RESEARCH ARTICLE

Epilepsia™

Perampanel for the treatment of people with idiopathic generalized epilepsy in clinical practice

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Abstract

Objective: This study was undertaken to evaluate perampanel (PER) when used under real-world conditions to treat people with idiopathic generalized epilepsy (IGE) included in the PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study.

Methods: The multinational, retrospective, pooled analysis PERMIT explored the use of PER in people with focal and generalized epilepsy treated in clinical practice across 17 countries. This subgroup analysis included PERMIT participants with IGE. Time points for retention and effectiveness measurements were 3, 6, and 12 months (last observation carried forward, defined as "last visit," was also applied to effectiveness). Effectiveness was evaluated by seizure type (total seizures, generalized tonic–clonic seizures [GTCS], myoclonic seizures, absence seizures) and included ≥50% responder rate and seizure freedom rate (defined as no seizures since at least the previous visit). Safety/tolerability was monitored throughout PER treatment and evaluated by documenting the incidence of adverse events (AEs), including psychiatric AEs and those leading to treatment discontinuation.

Results: The Full Analysis Set included 544 people with IGE (51.9% women, mean age = 33.3 years, mean epilepsy duration = 18.1 years). At 3, 6, and 12 months, 92.4%, 85.5%, and 77.3% of participants were retained on PER treatment, respectively (Retention Population, $n = 497$). At the last visit, responder and seizure freedom rates were, respectively, 74.2% and 54.6% (total seizures), 81.2% and 61.5% (GTCS), 85.7% and 66.0% (myoclonic seizures), and 90.5% and 81.0% (absence seizures) (Effectiveness Population, $n = 467$). AEs occurred in 42.9% of patients and included irritability (9.6%), dizziness/vertigo (9.2%), and somnolence (6.3%) (Tolerability Population, $n = 520$). Treatment discontinuation due to AEs was 12.4% over 12 months.

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Significance: This subgroup analysis of the PERMIT study demonstrated the effectiveness and good tolerability of PER in people with IGE when administered under everyday clinical practice conditions. These findings are in line with clinical trial evidence, supporting PER's use as broad-spectrum antiseizure medication for the treatment of IGE.

KEYWORDS

absence seizures, antiseizure medication, epilepsy, generalized tonic–clonic seizures, myoclonic seizures, real world

1 | INTRODUCTION

Idiopathic generalized epilepsies (IGEs) comprise four age-related syndromes—childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCS only)—which may show some degree of overlap.[1] IGEs are presumed to have a polygenetic etiology and account for 20%–25% of all epilepsies.[1–3] Age at onset is typically 3–25 years, depending on the syndrome.[1,4] IGEs are characterized by four generalized seizure types, which can manifest alone or in combination: GTCS, myoclonic seizures, absence seizures, and myoclonic–tonic–clonic seizures.[1] IGEs are also characterized by an electroencephalogram profile that includes normal background activity with generalized spike–wave and/or polyspike–wave discharges, which may be activated by hyperventilation and photic stimulation.[1,5] Treatment of IGE relies on using broad-spectrum antiseizure medications (ASMs), and valproate (VPA) has long been considered the first-choice treatment in this setting, because of its yet unsurpassed efficacy.[6,7] However, the use of VPA in women of childbearing age is limited due to its teratogenic effects, and its negative neurodevelopmental effects on in utero exposed children.[6–8] Moreover, in men, VPA can have detrimental effects on sperm quality and testicular function/volume and may cause infertility.[9,10] Although the prognosis for IGE is more favorable than for some other epilepsies, up to 15% of individuals with IGE remain refractory to treatment.[5,11]

The ASM perampanel (PER) acts as a noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor,[12,13] and it is widely approved for the treatment of focal onset seizures and the treatment of GTCS in people with IGE.[14–16] Approval of PER for the treatment of GTCS in IGE was based on the results of one phase 3, randomized, double-blind, placebo-controlled trial.[17,18] Clinical practice studies provide evidence on how a drug performs when used outside the relative restrictions of clinical trials,[19–21] but real-world evidence on the use of PER to specifically treat IGE is currently limited.[22–27]

The PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study included approximately 5200 people with focal and generalized epilepsy who were treated with PER in clinical practice.[28] The purpose of this study was to assess the real-world effectiveness and safety/tolerability of PER when used to treat people with IGE included in PERMIT.

2 | MATERIALS AND METHODS

2.1 | Study design

The PERMIT study was a multinational, retrospective, pooled analysis of PER clinical practice data from 44

Key points

- PERMIT is the largest pooled analysis of perampanel clinical practice data conducted to date
- A subgroup analysis was conducted of 544 participants from PERMIT with IGE
- At the last visit, seizure freedom rates were 54.6% (total seizures), 61.5% (generalized tonic–clonic), 66.0% (myoclonic), and 81.0% (absence)
- Adverse events occurred in 42.9% of subjects (irritability, 9.6%; dizziness/vertigo, 9.2%; somnolence, 6.3%) and led to discontinuation in 12.4%
- Perampanel was effective and generally well tolerated when used to treat people with IGE in everyday clinical practice

prospective, retrospective, and cross-sectional studies and work groups, full details of which have been published previously[28] (see Supplementary Materials and Methods for further details). Deidentified individual participant data were pooled together and assessed for a range of parameters, including demographic and baseline characteristics, PER dosing, effectiveness outcomes, and adverse events (AEs).[28]

As previously described, retention on PER treatment and its effectiveness were assessed after 3, 6, and 12 months, and effectiveness was additionally assessed as the last observation carried forward, independent of when it occurred (defined as the "last visit").[28] Safety/tolerability was assessed for the duration of PER treatment.[28] All studies included in PERMIT were approved by independent ethics committees, which were subsequently informed by letter about the PERMIT study, if required by local legislation.[28] All participants gave their informed consent prior to inclusion in the studies, according to the protocol. A post hoc analysis was conducted to evaluate the effectiveness and safety/tolerability of PER in the subgroup of people with IGE who were included in PERMIT.

2.2 | Study population

As previously reported, the studies included in PERMIT employed broad inclusion/exclusion criteria, to represent the wide variety of people with epilepsy (PWE) encountered in clinical practice.[28] The current study included all PWE from PERMIT who had IGE.

2.3 | Study assessments

Retention on PER treatment was assessed over 12 months. Effectiveness assessments were the percentage reduction from baseline in seizure frequency, responder rate, seizure freedom rate, and the proportions of PWE with unchanged or worsening seizure frequency. Response was defined as ≥50% seizure frequency reduction from baseline (i.e., prior to starting PER), and responder rate was calculated by comparing seizure frequency since the previous visit with seizure frequency at baseline. Seizure freedom was defined as no seizures since at least the prior visit (either 3 or 6 months, depending on time point).[28] Because the definition of "baseline" differed between studies included in PERMIT, baseline seizure frequency was standardized as number of seizures per month.

Effectiveness was assessed according to seizure type (all seizure types [including GTCS, myoclonic and absence seizures, defined as "total seizures"], GTCS, myoclonic seizures, absence seizures). Myoclonic–tonic–clonic seizures were included as GTCS. The percentage reduction from

baseline in the number of days per month with myoclonic seizures was included as an additional effectiveness assessment. Safety/tolerability was assessed by evaluating AEs, AEs leading to discontinuation over 12 months, psychiatric AEs, and the incidence of psychiatric AEs in participants who discontinued. Treatment information was also collected.

2.4 | Subgroup analyses

Retention, effectiveness, and safety/tolerability were assessed in two subanalyses. The first subanalysis was a comparison of the subgroups of PWE who had not previously been treated with VPA ("no previous VPA" subgroup) versus those who had previously been treated with VPA ("previous VPA" subgroup), for those PWE for whom previous ASMs were known. The rationale for this subanalysis was to assess the effectiveness and tolerability of PER in people who are resistant to VPA or for whom VPA has been previously tapered off due to AEs or fear of AEs (e.g., in women of childbearing age), and to determine whether the effectiveness and tolerability of PER in such individuals differs from its effectiveness and tolerability in those who are naïve to VPA treatment. The second subanalysis was a comparison of the subgroups of PWE with the following epileptic syndromes (as identified by each study): those with generalized epilepsy with GTCS only ("GE with GTCS only" subgroup), those with JME ("JME" subgroup), and those with syndromes with absence seizures (including CAE, JAE, and phantom absences of adulthood; "absence epilepsy" subgroup). Because the GE with GTCS only subgroup excluded PWE with myoclonic and absence seizures, effectiveness assessments for myoclonic and absence seizure frequency were only compared for the JME and absence epilepsy subgroups.

2.5 | Statistical analysis

Definitions of the analysis populations and details of the statistical methodology employed in PERMIT have been reported previously.[28] In brief, descriptive statistics were used for quantitative and qualitative variables, Kaplan–Meier methodology was used to assess retention over the first 12 months of PER treatment, and changes from baseline to the last visit in seizure frequency and the frequency of days with myoclonic seizures were assessed using the Wilcoxon test. For subgroup analyses, between-group differences in retention, effectiveness, and tolerability outcomes were assessed using the chi-squared test or Fischer exact test, as appropriate. For quantitative variables, the

Student *t*-test (Mann–Whitney test) or analysis of variance (Kruskal–Wallis test) was used. The significance level was set at 5% and the statistical package SPSS 28.0 was used for all analyses. As reported for the original PERMIT study, because complete information was not available for all PWE at every time point, the total number of PWE for whom data were available is given for each variable, and this was used as the denominator for frequency analyses.[28]

3 | RESULTS

3.1 | Study population

Of the 5193 PWE included in the final Full Analysis Set (FAS) of PERMIT,[28] 544 had IGE, representing the FAS for the current study population. Of these 544 PWE, 460 were from retrospective studies and 84 were from prospective studies. The Retention Population included 497 PWE, the Effectiveness Population included 467 PWE, and the Tolerability Population included 520 PWE. Demographic and baseline characteristics of the FAS are shown in Table 1. The most common seizure types at baseline (≥10% of PWE) were GTCS only (36.4%) and independent GTCS and myoclonic seizures (10.3%).

3.2 | PER treatment

Mean (SD) PER dose was 2.5 (1.2) mg/day at its initiation (median = 2.0, range = 2.0–8.0, *n* = 184) and 5.6 (2.4) mg/day at the last visit (median = 6.0, range = 1.0–16.0, *n* = 467). PER was initiated using a slow titration (<2 mg/week) in 56.3% (85/151) of PWE and a fast titration (2 mg/week) in 43.7% (66/151) of PWE. Median number of concomitant ASMs was 2.0 (range = 0–6.0, *n* = 487) at initiation of PER treatment and 1.0 (range = 0–4.0, *n* = 244) at the last visit. PER was initiated as monotherapy in 11.1% (54/487) of PWE, and at the last visit, 9.4% (23/244) of PWE were being treated with PER as monotherapy.

3.3 | Retention

The rates of retention on PER at 3, 6, and 12 months were 92.4% (459/497), 85.5% (376/440), and 77.3% (324/419), respectively (Figure 1). At 12 months, the retention rate was significantly higher in PWE for whom PER was initiated using a slow versus fast titration (86.2% [56/65] vs. 69.5% [41/59], *p* = .025). Overall, 22.7% (95/419) of PWE discontinued PER over 12 months: 11.5% (*n* = 48) due to AEs, 6.0% (*n* = 25) due to lack of efficacy, 1.0% (*n* = 4) due to both AEs

TABLE 1 Demographic and baseline characteristics (Full Analysis Set).

Total PWE, *N*	544
Sex	
n[a]	543
Female, *n* (%)	282 (51.9)
Male, *n* (%)	261 (48.1)
Age, years	
n[a]	535
Mean (SD)	33.3 (14.8)
Median (range)	30.0 (3.0–83.0)
Age category	
n[a]	541
<12 years, *n* (%)	10 (1.8)
≥12 and <18 years, *n* (%)	52 (9.6)
≥18 and <65 years, *n* (%)	461 (85.2)
≥65 years, *n* (%)	18 (3.3)
Age at epilepsy onset, years	
n[a]	508
Mean (SD)	15.3 (11.7)
Median (range)	14.0 (0–68.0)
Duration of epilepsy, years	
n[a]	508
Mean (SD)	18.1 (14.8)
Median (range)	14.0 (0–77.0)
Epileptic syndrome	
n[a]	412
No, *n* (%)	139 (33.7)
Yes, *n* (%)	273 (66.3)
Juvenile myoclonic epilepsy, *n* (%)	96 (23.3)
Generalized epilepsy with GTCS only, *n* (%)	77 (18.7)
Juvenile absence epilepsy, *n* (%)	33 (8.0)
Phantom absences of adulthood, *n* (%)	6 (1.5)
Jeavons syndrome, *n* (%)	2 (.5)
Childhood absence epilepsy, *n* (%)	1 (.2)
Epileptic syndrome unknown, *n* (%)	58 (14.1)
Presence of psychiatric comorbidity	
n[a]	432
No, *n* (%)	343 (79.4)
Yes, *n* (%)	89 (20.6)
Anxiety, *n* (%)	23 (5.3)
Depression, *n* (%)	23 (5.3)
Psychosis, *n* (%)	12 (2.8)
Hyperactivity, *n* (%)	11 (2.5)
Autism, *n* (%)	8 (1.9)
Behavioral disorder, *n* (%)	4 (.9)

(Continues)

TABLE 1 (Continued)

Total PWE, N	544
Personality disorder, n (%)	4 (.9)
Mood disorder, n (%)	3 (.7)
Anorexia, n (%)	2 (.5)
Irritability, n (%)	2 (.5)
Affective disorder, n (%)	1 (.2)
Psychogenic seizures, n (%)	1 (.2)
Substance abuse, n (%)	1 (.2)
Seizure type	
n[a]	544
Generalized tonic–clonic only, n (%)	198 (36.4)
Generalized tonic–clonic + myoclonic, n (%)	56 (10.3)
Generalized tonic–clonic + absence, n (%)	34 (6.3)
Myoclonic only, n (%)	33 (6.1)
Absence only, n (%)	17 (3.1)
Generalized tonic–clonic + myoclonic + absence, n (%)	16 (2.9)
Myoclonic + absence, n (%)	6 (1.1)
No seizures, n (%)	35 (6.4)
Type of seizure(s) unknown, n (%)	149 (27.4)
Number of previous ASMs[b]	
n[a]	386
Mean (SD)	3.7 (2.6)
Median (range)	3.0 (0–14.0)
0, n (%)	10 (2.6)
1, n (%)	77 (19.9)
2, n (%)	66 (17.1)
3, n (%)	53 (13.7)
4, n (%)	52 (13.5)
5, n (%)	43 (11.1)
6, n (%)	32 (8.3)
7, n (%)	25 (6.5)
≥8, n (%)	28 (7.3)
Most frequently used[c] previous ASMs[b]	
n[a]	288
Levetiracetam, n (%)	199 (69.1)
Valproate, n (%)	172 (59.7)
Lamotrigine, n (%)	111 (38.5)
Zonisamide, n (%)	78 (27.1)
Number of concomitant ASMs[d]	
n[a]	487
Mean (SD)	1.8 (1.1)
Median (range)	2.0 (0–6.0)
0, n (%)	54 (11.1)
1, n (%)	180 (37.0)

TABLE 1 (Continued)

Total PWE, N	544
2, n (%)	130 (26.7)
3, n (%)	85 (17.5)
≥4, n (%)	38 (7.8)
Most frequently used[c] concomitant ASMs[d]	
n[a]	471
Levetiracetam, n (%)	223 (47.3)
Valproate, n (%)	163 (34.6)

Abbreviations: ASM, antiseizure medication; GTCS, generalized tonic–clonic seizures; PER, perampanel; PWE, people with epilepsy.

[a]Number of PWE for whom data in question were available.

[b]≥20% of PWE.

[c]ASMs used prior to initiation of PER, including those used concomitantly when PER was initiated.

[d]ASMs used when PER was initiated.

and lack of efficacy, .7% ($n = 3$) due to seizure worsening, and 1.7% ($n = 7$) due to other reasons (financial problems, $n = 3$; pregnancy, $n = 2$; patient decision–not otherwise specified, $n = 1$; transferred to another hospital, $n = 1$). Reasons for discontinuation were unknown in 1.9% ($n = 8$) of PWE. Mean (95% confidence interval) time under PER treatment was 11.9 (11.5–12.3) months (Figure S1).

3.4 | Effectiveness

At baseline, 91.4% (342/374) of PWE had experienced at least one seizure in the past 3 months prior to treatment initiation; 77.1% (283/367) had GTCS, 28.9% (106/367) had myoclonic seizures, and 18.0% (66/367) had absence seizures. There were statistically significant reductions from baseline to the last visit in the frequencies of total seizures ($p < .001$), GTCS ($p < .001$), myoclonic seizures ($p = .002$), days with myoclonic seizures ($p < .001$), and absence seizures ($p = .003$; Figure 2). At the last visit, responder and seizure freedom rates for total seizures were 74.2% (331/446) and 54.6% (255/467), respectively, and the proportions of PWE with unchanged and worsening seizure frequency were 11.2% (50/445) and 5.8% (26/445), respectively (Figure 3A). Corresponding data for GTCS, myoclonic seizures, and absence seizures are presented in Figure 3B, C, and D, respectively.

3.5 | Safety and tolerability

The overall incidence of AEs was 42.9% (223/520 PWE; Table 2). Among these AEs, the most common (≥5% of PWE) were irritability (9.6%), dizziness/vertigo (9.2%), and somnolence (6.3%). In the subgroup of PWE for
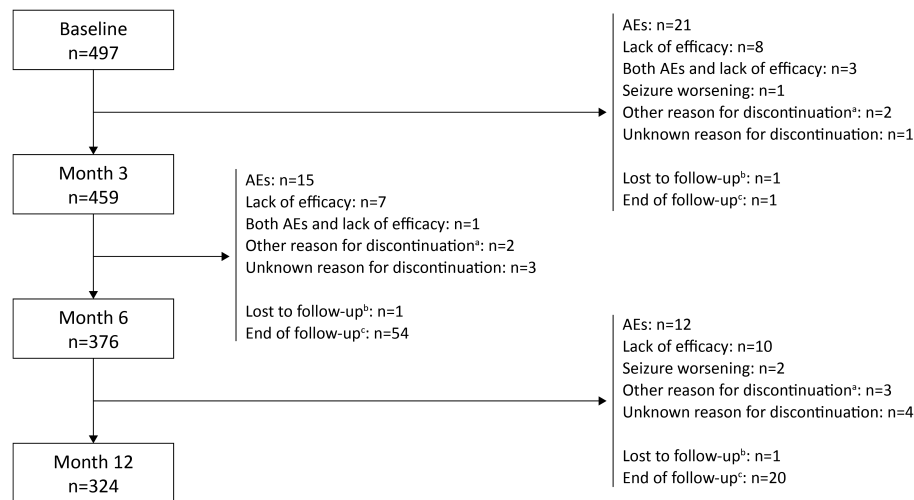
FIGURE 1 Disposition of people with epilepsy (Retention Population). [a]Other reasons for discontinuation were financial problems ($n=3$), pregnancy ($n=2$), patient decision–not otherwise specified ($n=1$), and transferred to another hospital ($n=1$). [b]"Lost to follow-up" refers to participants who started in the study but whose subsequent follow-up status (i.e., still receiving treatment or discontinued treatment) could not be ascertained. [c]"End of follow-up" refers to participants whose study ended before the next assessment time point. AE, adverse event.

whom speed of PER titration was known ($n=151$), the incidence of AEs did not differ significantly when PER was initiated using slow versus fast titration (37.6% [32/85] vs. 33.3% [22/66], $p=.583$). Over 12 months, AEs led to the discontinuation of 12.4% (52/419) of PWE, and the most common AEs in PWE who discontinued (>1% of PWE) were irritability (3.3%) and dizziness/vertigo (2.6%). The incidence of psychiatric AEs was 21.9% (113/517) of PWE, and 7.7% (37/478) of PWE with psychiatric AEs discontinued. The only psychiatric AE that was reported in >1% of PWE who discontinued was irritability (2.9%).

3.6 | Subgroup analyses

3.6.1 | Previous use of VPA

Of the 544 PWE with IGE in the FAS, the type of ASMs previously used was known for 288, of whom 116 (40.3%) PWE had not previously been treated with VPA ("no previous VPA" subgroup) and 172 (59.7%) had previously been treated with VPA ("previous VPA" subgroup). The Retention, Effectiveness, and Tolerability Populations contained 265 PWE (no previous VPA, $n=100$; previous VPA, $n=165$), 257 PWE (no previous VPA, $n=104$; previous VPA, $n=153$), and 287 PWE (no previous VPA, $n=115$; previous VPA, $n=172$), respectively.

For the no previous VPA versus previous VPA subgroups, there were no significant differences in retention rate at Month 3 (97.0% [97/100] vs. 93.3% [154/165]), Month 6 (90.7% [88/97] vs. 87.7% [142/162]), and Month 12 (81.5% [75/92] vs. 80.1% [129/161]). There were no statistically significant differences between subgroups in

responder rate, seizure freedom rate, and the proportions of PWE with unchanged and worsening seizure frequency, for total seizures, GTCS, myoclonic seizures, and absence seizures, at any time point (Table S1). There were also no statistically significant differences between subgroups in safety and tolerability (Table S2A).

3.6.2 | Epilepsy syndromes (GE with GTCS only, JME, absence epilepsy)

Of the 544 PWE with IGE in the FAS, 212 had either GE with GTCS only ($n=77$), JME ($n=96$), or absence epilepsy ($n=40$). The Retention, Effectiveness, and Tolerability Populations contained 206 PWE (GE with GTCS only, $n=73$; JME, $n=93$; absence epilepsy, $n=40$), 206 PWE (GE with GTCS only, $n=77$; JME, $n=91$; absence epilepsy, $n=38$), and 213 PWE (GE with GTCS only, $n=77$; JME, $n=96$; absence epilepsy, $n=40$), respectively. For the GE with GTCS only, JME, and absence epilepsy subgroups, there were no statistically significant differences in retention at Month 3 (97.3% [71/73] vs. 93.5% [87/93] vs. 90.0% [36/40]), Month 6 (86.3% [63/73] vs. 88.6% [78/88] vs. 89.5% [34/38]), and Month 12 (81.4% [57/70] vs. 81.7% [67/82] vs. 81.6% [31/38]).

At the last visit, there were no statistically significant differences between subgroups in responder rate, seizure freedom rate, and the proportions of PWE with unchanged and worsening seizure frequency for total seizures, GTCS, myoclonic seizures, and absence seizures, and there were very few statistically significant differences between subgroups at Month 3, Month 6, and Month 12 (Table 3). There were no statistically significant differences between subgroups in safety and tolerability (Table S2B).
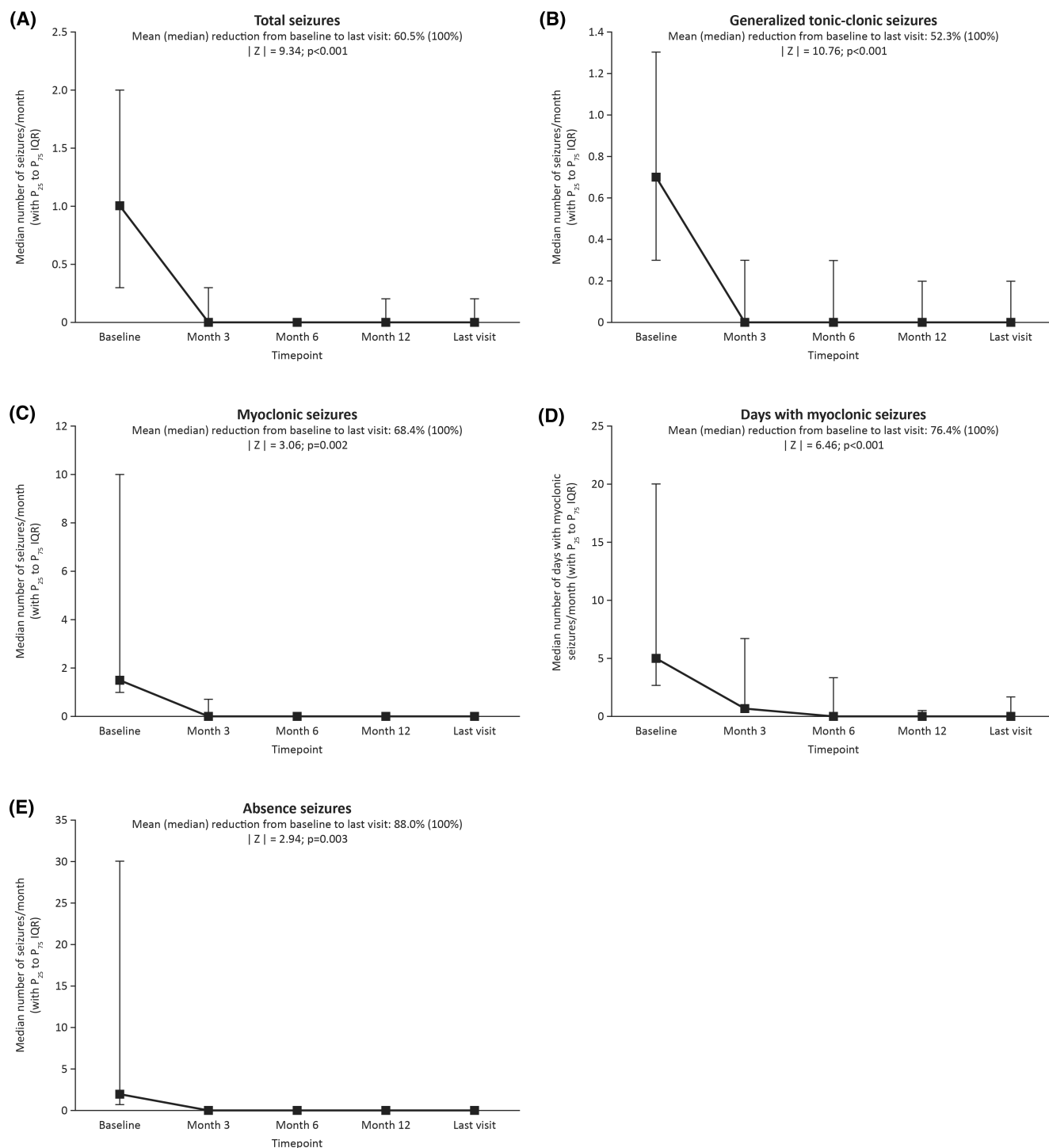
FIGURE 2 Median monthly frequencies (with P_{25} and P_{75} interquartile range [IQR]) at baseline, Month 3, Month 6, Month 12, and the last visit for (A) total seizures, (B) generalized tonic–clonic seizures, (C) myoclonic seizures, (D) days with myoclonic seizures, and (E) absence seizures (Effectiveness Population). P, percentile.

4 | DISCUSSION

This subgroup analysis of the PERMIT study demonstrated that PER was effective and generally well tolerated when used to treat >500 people with IGEs under real-world clinical practice conditions. Treatment with PER resulted

in statistically significant reductions from baseline in the monthly frequencies of total seizures, GTCS, myoclonic seizures, days with myoclonic seizures, and absence seizures. At the last visit, rates of seizure freedom ranged from 54.6% for total seizures to 81.0% for absence seizures, and responder rates ranged from 74.2% for total seizures to
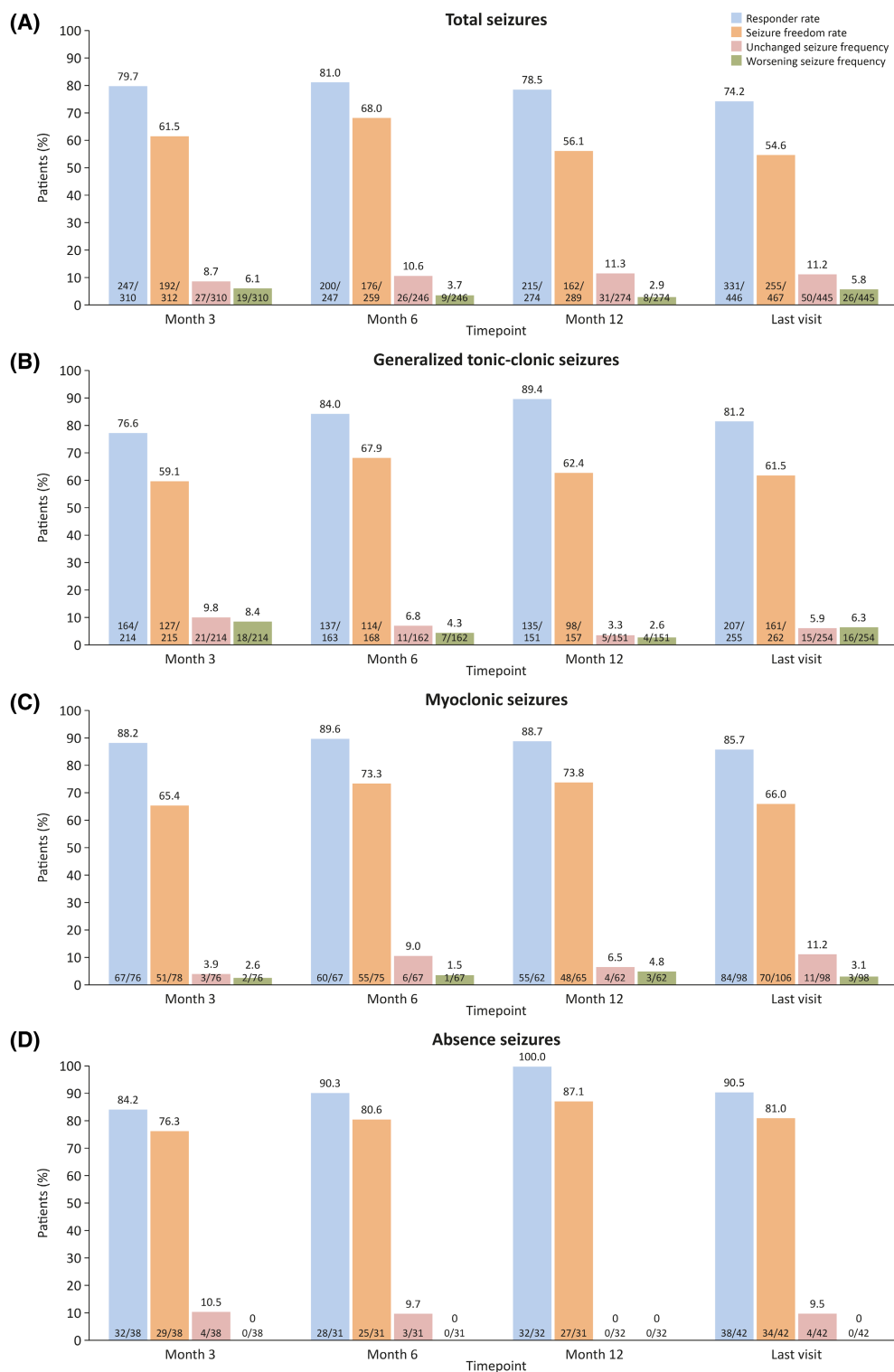
FIGURE 3 Responder rate, seizure freedom rate, and the percentages of people with epilepsy (PWE) with unchanged and worsening seizure frequency (relative to baseline) at Month 3, Month 6, Month 12, and the last visit for (A) total seizures, (B) generalized tonic–clonic seizures, (C) myoclonic seizures, and (D) absence seizures (Effectiveness Population). Response was defined as ≥50% reduction in seizure frequency from baseline, and responder rate was calculated by comparing seizure frequency since the previous visit with seizure frequency at baseline. Seizure freedom was defined as no seizures since at least the prior visit; therefore, seizure freedom rates at Month 3, Month 6, and the last visit represent the percentages of PWE who had no seizures for ≥3 months, and the seizure freedom rate at Month 12 represents the percentage of PWE who had no seizures for ≥6 months.

90.5% for absence seizures. The proportion of PWE who experienced worsening seizure frequency was low across all seizure types, ranging from 0% for absence seizures to 6.3% for GTCS. Subgroup analysis demonstrated that PER was equally effective, in terms of seizure freedom and responder rates, in PWE who had and had not previously been treated with VPA across all time points. The effectiveness of PER was also similar in the subgroups of PWE with GE with GTCS only, JME, and absence epilepsy, with no significant between-group differences at the last visit and only isolated between-group differences at earlier time points.

The most frequent AEs (irritability, dizziness/vertigo, and somnolence) and AEs leading to discontinuation (irritability, dizziness/vertigo, nausea/vomiting, and somnolence) were consistent with PER's known safety profile,[14] with no new or unexpected safety signals observed. Psychiatric AEs are commonly associated with PER treatment, occurring in ≥1/100 to <1/10 of PWE in clinical trials.[14] In the current study, psychiatric AEs were reported for 21.9% of PWE. The higher rate of psychiatric AEs observed in the current study in comparison with clinical trials is likely to reflect that >20% of PWE had psychiatric

TABLE 2 Summary of AEs (Tolerability Population).

Total PWE, N	N = 520
PWE with any AE, n (%)	223 (42.9)
Most frequently reported AEs, n (%)[a]	
Irritability	50 (9.6)
Dizziness/vertigo	48 (9.2)
Somnolence	33 (6.3)
PWE with AEs leading to discontinuation, n (%)	52 (12.4)[b]
Most frequently reported AEs[c] in PWE who discontinued, n (%)	
Irritability	14 (3.3)[b]
Dizziness/vertigo	11 (2.6)[b]
Nausea/vomiting	4 (1.0)[b]
Somnolence	4 (1.0)[b]
PWE with any psychiatric AE, n (%)	113 (21.9)[d]
PWE with psychiatric AE who discontinued, n (%)[e]	37 (7.7)[f]
Most frequently reported psychiatric AEs[g] in PWE who discontinued, n (%)[d]	
Irritability	14 (2.9)[f]
Anxiety	3 (.6)[f]

Abbreviations: AE, adverse event; PWE, people with epilepsy.

[a]≥5% of PWE.

[b]n = 419.

[c]≥1% of PWE.

[d]n = 517.

[e]These PWE had psychiatric AEs, but it was not possible to determine whether it was these AEs that led to discontinuation.

[f]n = 478.

[g]≥.5% of PWE.

comorbidities at baseline (Table 1), whereas PWE with psychiatric comorbidities are usually excluded from participating in clinical trials.[19,21] The only psychiatric AE that occurred in >1% of PWE who discontinued was irritability (2.9%). There were no statistically significant differences in safety and tolerability outcomes in either the subgroups of PWE who had and had not previously been treated with VPA, or the subgroups diagnosed with GE with GTCS only, JME, and absence epilepsy.

Treatment retention is recognized as a useful means of assessing the overall effectiveness and tolerability of ASMs in the real-world setting.[29] In the current study, retention rates were high, with more than three quarters of PWE retained on PER treatment after 12 months. Moreover, retention rates did not differ significantly between the subgroups of PWE analyzed. Taken together, the findings of the current study therefore support the view that PER is a broad-spectrum ASM suitable for the treatment of people with IGE, regardless of seizure type, epileptic syndrome, or prior treatment with VPA.[30,31]

The effectiveness of PER in the current study was greater than that observed in the phase 3 trial of adjunctive PER in PWE with drug-resistant GTCS in IGE and the subsequent open-label extension study.[17,18,32] This is likely to reflect that, in clinical practice, treatment is adjusted for each person to optimize effectiveness and tolerability, rather than according to a clinical trial protocol. Also, whereas PWE in the clinical trial were required to have drug-resistant epilepsy and be taking stable doses of 1–3 concomitant ASMs, 11.1% of PWE in the current study received PER as monotherapy at treatment initiation and 9.4% were being treated with PER as monotherapy at the last visit, indicating that a sizeable proportion of PWE in the current study were less refractory to treatment than those recruited for the clinical trial.

To our knowledge, only six studies have previously investigated the use of PER specifically in PWE with IGE in clinical practice,[22–25] three of which were included in PERMIT.[22–24] The fourth was an Australian multicenter, retrospective cohort study, which demonstrated that PER was effective and well tolerated as a late adjunctive therapy in 387 PWE with drug-resistant IGE, focal epilepsy, or developmental epileptic encephalopathy treated for a median of 12 months.[25] In the IGE group, the responder and seizure freedom rates were substantially lower than those observed in the current study; however, this is likely to reflect that PWE in the study were more refractory to treatment than those included in PERMIT, because 56.7% were being treated with ≥3 concomitant ASMs at baseline[25] (compared with 25.3% in the current study). The fifth study was an Italian, single-center, retrospective, observational study, which demonstrated that PER was effective and well

TABLE 3 Responder rate, seizure freedom rate, and the percentages of PWE with unchanged and worsening seizure frequency (relative to baseline) at Month 3, Month 6, Month 12, and the last visit for total seizures, GTCS, myoclonic seizures, and absence seizures in PWE in the GE with GTCS only, JME, and absence epilepsy subgroups (Effectiveness Population).

	GE with GTCS, $n=77$	JME, $n=96$	Absence epilepsy, $n=40$	p
Total seizures, % (n/N)				
Responder rate				
Month 3	81.4 (57/70)	89.9 (71/79)	85.3 (29/34)	NS
Month 6	87.5 (56/64)	91.3 (63/69)	84.4 (27/32)	NS
Month 12	93.1 (54/58)	86.8 (59/68)	93.8 (30/32)	NS
Last visit	90.9 (70/77)	84.3 (75/89)	89.5 (34/38)	NS
Seizure freedom rate				
Month 3	58.6 (41/70)	74.7 (59/79)	64.7 (22/34)	NS
Month 6	73.4 (47/64)	83.3 (60/72)	65.6 (21/32)	NS
Month 12	67.2 (39/58)	77.9 (53/68)	78.1 (25/32)	NS
Last visit	62.3 (48/77)	74.7 (68/91)	76.3 (29/38)	NS
Unchanged seizure frequency				
Month 3	10.0 (7/70)	3.8 (3/79)	5.9 (2/34)	NS
Month 6	9.4 (6/64)	7.2 (5/69)	6.3 (2/32)	NS
Month 12	1.7 (1/58)	7.4 (5/68)	0 (0/32)	NS
Last visit	2.6 (2/77)	10.1 (9/89)	2.6 (1/38)	NS
Worsening seizure frequency				
Month 3	5.7 (4/70)	2.5 (2/79)	5.9 (2/34)	NS
Month 6	3.1 (2/64)	1.4 (1/69)	9.4 (3/32)	NS
Month 12	0 (0/58)	4.4 (3/68)	3.1 (1/32)	NS
Last visit	2.6 (2/77)	4.5 (4/89)	5.3 (2/38)	NS
Generalized tonic–clonic seizures, % (n/N)				
Responder rate				
Month 3	81.3 (52/64)	81.1 (43/53)	73.1 (19/26)	NS
Month 6	87.9 (51/58)	89.6 (43/48)	76.0 (19/25)	NS
Month 12	92.3 (48/52)	93.5 (43/46)	96.0 (24/25)	NS
Last visit	91.5 (65/71)	83.6 (46/55)	89.3 (25/28)	NS
Seizure freedom rate				
Month 3	54.7 (35/64)	66.0 (35/53)	50.0 (13/26)	NS
Month 6	70.7 (41/58)	79.2 (38/48)	56.0 (14/25)	NS
Month 12	63.5 (33/52)	69.6 (32/46)	72.0 (18/25)	NS
Last visit	59.2 (42/71)	65.5 (36/55)	67.9 (19/28)	NS
Unchanged seizure frequency				
Month 3	9.4 (6/64)	11.3 (6/53)	3.8 (1/26)	NS
Month 6	6.9 (4/58)	6.3 (3/48)	16.0 (4/25)	NS
Month 12	1.9 (1/52)	2.2 (1/46)	0 (0/25)	NS
Last visit	2.8 (2/71)	9.1 (5/55)	0 (0/28)	NS
Worsening seizure frequency				
Month 3	6.3 (4/64)	3.8 (2/53)	19.2 (5/26)	.045
Month 6	3.4 (2/58)	2.1 (1/48)	8.0 (2/25)	NS
Month 12	0 (0/52)	2.2 (1/46)	4.0 (1/25)	NS
Last visit	1.4 (1/71)	3.6 (2/55)	10.7 (3/28)	NS

(Continues)

TABLE 3 (Continued)

	GE with GTCS, $n = 77$	JME, $n = 96$	Absence epilepsy, $n = 40$	p
Myoclonic seizures, % (n/N)				
Responder rate				
Month 3	-	89.3 (50/56)	0 (0/1)	NS
Month 6	-	91.8 (45/49)	100.0 (2/2)	NS
Month 12	-	85.1 (40/47)	100.0 (2/2)	NS
Last visit	-	83.1 (54/65)	66.7 (2/3)	NS
Seizure freedom rate				
Month 3	-	69.6 (39/56)	0 (0/1)	NS
Month 6	-	82.7 (43/52)	0 (0/2)	.038
Month 12	-	80.9 (38/47)	50.0 (1/2)	NS
Last visit	-	76.1 (51/67)	33.3 (1/3)	NS
Unchanged seizure frequency				
Month 3	-	5.4 (3/56)	0 (0/1)	NS
Month 6	-	6.1 (3/49)	0 (0/2)	NS
Month 12	-	8.5 (4/47)	0 (0/2)	NS
Last visit	-	12.3 (8/65)	33.3 (1/3)	NS
Worsening seizure frequency				
Month 3	-	1.8 (1/56)	100.0 (1/1)	.035
Month 6	-	2.0 (1/49)	0 (0/2)	NS
Month 12	-	6.4 (3/47)	0 (0/2)	NS
Last visit	-	4.6 (3/65)	0 (0/3)	NS
Absence seizures, % (n/N)				
Responder rate				
Month 3	-	90.9 (10/11)	100.0 (17/17)	NS
Month 6	-	88.9 (8/9)	100.0 (13/13)	NS
Month 12	-	100.0 (10/10)	100.0 (14/14)	NP
Last visit	-	92.3 (12/13)	100.0 (17/17)	NS
Seizure freedom rate				
Month 3	-	81.8 (9/11)	100.0 (17/17)	NS
Month 6	-	88.9 (8/9)	100.0 (13/13)	NS
Month 12	-	100.0 (9/9)	100.0 (14/14)	NP
Last visit	-	92.3 (12/13)	100.0 (17/17)	NS
Unchanged seizure frequency				
Month 3	-	9.1 (1/11)	0 (0/17)	NS
Month 6	-	11.1 (1/9)	0 (0/13)	NS
Month 12	-	0 (0/10)	0 (0/14)	NP
Last visit	-	7.7 (1/13)	0 (0/17)	NS
Worsening seizure frequency				
Month 3	-	0 (0/11)	0 (0/17)	NP
Month 6	-	0 (0/9)	0 (0/13)	NP
Month 12	-	0 (0/10)	0 (0/14)	NP
Last visit	-	0 (0/13)	0 (0/17)	NP

Note: Response was defined as ≥50% reduction in seizure frequency from baseline, and responder rate was calculated by comparing seizure frequency since the previous visit with seizure frequency at baseline. Seizure freedom was defined as no seizures since at least the prior visit; therefore, seizure freedom rates at Month 3, Month 6, and the last visit represent the percentages of PWE who had no seizures for ≥3 months, and the seizure freedom rate at Month 12 represents the percentage of PWE who had no seizures for ≥6 months.

Abbreviations: GE, generalized epilepsy; GTCS, generalized tonic–clonic seizures; JME, juvenile myoclonic epilepsy; NP, not possible to perform test for statistical significance; NS, not significant; PWE people with epilepsy.

tolerated as first add-on and second-line monotherapy in 20 PWE with childhood absence epilepsy over a mean follow-up duration of 10.2 months.[26] The final study was an Italian, multicenter, observational, retrospective study, in which PER was shown to be effective and well tolerated as only add-on therapy in 503 PWE with focal, generalized, or undetermined epilepsy treated for up to 12 months, although outcomes were not reported separately for PWE with generalized epilepsy.[27]

No ASM has class I or II evidence of efficacy as initial monotherapy in people with IGE,[33] and treatment options are currently limited. Certain ASMs—particularly sodium channel blockers, such as carbamazepine, phenytoin, and in some instances also lamotrigine—can worsen seizure control in IGE and/or precipitate absence or myoclonic status epilepticus.[33–39] In addition, because IGEs are associated with multiple seizure types, PWE with IGE typically require treatment with a broad-spectrum ASM.[33] Studies such as the first SANAD (Standard and New Antiepileptic Drugs) trials and KOMET (Keppra vs Older Monotherapy in Epilepsy Trial) have established that valproate is more effective than lamotrigine, topiramate, and levetiracetam in treating generalized onset seizures.[40–42] Valproate is therefore typically considered the ASM of choice in the treatment of IGE.[33] However, its use is limited in women of childbearing age due to its well-established teratogenic and neurodevelopmental effects.[43,44] Lamotrigine is also commonly used to treat IGE, although it can aggravate myoclonic seizures or myoclonus.[33,45] Other broad-spectrum ASMs used as adjunctive treatment in IGE include zonisamide, clobazam, and phenobarbital.[33] A previous post hoc analysis of PERMIT demonstrated that PER was associated with a reduction in myoclonic seizure frequency.[46] The findings from the current study additionally demonstrate that PER was associated with statistically significant reductions in the frequencies of GTCS and absence seizures. The current study also indicates that PER is effective in PWE previously treated with VPA, but because data on the use of PER during pregnancy are currently limited to small case series,[47,48] further evidence for its use in this setting is required to determine whether it could potentially provide an alternative to VPA for women of childbearing age. Finally, unlike some other broad-spectrum ASMs that are not effective against all IGE syndromes (e.g., ethosuximide[33,49]), PER appears to be an effective treatment option for PWE with GE with GTCS only, JME, and absence epilepsy.

As for the aforementioned myoclonic seizure study,[46] this study is limited in being a post hoc subgroup analysis of PERMIT, which itself has acknowledged methodological limitations, as it was a retrospective pooled analysis of studies that were heterogeneous in terms of their objectives and information reported, and which

therefore did not have complete data available for all PWE at all time points.[28] The subgroup analysis that compared outcomes in PWE previously treated with VPA versus those who were naïve to VPA treatment was limited because it was not possible to determine the reason(s) for PER initiation in PWE who were previously treated with VPA (i.e., lack of effectiveness vs. tolerability concerns with VPA). Because all the studies included in PERMIT were conducted under clinical practice conditions, documentation of AEs is likely to have relied on self-reporting by PWE, which may have resulted in underreporting. In addition, several factors may result in the overestimation of clinical benefit in pooled analyses of real-world studies, including potential selection bias in retrospective analyses, regression to the mean, and the bias caused by early discontinuation of PWE who do not respond to treatment.[28,46]

5 | CONCLUSIONS

In this subanalysis of PERMIT, PER was effective in reducing the frequency of GTCS, myoclonic seizures, and absence seizures when used to treat people with IGE under everyday clinical practice conditions, with high retention, response, and seizure freedom rates over 1 year of treatment. No new or unexpected safety findings were observed. These findings support data from clinical trials, providing further evidence of the potential use of PER as a broad-spectrum ASM for the treatment of IGE.

CONFLICT OF INTEREST STATEMENT
E.T. reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, BIAL-Portela & Ca, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Sanofi, Jazz

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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