been maintained throughout successive interim analyses of the study, even with the increasing numbers of patient records assessed. These data suggest that daily oral doses of perampanel are generally well tolerated, and the TEAEs reported here are consistent with the known safety profile of perampanel.¹⁻⁷

Titration rates in RCTs are defined by nonclinical factors, such as the need to use a standardized study design and the inherent difficulty of recruiting patients into trials if the potential duration of exposure to placebo is perceived

FIGURE 3 Retention rates (A) for the overall population, (B) by maximum perampanel dose, and (C) by modal perampanel dose, over 24 months following initiation of perampanel treatment^a (Safety Analysis Set [N = 1121]). 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. ^aAs patients initiated treatment on perampanel at different times, changes in the denominator correspond with the decreasing number of patients who could have been on perampanel treatment at each successive timepoint, due to reaching the cutoff date for the analysis



by patients to be too long. Given that steady state for most medications is approximately five half-lives,¹¹ drugs with long half-lives such as perampanel are advantageous as they could provide coverage in the event of a missed dose. Perampanel has a half-life of 105 hours, with steady state occurring 2–3 weeks after administration,^{2,12} and should be uptitrated no faster than weekly in 2-mg increments, as done in the phase III studies and per US prescribing information.¹⁻⁷ In real-world terms, this titration rate may be considered by many clinicians to be too fast for a drug with such a long half-life. Data from the PROVE Study demonstrate that in real-world clinical care of patients with epilepsy, titration of perampanel often occurred more slowly than in the phase III studies, and perampanel doses achieved were generally lower

than the maximum approved dose of 12 mg/day. These strategies may have been used to increase tolerability of perampanel treatment, and therefore, these data could support the contention that slower titration rates may be better tolerated for medications with longer half-lives. Furthermore, in this interim analysis, discontinuation rates due to TEAEs were lower in patients with slower titration (every 2 weeks [29.6%] or 3 weeks [11.8%] versus weekly [32.2%]). A pooled analysis of phase III studies of perampanel in patients with focal seizures demonstrated that the incidence of TEAEs related to hostility and/or aggression increased in a dose-dependent manner.¹³ Given this, and while discontinuations due to such TEAEs were observed in the PROVE Study, it is possible that TEAEs related to hostility and/or aggression may be

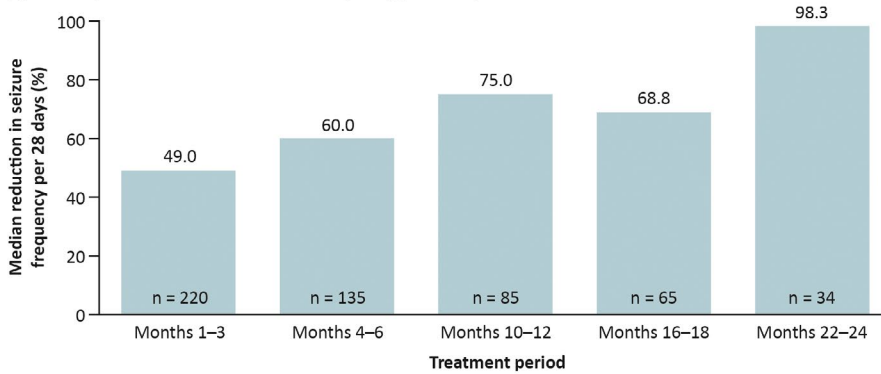
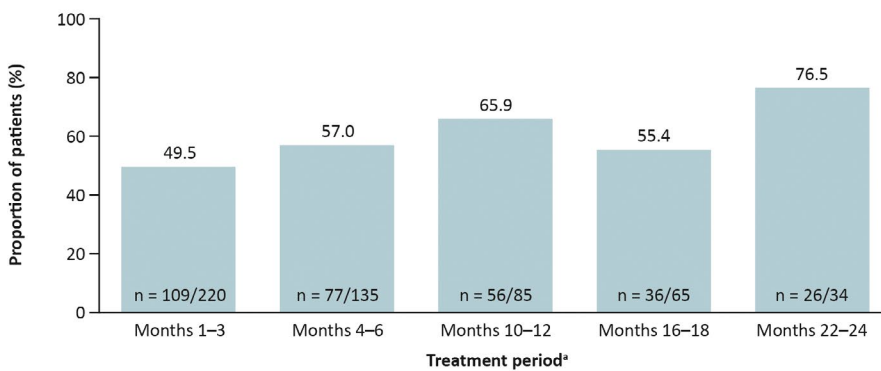
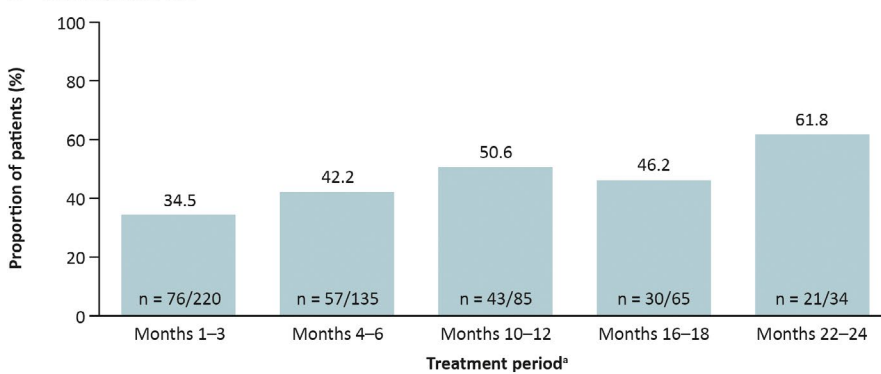
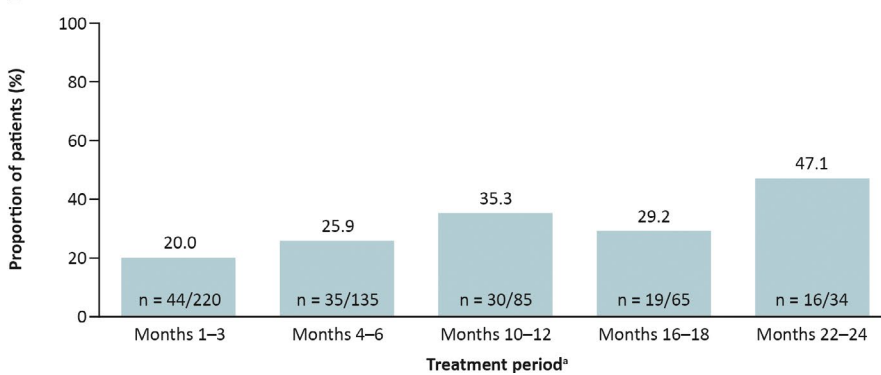
A Median percent reduction in seizure frequency per 28 days**B** $\geq 50\%$ responder rate**C** $\geq 75\%$ responder rate**D** Seizure-freedom rate

FIGURE 4 (A) Seizure-frequency reductions, (B) 50% and (C) 75% responder rates, and (D) seizure-freedom rates (Full Analysis Set [N = 243]). ^aEach treatment period only includes patients who completed that period

managed primarily through different titration strategies (including slower titration) and dose reduction, reducing the likelihood of discontinuation being required.

It should also be noted that 60% of patients were receiving either two or three concomitant ASMs at baseline; therefore,

most patients were receiving peramppanel as their 3rd or 4th ASM. This would indicate that during the time period of this interim analysis, peramppanel was being selected for patients with highly refractory seizures. The robust efficacy observed here is therefore particularly promising considering the

TABLE 2 Summary of TEAEs, most common TEAEs (occurring in $\geq 3\%$ of patients), and most common TEAEs related to hostility and/or aggression (occurring in $\geq 2\%$ of patients; Safety Analysis Set)

	Perampanel (N = 1121)
TEAEs, n (%)	500 (44.6)
Serious TEAEs, n (%)	32 (2.9)
Deaths	10 (0.9)
TEAEs leading to perampanel dose adjustment, n (%)	398 (35.5)
Withdrawal	279 (24.9)
Dose reduction	126 (11.2)
Dose increase	6 (0.5)
Dose interruption	8 (0.7)
Most common ($\geq 3\%$ of patients) TEAEs, ^a n (%)	
Dizziness	103 (9.2)
Aggression	61 (5.4)
Irritability	50 (4.5)
Somnolence	44 (3.9)
Fatigue	43 (3.8)
TEAEs related to hostility and/or aggression, ^a n %	186 (16.6)
Most common ($\geq 2\%$ of patients) TEAEs related to hostility and/or aggression, ^a n (%)	
Aggression	61 (5.4)
Irritability	50 (4.5)
Anger	29 (2.6)
Agitation	25 (2.2)
Abnormal behavior	22 (2.0)

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 perampanel 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: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

^aPreferred term based on MedDRA version 21.1.

patient cohort, together with the lower doses of perampanel selected (generally 8 mg/day or lower), compared with those used in the randomized clinical trials.

Our data complement other real-world studies of perampanel in various patient populations. A study in patients aged ≥ 12 years with idiopathic generalized epilepsy in Spain found an 83.2% retention rate at 1 year and 59.1% of patients were seizure free for at least the previous 6 months compared with a 59.1% retention rate at 1 year and 35.3% of patients seizure free at Months 10–12 in the current analysis.¹⁴ In another study, patients aged ≥ 12 years with focal seizures had a 60.6% retention rate

at 1 year and 7.2% were seizure free.¹⁵ In patients aged ≤ 18 years in Taiwan, 51% retention was observed at 1 year and 26.9% of patients were seizure free for at least the previous 3 months¹⁶; and in patients with refractory epilepsy treated at a single center in Austria, treatment response, defined as status epilepticus cessation or electroencephalography improvement, was observed in 17% of patients.¹⁷ In a post-approval study of perampanel treatment for adults and children with treatment-resistant epilepsy, the mean duration of treatment was 8.2 ± 6.2 months; 51% achieved a 50% response rate¹⁸, which was similar to the findings in our study in which 57% of patients achieved a 50% response rate at Months 4–6 and 65.9% of patients achieved a 50% response rate at Months 10–12. In addition, perampanel monotherapy was assessed in the real-world Study 504, which reported a retention rate of 74% at 6 months, with 45% of patients seizure free for the first 3 months of perampanel monotherapy.¹⁹

Limitations of PROVE include those commonly associated with real-world, retrospective, observational studies, including the absence of a placebo arm and the lack of blinding. Specific challenges are associated with reliably capturing all relevant information as part of patient medical records across all study sites. As a retrospective study, these data were collected prior to the conception and initiation of the study, and therefore, variable approaches toward record-keeping between different study sites would be expected. For example, while some sites maintained detailed seizure diaries, others may have only recorded improvements or worsening of seizures without systematically documenting seizure counts. In addition, TEAEs may not have been recorded consistently between sites, and not all baseline concomitant ASM treatments were captured. Due to incomplete information, the number of patients with efficacy outcomes at the later timepoints was low, particularly during Months 22–24 (n = 34).

However, real-world, retrospective studies such as PROVE offer key advantages over prospective RCTs. Less restrictive inclusion and exclusion criteria result in more heterogeneous patient populations being included, therefore making outcomes more relevant to the population at large.^{10,20} Titration and dosing are also predefined aspects of RCTs, whereas retrospective studies reflect titration schedules adjusted as the clinician determines to be appropriate for each individual patient.¹⁰ Longer drug exposures can also be achieved, allowing patients to stay on treatment beyond the standard timeframes of the double-blind period of a RCT, enabling the detection of longer-term safety signals and the assessment of long-term retention on drug treatment.^{10,20} PROVE can be considered truly retrospective because patient recruitment only occurred after the patients had initiated treatment on perampanel. Thus, participation in the study was not a factor influencing the clinical judgment to start perampanel.

Collectively, these factors contribute to PROVE being more reflective of the real-world clinical care of patients with epilepsy than is achievable in the phase II and III RCTs that occur earlier in the development cycle of an ASM. Under such circumstances, retention on therapy with a branded ASM, which is likely to be more expensive than generic options, could be indicative of perceived clinical benefits not captured by standard seizure counts, such as reduced seizure severity or improved daytime tolerability with once-daily dosing at night.

Overall, these interim data suggest that daily oral doses of perampanel are generally well tolerated, with encouraging retention rates for up to 2 years in patients with epilepsy treated during routine clinical care. A subgroup analyses of this dataset, based on the pediatric (aged <12 years) and adolescent (aged 12 to <18 years) populations, is to be reported elsewhere. PROVE completed in March 2019 and assessments based on the final patient cohort (N = 1703), and the pediatric and adolescent subgroups will also be published separately.

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CONFLICT OF INTEREST

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. 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, Engage Pharma, Eisai, Greenwich Biosciences, Lundbeck, Otsuka, SK Life Science, Sunovion, and UCB Pharma; has received speaker bureau honoraria from Aquestive, Eisai, Greenwich Biosciences,

LivaNova, SK Life Science, Sunovion, and UCB Pharma; and is a member of the Epilepsy Study Consortium. Marcelo Lancman has received research grant support from Eisai. 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 Ltd. Manoj Malhotra is an employee of Eisai Inc.

AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of the data and reviewed each draft of the manuscript; Robert T. Wechsler, Anna Patten, and Manoj Malhotra contributed to the conception and design of the study; James Wheless, Robert T. Wechsler, Marcelo Lancman, and Sami Aboumatar contributed to the acquisition of the data; Anna Patten conducted the analysis of the data.

ETHICAL PUBLICATION STATEMENT

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.

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SUPPORTING INFORMATION

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

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