Neurol Ther
https://doi.org/10.1007/s40120-024-00618-5

ORIGINAL RESEARCH

Perampanel for Treatment of People with a Range of Epilepsy Aetiologies in Clinical Practice: Evidence from the PERMIT Extension Study

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Received: January 30, 2024 / Accepted: April 5, 2024

ABSTRACT

Introduction: It is important to assess the effectiveness of an antiseizure medication in treating different epilepsy aetiologies to optimise individualised therapeutic approaches. Data from the PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) Extension study were used to assess the effectiveness and safety/tolerability of perampanel (PER) when used to treat individuals with a range of epilepsy aetiologies in clinical practice.

Methods: A post hoc analysis was conducted of PERMIT Extension data from individuals with a known aetiology. Retention was assessed after 3, 6 and 12 months. Effectiveness was assessed after 3, 6 and 12 months and at the last visit (last observation carried forward). Effectiveness assessments included responder rate (≥ 50% seizure frequency reduction) and seizure freedom rate (no seizures since at least the prior visit). Safety/tolerability was assessed

Prior Presentation: Information from this study was previously presented as a poster at the 77th American Epilepsy Society Annual Meeting (AES 2023), Orlando, Florida, USA; 1–5 December, 2023.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-024-00618-5.

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Published online: 28 April 2024

by evaluating adverse events (AEs) and AEs leading to discontinuation.
Results: PERMIT Extension included 1945 individuals with structural aetiology, 1012 with genetic aetiology, 93 with an infectious aetiology, and 26 with an immune aetiology. Retention rates at 12 months were 61.1% (structural), 65.9% (genetic), 56.8% (infectious) and 56.5% (immune). At the last visit, responder rates (total seizures) were 43.3% (structural), 68.3% (genetic), 37.0% (infectious) and 20.0% (immune), and corresponding seizure freedom rates were 15.8%, 46.5%, 11.1% and 5.0%, respectively. AE incidence rates were 58.0% (structural), 46.5% (genetic), 51.1% (infectious) and 65.0% (immune), and corresponding rates of discontinuation due to AEs over 12 months were 18.9%, 16.4%, 18.5% and 21.7%, respectively. The types of AEs reported were generally consistent across aetiology subgroups, with no idiosyncratic AEs emerging.
Conclusion: Although PER was effective and generally well tolerated when used to treat individuals with a range of epilepsy aetiologies in clinical practice, variability in its effectiveness and tolerability across the subgroups indicates that PER may be particularly useful for individuals with specific epilepsy aetiologies.

Keywords: Anticonvulsant; Antiepileptic drug; Antiseizure medication; Focal seizures; Generalized seizures; Real-world

Key Summary Points

Why carry out this study?

The effectiveness and safety/tolerability of an antiseizure medication may vary depending on the aetiology of the epilepsy it is used to treat.

Greater understanding of how antiseizure medications perform in individuals with different epilepsy aetiologies will help inform individualised therapeutic approaches.

In this study, real-world data from the PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) Extension study were analysed to assess the effectiveness and safety/tolerability of perampanel when used to treat individuals with a range of epilepsy aetiologies in clinical practice.

What was learned from the study?

Perampanel was effective and generally well tolerated when used to treat individuals with a range of epilepsy aetiologies in clinical practice, but its effectiveness and tolerability varied between subgroups with structural, genetic, infectious and immune aetiologies.

Overall, perampanel demonstrated good retention over the long term.

INTRODUCTION

The International League Against Epilepsy (ILAE) has outlined six categories of epilepsy aetiology in the 2017 ILAE classification of epilepsies: structural, genetic, infectious, metabolic, immune, and unknown [1]. The ILAE emphasises that all attempts should be made to identify the aetiology and recommends that the aetiology of an individual's epilepsy should be considered from the moment the individual first experiences an epileptic seizure and at each stage along the diagnostic care pathway [1]. The identification of epilepsy aetiology has implications in the selection of treatment, and it is hoped that earlier and more precise diagnosis

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and greater understanding of aetiology will help facilitate the development of individualised therapies, which could improve the efficacy of treatment at the individual patient level [1, 2].

Perampanel (PER) is an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that inhibits excitation of postsynaptic membranes via selective inhibition of glutamate receptors [3], with broad-spectrum activity as an antiseizure medication (ASM) [4–6]. PER was assessed in an extensive clinical trials programme [7–10], as a result of which it has been approved in over 70 countries for the treatment of both focal-onset seizures, and generalised tonic–clonic seizures in people with idiopathic generalised epilepsy (IGE) [11, 12].

The majority of people with epilepsy encountered in clinical practice are excluded from participating in clinical trials [13, 14]. It is therefore important to assess the effectiveness, safety and tolerability of an ASM when used in routine clinical practice in individuals who are more diverse in terms of demographic and clinical characteristics (particularly comorbidities and associated polypharmacy) than those recruited for clinical trials [13]. Indeed, studies have shown that epilepsy is associated with a high prevalence of many psychiatric and somatic conditions [15–18] and a high use of central nervous system-acting medications [19]. Therefore, the exclusion of individuals with comorbidities and those taking several concomitant medications will affect the extrapolation of the results obtained during clinical trials. One category of people with epilepsy often excluded from clinical trials is the elderly population, despite the high prevalence of epilepsy in this age group [20]. This is due to the increased likelihood of adverse events (AEs), altered pharmacokinetics, presence of comorbidities and associated polypharmacy increasing drug–drug interactions in this population [21]. Clinical trials also fail to recruit individuals with cognitive and behavioural problems, as suggested by a recent study showing that approximately three-quarters of clinical trials conducted in the USA directly or indirectly excluded those with intellectual disability [22].

The PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) Extension study included over 6800 people with epilepsy who were treated with PER in clinical practice and is the largest pooled analysis of PER real-world data conducted to date [23]. Presented here is a post hoc analysis of data from PERMIT Extension that was conducted to compare the effectiveness and safety/tolerability of PER between subgroups of participants with different types of epilepsy aetiology.

METHODS

Study Design

Full details of the PERMIT Extension study have been published previously [23], as were the details of the two studies included in PERMIT Extension, the PERMIT [20] and the Perampanel Real-world Evidence (PROVE) studies [24]. The current study included all individuals from PERMIT Extension for whom the type of epilepsy aetiology was known, as defined by the treating clinician according to the information collected in the subject's clinical chart. Individuals diagnosed with unknown aetiology included those specifically diagnosed with unknown aetiology and those for whom information on aetiology was missing.

As previously reported, each study in PERMIT was approved by its own independent ethics committee, and all committees were notified about PERMIT. Further approval was not required for participation in PERMIT, as per current legislation. In PROVE, the study protocol was approved by institutional review boards or independent ethics committees at each site. PROVE was conducted under a waiver of consent, due to its retrospective design, which was approved by the ethics committees at each site, and no sites requiring consent were included in the study. All studies included in this article were approved by the appropriate ethics committees and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Assessments

Retention, effectiveness and tolerability were assessed as previously described for the total PERMIT Extension population [23]. Effectiveness was assessed by seizure type (total, focal, generalised) by evaluating changes in seizure frequency, responder rate and seizure freedom rate. Seizure freedom was defined as no seizures since at least the previous visit. Response was defined as at least 50% seizure frequency reduction from baseline, assessed since the previous visit, and therefore included individuals experiencing seizure freedom. Tolerability was assessed by evaluating AEs. Information on PER dosing and use of concomitant ASMs was also collected.

Statistical Analysis

The full analysis set (FAS) included all people with epilepsy treated with PER. Outcomes were analysed for the retention, effectiveness and tolerability populations, as previously defined in the PERMIT Extension primary publication [23]. Descriptive statistics were used for all assessments with qualitative variables being summarised as absolute frequencies and percentages, and quantitative variables being summarised as mean, standard deviation (SD), median, minimum, maximum, and 95% confidence intervals (CI) or interquartile range (IQR; 25th–75th percentile [P25–P75]), as described in the original study [23]. Retention on PER treatment over 12 months was assessed using Kaplan–Meier methodology and compared between aetiology subgroups using the log rank test. Subgroups analysed using the log rank test were mutually exclusive (i.e. an individual could not be categorised in more than one subgroup). As in the original study, since data were not available for all participants at every timepoint, the total number of individuals for whom data were available is stated for each outcome and timepoint and this value was used as the denominator for frequency analyses [23].

Outcomes were assessed for the total aetiology population and subanalyses were conducted for subgroups of individuals with specific epilepsy aetiologies (structural, genetic, infection, immune and unknown aetiology; ILAE 2017 classification [1]) but statistical analyses between the different groups were not carried out. For those with epilepsy with a structural aetiology, additional subgroup analyses were carried out for the subgroups of participants with tumour, vascular or traumatic brain injury (TBI) aetiology. For these additional analyses, retention at 12 months, responder and seizure freedom rates at the last visit, and the proportions of individuals experiencing AEs and discontinuing because of AEs over 12 months were compared between the tumour, vascular and TBI subgroups using the Pearson's chi-square test.

RESULTS

Study Population

Of the 6822 people with epilepsy included in PERMIT Extension, the aetiology was known for 5582 (FAS), of whom 1945 (34.8%) had a structural aetiology, 1012 (18.1%) had a genetic aetiology, 93 (1.7%) had an infectious aetiology, and 26 (0.5%) had an immune aetiology. In 2506 (44.9%) participants the aetiology was unknown; information on outcomes for this subgroup is presented as Supplementary Material (Results for unknown aetiology subgroup; Supplementary Figs. S1, S2 and S3). The numbers of individuals included in the retention, effectiveness and tolerability populations are presented by aetiology subgroup in Supplementary Table S1.

In the total aetiology population FAS, 51.4% were female, the median age was 35.0 years, the median age at epilepsy onset was 10.6 years, the median duration of epilepsy was 18.0 years, and the mean number of previous ASMs (including concomitant ASMs) was 4.6 (Table 1). Learning disability was present in 15.7% of the population and 23.9% had psychiatric comorbidity at baseline (most commonly, depression [6.8%] and anxiety [5.6%]). Seizure types at baseline were focal only (76.9%), generalised only (19.0%), and focal plus generalised (4.1%).

Table 1 Demographic and baseline characteristics for the total population and by aetiology subgroup (FAS)

Characteristic	Total population	Aetiology subgroup				
		Structural	Genetic	Infectious	Immune	Unknown
	N = 5582	*N* = 1945	*N* = 1012	*N* = 93	*N* = 26	*N* = 2506
Sex						
N[a]	5564	1940	1008	92	26	2498
Female, *n* (%)	2858 (51.4)	960 (49.5)	549 (54.5)	45 (48.9)	17 (65.4)	1287 (51.5)
Male, *n* (%)	2706 (48.6)	980 (50.5)	459 (45.5)	47 (51.1)	9 (34.6)	1211 (48.5)
Age, years						
N[a]	5361	1874	985	93	26	2383
Mean (SD)	36.4 (17.0)	42.5 (16.4)	30.0 (15.3)	38.4 (15.4)	34.8 (12.0)	34.1 (16.8)
Median (range)	35.0 (0.3–97.0)	42.0 (2.0–97.0)	27.0 (0.3–85.0)	39.0 (6.0–75.0)	34.0 (16.0–59.0)	33.0 (1.0–91.0)
Age category						
N[a]	5461	1877	1000	93	26	2465
< 12 years, *n* (%)	285 (5.2)	16 (0.9)	67 (6.7)	3 (3.2)	0	199 (8.1)
≥ 12 to < 18 years, *n* (%)	504 (9.2)	81 (4.3)	145 (14.5)	7 (7.5)	2 (7.7)	269 (10.9)
≥ 18 to < 65 years, *n* (%)	4346 (79.6)	1590 (84.7)	764 (76.4)	81 (87.1)	24 (92.3)	1887 (76.6)
≥ 65 years, *n* (%)	326 (6.0)	190 (10.1)	24 (2.4)	2 (2.2)	0	110 (4.5)
Age at epilepsy onset, years						
N[a]	5187	1756	951	89	25	2366
Mean (SD)	15.0 (16.5)	17.1 (19.4)	12.6 (12.1)	13.8 (16.0)	16.3 (18.3)	14.5 (15.4)
Median (range)	10.6 (0.0–97.0)	10.2 (0.0–97.0)	11.0 (0.0–84.0)	8.0 (0.0–60.0)	10.0 (0.0–56.0)	10.0 (0.0–90.0)
Duration of epilepsy, years						
N[a]	5286	1807	956	89	25	2409
Mean (SD)	21.2 (15.7)	25.2 (16.5)	17.5 (13.6)	24.4 (16.8)	18.7 (13.1)	19.7 (15.2)
Median (range)	18.0 (0.0–82.0)	23.0 (0.0–77.0)	14.0 (0.0–77.0)	21.0 (1.0–67.0)	14.0 (2.0–41.0)	16.0 (0.0–82.0)

Table 1 continued

Characteristic	Total population	Aetiology subgroup				
		Structural	Genetic	Infectious	Immune	Unknown
	N = 5582	*N* = 1945	*N* = 1012	*N* = 93	*N* = 26	*N* = 2506
Presence of learning disability						
N[a]	3899	1176	671	34	15	2005
Yes, *n* (%)	611 (15.7)	282 (24.0)	144 (21.5)	13 (38.2)	0 (0)	172 (8.6)
No, *n* (%)	3288 (84.3)	894 (76.0)	527 (78.5)	21 (61.8)	15 (100)	1833 (91.4)
Presence of psychiatric comorbidity						
N[a]	3781	1035	838	44	15	1849
Yes, *n* (%)	902 (23.9)	265 (25.6)	180 (21.5)	20 (45.5)	4 (26.7)	433 (23.4)
No, *n* (%)	2879 (76.1)	770 (76.4)	658 (78.5)	24 (54.5)	11 (73.3)	1416 (76.6)
Most frequent types of psychiatric comorbidity[b]						
N[a]	3781	1035	838	44	15	1849
Depression, *n* (%)	256 (6.8)	32 (3.1)	59 (7.0)	4 (9.1)	1 (6.7)	160 (8.7)
Anxiety, *n* (%)	210 (5.6)	30 (2.9)	51 (6.1)	2 (4.5)	0	127 (6.9)
Hyperactivity, *n* (%)	59 (1.6)	3 (0.3)	24 (2.9)	2 (4.5)	0	30 (1.6)
Autism, *n* (%)	44 (1.2)	1 (0.1)	18 (2.1)	1 (2.3)	0	24 (1.3)
Seizure type						
N[a]	5014	1840	985	90	26	2073
Focal only	3855 (76.9)	1713 (93.1)	87 (8.8)	87 (96.7)	24 (92.3)	1944 (93.8)
Generalised only	954 (19.0)	24 (1.3)	873 (88.6)	1 (1.1)	2 (7.7)	56 (2.7)
Both focal and generalised	205 (4.1)	103 (5.6)	25 (2.5)	2 (2.2)	0	73 (3.5)
Number of previous ASMs[c]						
N[a]	5094	1788	832	82	25	2367
Mean (SD)	4.6 (3.8)	5.9 (3.6)	3.6 (3.1)	5.8 (3.1)	6.8 (3.6)	3.8 (3.8)
Median (range)	4.0 (0–22.0)	5.0 (0–19.0)	3.0 (0–16.0)	5.0 (1–16.0)	7.0 (1–14.0)	3.0 (0–22.0)
Number of previous ASMs[c]						
N[a]	5094	1788	832	82	25	2367
0, *n* (%)	702 (13.8)	13 (0.7)	109 (13.1)	0	0	580 (24.5)

Table 1 continued

Characteristic	Total population	Aetiology subgroup				
		Structural	Genetic	Infectious	Immune	Unknown
	N = 5582	*N* = 1945	*N* = 1012	*N* = 93	*N* = 26	*N* = 2506
1, *n* (%)	595 (11.7)	150 (8.4)	143 (17.2)	6 (7.3)	1 (4.0)	295 (12.5)
2, *n* (%)	540 (10.6)	183 (10.2)	116 (13.9)	2 (2.4)	2 (8.0)	237 (10.0)
3, *n* (%)	512 (10.1)	181 (10.1)	103 (12.4)	8 (9.8)	1 (4.0)	219 (9.3)
4, *n* (%)	491 (9.6)	184 (10.3)	87 (10.5)	17 (20.7)	6 (24.0)	197 (8.3)
5, *n* (%)	427 (8.4)	186 (10.4)	69 (8.3)	11 (13.4)	2 (8.0)	161 (6.8)
6, *n* (%)	430 (8.4)	210 (11.7)	64 (7.7)	6 (7.3)	3 (12.0)	148 (6.3)
7, *n* (%)	321 (6.3)	139 (7.8)	44 (5.3)	13 (15.9)	2 (8.0)	122 (5.2)
8, *n* (%)	275 (5.4)	127 (7.1)	32 (3.8)	6 (7.3)	3 (12.0)	108 (4.6)
9, *n* (%)	232 (4.6)	112 (6.3)	19 (2.3)	4 (4.9)	1 (4.0)	94 (4.0)
≥ 10, *n* (%)	569 (11.2)	303 (16.9)	46 (5.5)	9 (11.0)	5 (20.0)	206 (8.7)
Most frequently used[d] previous ASMs[c]						
N[a]	2735	504	661	38	4	1528
Levetiracetam, *n* (%)	1148 (42.0)	294 (58.3)	351 (53.1)	21 (55.3)	3 (75.0)	479 (31.3)
Valproate, *n* (%)	867 (31.7)	207 (41.1)	312 (47.2)	24 (63.2)	3 (75.0)	321 (21.0)
Lamotrigine, *n* (%)	694 (25.4)	147 (29.2)	219 (33.1)	13 (34.2)	0	315 (20.6)
Topiramate, *n* (%)	582 (21.3)	125 (24.8)	155 (23.4)	20 (52.6)	2 (50.0)	280 (18.3)
Oxcarbazepine, *n* (%)	560 (20.5)	108 (21.4)	82 (12.4)	17 (44.7)	1 (25.0)	352 (23.0)
Carbamazepine, *n* (%)	557 (20.4)	193 (38.3)	113 (17.1)	19 (50.0)	1 (25.0)	231 (15.1)
Lacosamide, *n* (%)	524 (19.2)	116 (23.0)	97 (14.7)	9 (23.7)	1 (25.0)	301 (19.7)
Clobazam, *n* (%)	489 (17.9)	105 (20.8)	126 (19.1)	16 (42.1)	3 (75.0)	239 (15.6)
Zonisamide, *n* (%)	454 (16.6)	83 (16.5)	153 (23.1)	8 (21.1)	1 (25.0)	209 (13.7)
Clonazepam, *n* (%)	325 (11.9)	83 (16.5)	103 (15.6)	7 (18.4)	1 (25.0)	131 (8.6)

Table 1 continued

Characteristic	Total population	Aetiology subgroup				
		Structural	Genetic	Infectious	Immune	Unknown
	N = 5582	*N* = 1945	*N* = 1012	*N* = 93	*N* = 26	*N* = 2506
Phenytoin, *n* (%)	288 (10.5)	77 (15.3)	68 (10.3)	9 (23.7)	0	134 (8.8)
Number of concomitant ASMs						
N[a]	5476	1915	946	91	26	2498
Mean (SD)	2.2 (1.2)	2.3 (1.1)	2.0 (1.2)	2.8 (1.4)	2.8 (1.1)	2.2 (1.2)
Median (range)	2.0 (0–7.0)	2.0 (0–7.0)	2.0 (0–6.0)	3.0 (0–6.0)	3.0 (1–5.0)	2.0 (0–7.0)
Number of concomitant ASMs						
N[a]	5476	1915	946	91	26	2498
0, *n* (%)	355 (6.5)	83 (4.3)	86 (9.1)	4 (4.4)	0	182 (7.3)
1, *n* (%)	1142 (20.9)	382 (19.9)	259 (27.4)	11 (12.1)	3 (11.5)	487 (19.5)
2, *n* (%)	1854 (33.9)	673 (35.1)	306 (32.3)	26 (28.6)	8 (30.8)	841 (33.7)
3, *n* (%)	1439 (26.3)	548 (28.6)	188 (19.9)	22 (24.2)	8 (30.8)	673 (26.9)
4, *n* (%)	531 (9.7)	182 (9.5)	89 (9.4)	19 (20.9)	5 (19.2)	236 (9.4)
≥ 5, *n* (%)	155 (2.8)	47 (2.5)	18 (1.9)	9 (9.9)	2 (7.7)	79 (3.2)
Most frequently used[d] concomitant ASMs						
N[a]	5433	1898	925	90	26	2494
Levetiracetam, *n* (%)	1962 (36.1)	702 (37.0)	389 (42.1)	31 (34.4)	15 (57.7)	825 (33.1)
Lamotrigine, *n* (%)	1293 (23.8)	491 (25.9)	199 (21.5)	23 (25.6)	5 (19.2)	575 (23.1)
Lacosamide, *n* (%)	1212 (22.3)	417 (22.0)	113 (12.2)	26 (28.9)	8 (30.8)	648 (26.0)
Valproate, *n* (%)	1137 (20.9)	363 (19.1)	290 (31.4)	25 (27.8)	5 (19.2)	454 (18.2)
Carbamazepine, *n* (%)	808 (14.9)	446 (23.5)	58 (6.3)	25 (27.8)	6 (23.1)	273 (10.9)
Zonisamide, *n* (%)	737 (13.6)	245 (12.9)	130 (14.1)	9 (10.0)	6 (23.1)	347 (13.9)
Clobazam, *n* (%)	689 (12.7)	311 (16.4)	58 (6.3)	30 (33.3)	7 (26.9)	259 (10.4)

Table 1 continued

Characteristic	Total population	Aetiology subgroup				
		Structural	Genetic	Infectious	Immune	Unknown
	N = 5582	*N* = 1945	*N* = 1012	*N* = 93	*N* = 26	*N* = 2506
Topiramate, *n* (%)	563 (10.4)	182 (9.6)	101 (10.9)	18 (20.0)	7 (26.9)	255 (10.2)
Oxcarbazepine, *n* (%)	554 (10.2)	200 (10.5)	27 (2.9)	18 (20.0)	3 (11.5)	306 (12.3)

ASM antiseizure medication, *FAS* full analysis set, *SD* standard deviation

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

[b]≥ 1% of people in total aetiology population

[c]Including concomitant ASMs

[d]≥ 10% of people in total aetiology population

Aetiology Subgroups

The proportion of female subjects was higher in the immune aetiology subgroup than in the other subgroups (65.4% vs. 48.9–54.5%) (Table 1). The median age was lower in the genetic aetiology subgroup than in the other subgroups (27.0 vs. 33.0–42.0 years). The proportion of individuals with learning disability at baseline was higher in the infectious aetiology subgroup than in the other subgroups (38.2% vs. 8.6–26.7%), as was the proportion of individuals with psychiatric comorbidity at baseline (45.5% vs. 21.5–26.7%). Most individuals in the structural, infectious, immune and unknown aetiology subgroups had focal seizures only (92.3–96.7%) whereas most of the genetic aetiology subgroup had generalised seizures only (88.6%). The mean number of previous ASMs (including concomitant ASMs) was lowest in the genetic aetiology subgroup (3.6) and highest in the immune aetiology subgroup (6.8), but the mean number of concomitant ASMs at baseline was similar between subgroups (2.0–2.8).

Treatment

In the total aetiology population, the mean PER dose was 2.8 mg/day at initiation and 6.1 mg/day at the last visit (Supplementary Table S2). PER was initiated as monotherapy in 6.5% of individuals and, at the last visit, 1.4% were being treated with PER monotherapy. The mean number of concomitant ASMs used at the time of PER initiation was 2.2 and the most frequently used concomitant ASMs (≥ 20% of the total population) were levetiracetam (36.1%), lamotrigine (23.8%), lacosamide (22.3%) and valproate (20.9%).

Treatment by Aetiology Subgroup

PER treatment by aetiology subgroup is presented in Supplementary Table S2.

Retention

In the total aetiology population, retention rates after 3, 6 and 12 months were 88.1%, 77.4% and 61.1%, respectively (Fig. 1). The mean time under PER treatment over 12 months was 10.5 months (95% CI, 10.4–10.7; Fig. 2a). It was not possible to estimate the median time under PER treatment because the high number of censored events. The most common documented reasons for discontinuation over 12 months (≥ 5% of population) were AEs (16.2%) and lack of efficacy (9.4%); reasons for discontinuation were unknown for 8.1% of individuals (Supplementary Table S3).

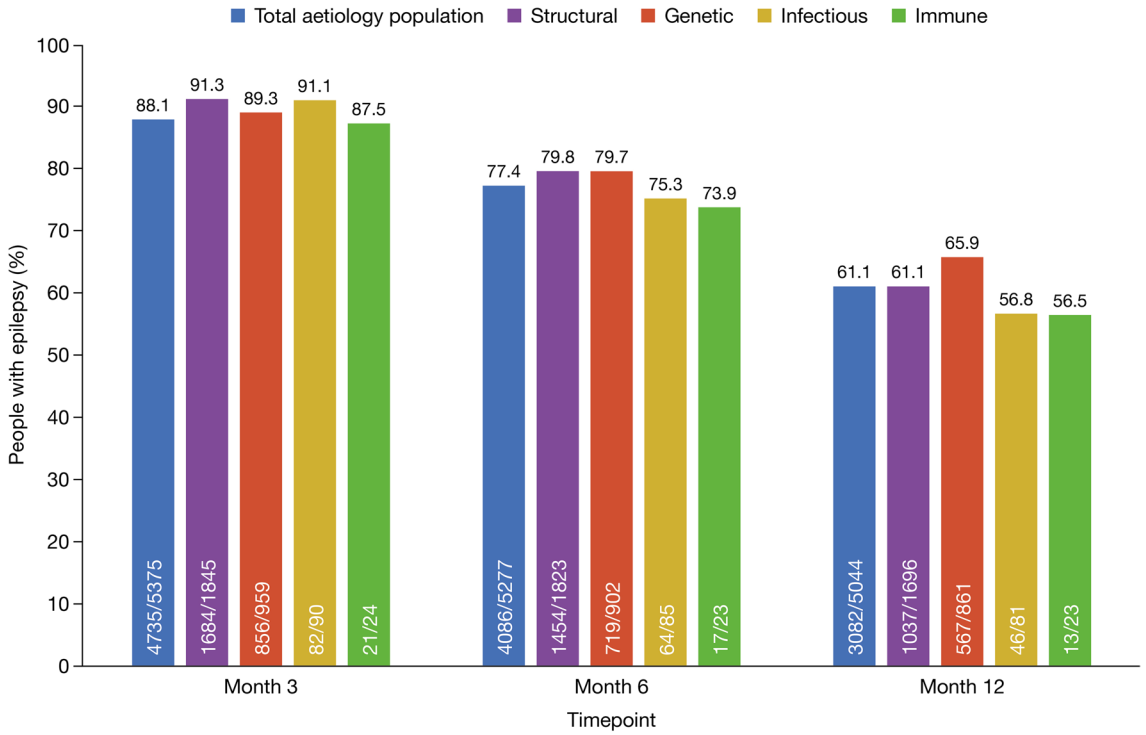


Fig. 1 Retention rates after 3, 6 and 12 months of PER treatment in the total aetiology population and by aetiology subgroup (retention population). *PER* perampanel

Retention by Aetiology Subgroup

Retention rates after 3, 6 and 12 months by aetiology subgroup ranged from 87.5% to 91.3%, 73.9% to 79.8% and 56.5% to 65.9%, respectively (Figs. 1, 2b). After 12 months, retention was highest in individuals with a genetic aetiology (65.9%) and lowest in those with an immune aetiology (56.5%). The mean (95% CI) times under PER treatment over 12 months in the structural, genetic, infectious, and immune aetiology subgroups were 10.6 (10.4–10.8), 10.8 (10.5–11.1), 9.8 (8.8–10.8) and 9.2 (7.3–11.1) months, respectively, and there were significant differences between the aetiology subgroups in retention on PER treatment ($p=0.002$; Fig. 2b). Discontinuation due to AEs was highest in the immune aetiology subgroup (21.7%) and discontinuation due to lack of efficacy was highest in the infectious aetiology subgroup (17.3%) (Supplementary Table S3).

Effectiveness

In the total aetiology population, the monthly frequency of total seizures decreased significantly from baseline to last visit ($p<0.001$; Supplementary Fig. S4A; Supplementary Table S4), responder rates for total seizures at 12 months and the last visit were 57.2% and 48.9%, respectively, and corresponding seizure freedom rates were 23.2% and 20.9%, respectively (Fig. 3a). Similarly, the monthly frequency of focal seizures decreased significantly from baseline to the last visit ($p<0.001$; Supplementary Fig. S4A; Supplementary Table S4), responder rates for focal seizures at 12 months and the last visit were 52.3% and 43.4%, respectively, and corresponding seizure freedom rates were 17.6% and 15.1%, respectively (Fig. 4a). The monthly frequency of generalised seizures also decreased significantly from baseline to the last visit ($p<0.001$; Supplementary Fig. S4A;

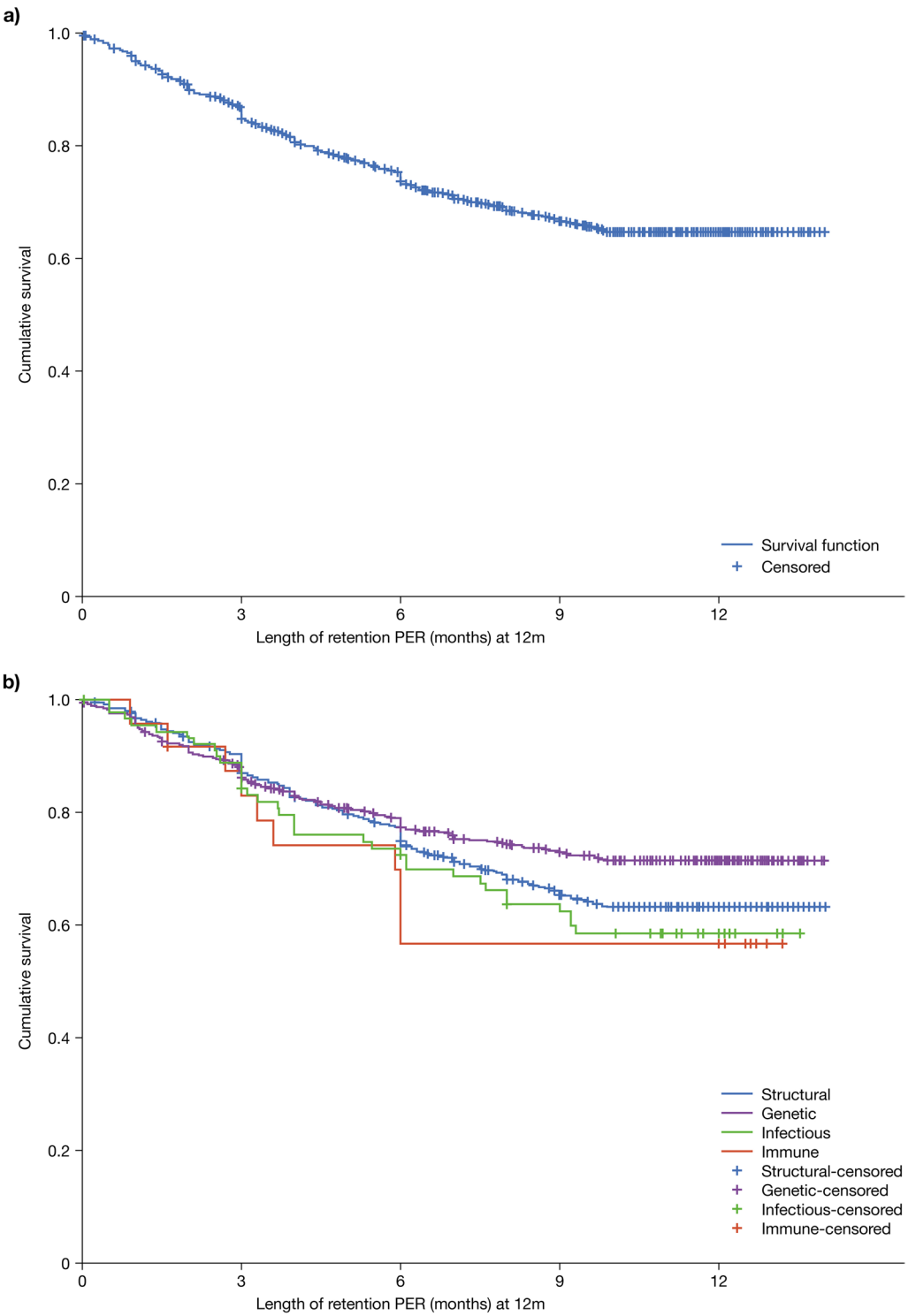


Fig. 2 Kaplan–Meier plot for retention on PER treatment over 12 months **a** in the total aetiology population and **b** by aetiology subgroup (structural, genetic, infectious and immune aetiologies; retention population). Statistically significant differences were observed between aetiologies ($p = 0.002$; log rank test). *PER* perampanel

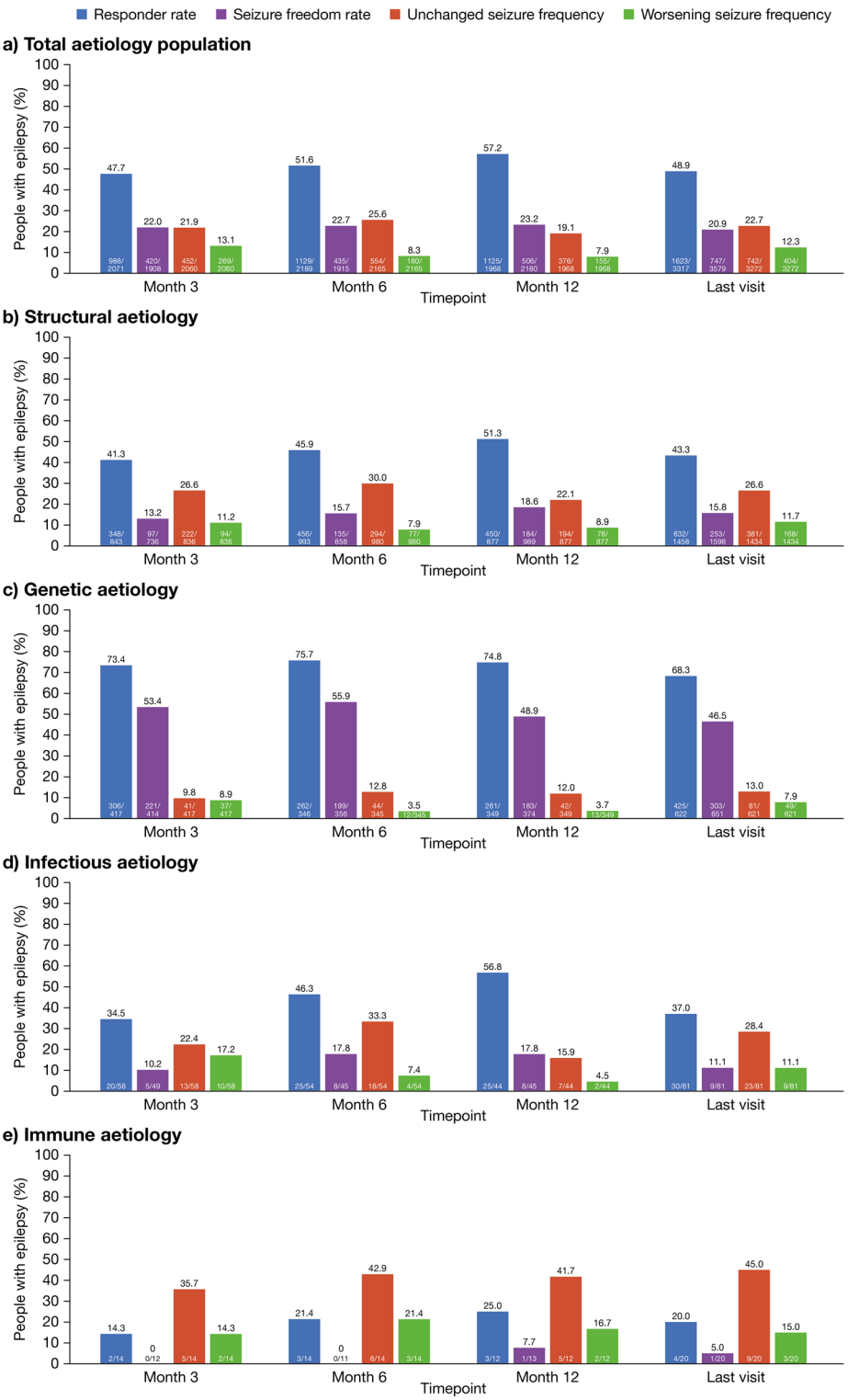


Fig. 3 Responder rate, seizure freedom rate and the proportions of individuals with unchanged and worsening seizure frequency for total seizures at 3, 6 and 12 months and the last visit in **a** total aetiology population, **b** structural aetiology subgroup, **c** genetic aetiology subgroup, **d** infectious aetiology subgroup and **e** immune aetiology subgroup (effectiveness population)

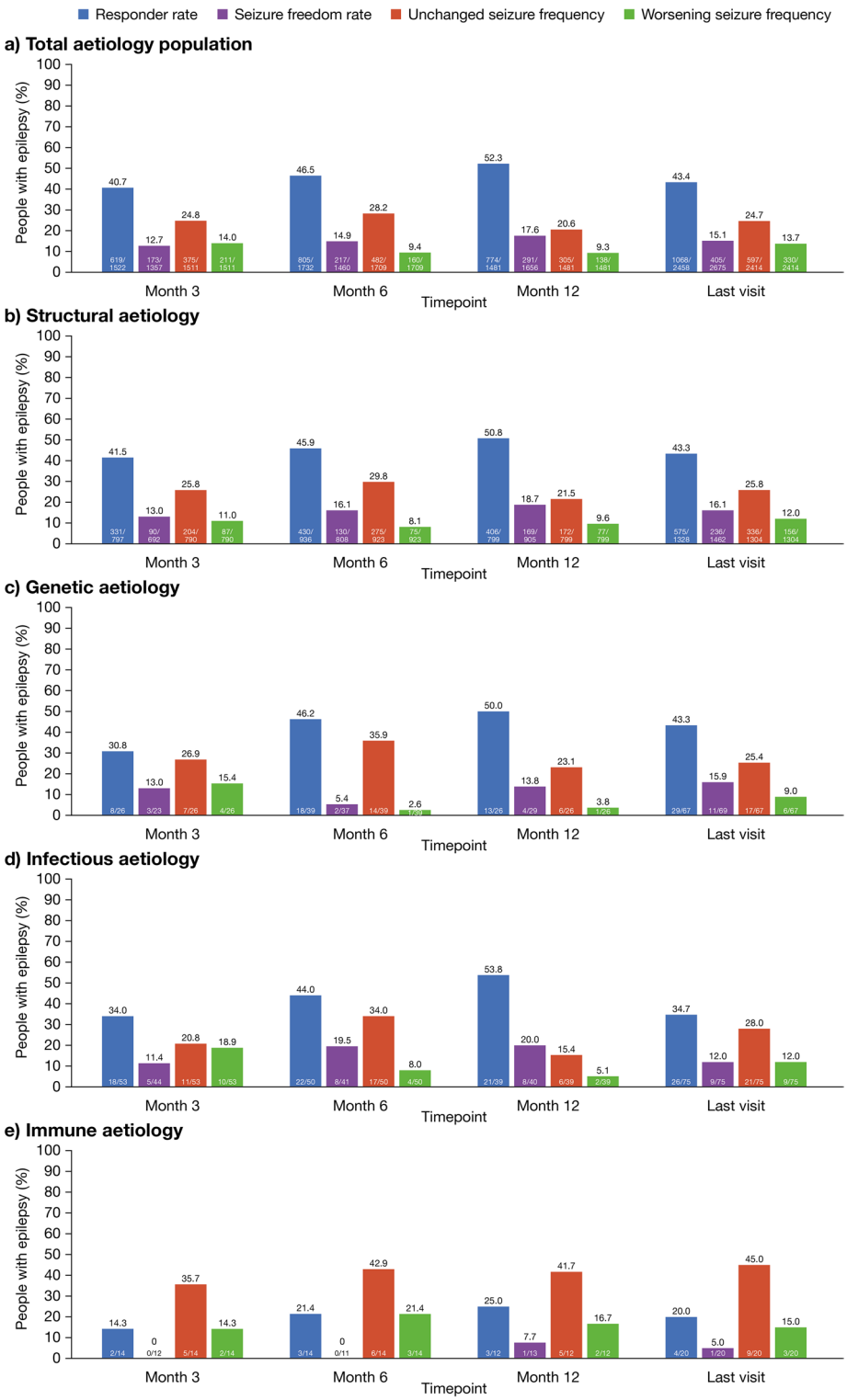
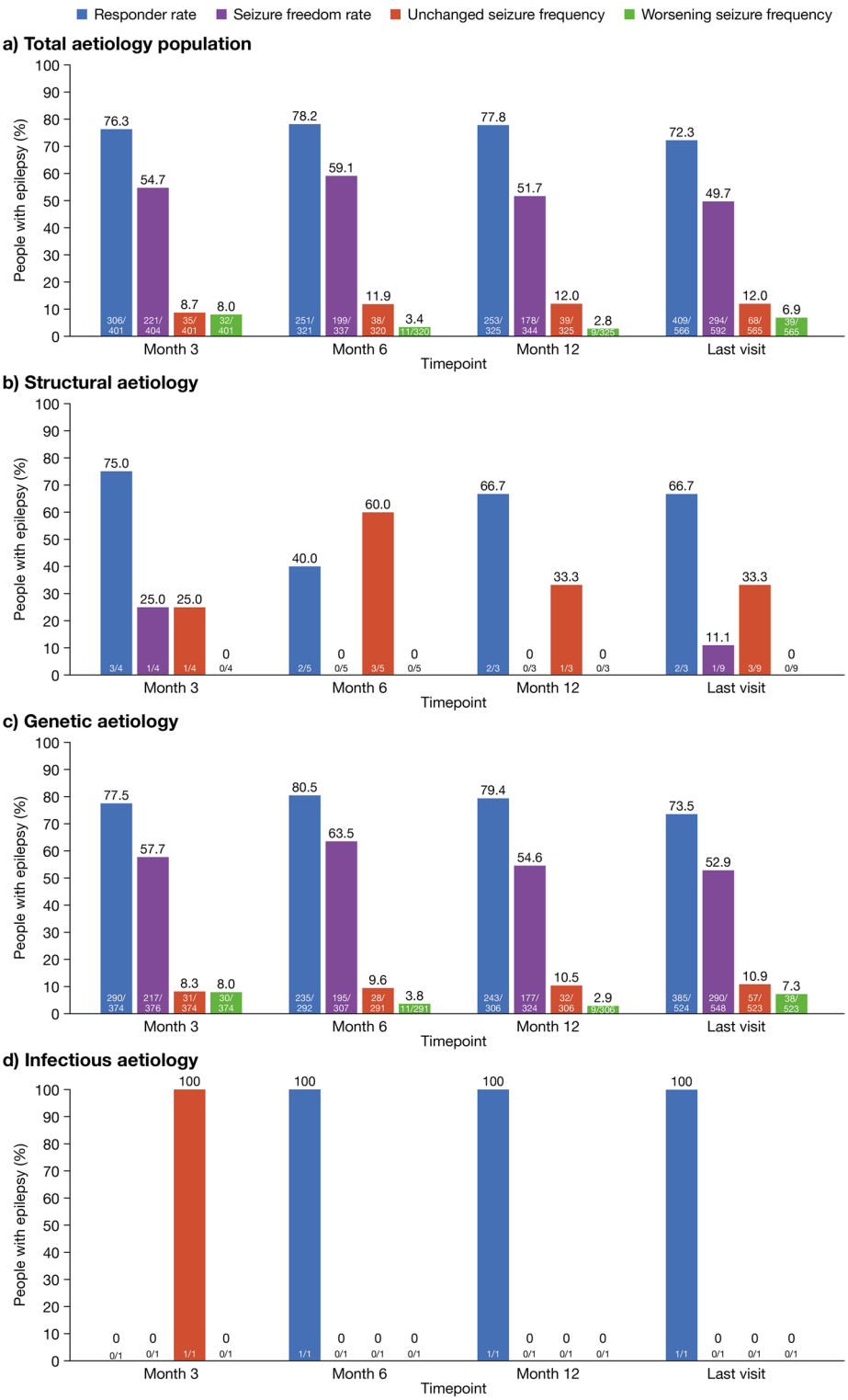


Fig. 4 Responder rate, seizure freedom rate and the proportions of individuals with unchanged and worsening seizure frequency for focal seizures at 3, 6 and 12 months and the last visit in **a** total aetiology population, **b** structural aetiology subgroup, **c** genetic aetiology subgroup, **d** infectious aetiology subgroup and **e** immune aetiology subgroup (effectiveness population)



Supplementary Table S4), responder rates for generalised seizures at 12 months and the last visit were 77.8% and 72.3%, respectively, and corresponding seizure freedom rates were 51.7% and 49.7%, respectively (Fig. 5a). The proportions of individuals with unchanged and

◂**Fig. 5** Responder rate, seizure freedom rate and the proportions of individuals with unchanged and worsening seizure frequency for generalised seizures at 3, 6 and 12 months and the last visit in **a** total aetiology population, **b** structural aetiology subgroup, **c** genetic aetiology subgroup and **d** infectious aetiology subgroup (effectiveness population). Note: there were no individuals in the immune aetiology subgroup who had data available for generalised seizures

worsening seizure frequencies are presented by seizure type in Figs. 3, 4 and 5.

Effectiveness by Aetiology Subgroup

In the structural aetiology subgroup, the monthly frequencies of total and focal seizures decreased significantly from baseline to the last visit ($p<0.001$ for both; Supplementary Fig. S4B; Supplementary Table S4). The monthly frequency of generalised seizures also decreased, but the change was not statistically significant. In the genetic aetiology subgroup, there were significant decreases from baseline to the last visit in the frequencies of total seizures ($p<0.001$), focal seizures ($p=0.007$) and generalised seizures ($p<0.001$) (Supplementary Fig. S4C; Supplementary Table S4). In the infectious aetiology subgroup, there were significant decreases from baseline to the last visit in the frequencies of total seizures ($p=0.008$) and focal seizures ($p=0.021$) (Supplementary Fig. S4D; Supplementary Table S4). The monthly frequency of generalised seizures also decreased, but the sample size was too small to test for statistical significance ($n=2$). In the immune aetiology subgroup, information was only available for focal seizures, for which there was a non-significant increase in frequency from baseline to the last visit (Supplementary Fig. S4E; Supplementary Table S4).

Responder rate, seizure freedom rate and the proportions of individuals with unchanged and worsening seizure frequency are presented by aetiology subgroup for total, focal and generalised seizures in Figs. 3, 4 and 5, respectively. Responder rates for total seizures ranged from 25.0% (immune aetiology) to 74.8% (genetic aetiology) at 12 months, and from 20.0% (immune aetiology) to 68.3% (genetic aetiology) at the last visit. Responder rates for focal seizures ranged from 25.0% (immune aetiology) to 53.8% (infectious aetiology) at 12 months, and from 20.0% (immune aetiology) to 43.3% (structural and genetic aetiology) at the last visit. Responder rates for generalised seizures ranged from 66.7% (structural aetiology) to 100% (infectious aetiology) at 12 months, and from 66.7% (structural aetiology) to 100% (infectious aetiology) at the last visit (not assessed for the immune aetiology subgroup). Seizure freedom rates for total seizures ranged from 7.7% (immune aetiology) to 48.9% (genetic aetiology) at 12 months, and from 5.0% (immune aetiology) to 46.5% (genetic aetiology) at the last visit. Seizure freedom rates for focal seizures ranged from 7.7% (immune aetiology) to 20.0% (infectious aetiology) at 12 months, and from 5.0% (immune aetiology) to 16.1% (structural aetiology) at the last visit. Seizure freedom rates for generalised seizures ranged from 0% (structural and infectious aetiologies) to 54.6% (genetic aetiology) at 12 months, and from 0% (infectious aetiology) to 52.9% (genetic aetiology) at the last visit. The rate of total seizure worsening at the last visit was highest in the immune aetiology subgroup (15.0%) and lowest in the genetic aetiology subgroup (7.9%). The rate of focal seizure worsening at the last visit was highest in the immune aetiology subgroup (15.0%) and lowest in the genetic aetiology subgroup (9.0%). The rate of generalised seizure worsening at the last visit was low across subgroups, being highest in the genetic aetiology subgroup (7.3%) and lowest in the structural and infectious aetiology subgroups (both 0%).

Safety and Tolerability

In the total aetiology population, the proportion of people with epilepsy experiencing AEs was 51.8%, and the most frequently reported AEs (≥ 5% of the study population) were dizziness/vertigo (14.0%), somnolence (9.0%), irritability (7.5%) and behavioural disorders (5.8%) (Supplementary Table S5). Over 12 months, 18.5% of individuals discontinued because of AEs, and the most common AEs leading to discontinuation (≥ 2% of the study population) were dizziness/vertigo (4.2%), behavioural disorders (2.6%),

irritability (2.6%) and somnolence (2.4%). Psychiatric AEs were experienced by 22.1% of the study population and 11.4% of those who discontinued because of AEs had psychiatric AEs (although it was not possible to determine if it was the psychiatric AEs that led to discontinuation, or other types of AE). In total, 34.2% of individuals who experienced psychiatric AEs and 39.5% of those who discontinued with psychiatric AEs had psychiatric comorbidities at baseline. The mean (SD) PER dose in those who discontinued with psychiatric AEs was 4.3 (2.6) mg/day (median, 4; range, 1–16).

Safety and Tolerability by Aetiology Subgroup

The proportion of individuals who experienced AEs ranged from 46.5% in the genetic aetiology subgroup to 65.0% in the immune aetiology subgroup (Supplementary Table S5). The most frequently reported AEs were generally similar across subgroups and mirrored those in the total aetiology population. The rate of discontinuation due to AEs over 12 months ranged from 16.4% in the genetic aetiology subgroup to 21.7% in the immune aetiology subgroup, with the most common AEs leading to discontinuation being generally similar across subgroups and consistent with the total aetiology population. The proportion of individuals experiencing psychiatric AEs ranged from 15.9% in the infectious aetiology subgroup to 25.0% in the immune aetiology subgroup, and the proportion of those discontinuing because of AEs who had psychiatric AEs ranged from 7.0% in the infectious aetiology subgroup to 20.0% in the immune aetiology subgroup.

Structural Aetiology Subgroups

Study Populations and Treatment

Of the 1945 study participants with a structural aetiology, 127 (6.5%) had a tumour aetiology, 93 (4.8%) had a vascular aetiology and 73 (3.8%) had a TBI aetiology (Table 2). In the tumour aetiology subgroup, the retention, effectiveness and tolerability populations included 126, 119 and 116 individuals, respectively. The corresponding populations for the vascular and TBI aetiology subgroups included 89, 89 and 91, and 73, 57 and 71 individuals, respectively.

In the tumour aetiology subgroup, 54.0% were male, the median age was 46.0 years, and the median duration of epilepsy was 6.5 years; learning disability and psychiatric comorbidity were present in 5.6% and 15.9% of individuals, respectively (Table 2). The mean number of previous ASMs (including concomitant ASMs) was 2.9. Nearly all individuals (99.2%) had only focal seizures at baseline (one individual [0.8%] had both focal and generalised seizures). The mean (SD) PER dose was 2.6 (1.4) mg/day (median, 2.0 mg/day; IQR, 2–2 mg/day; $n=54$) at treatment initiation and 5.7 (2.5) mg/day (median, 6.0 mg/day; IQR, 4–8 mg/day; $n=108$) at the last visit. At baseline, 16.4% (18/110) of individuals received PER as monotherapy and at the last visit 3.0% (1/33) were receiving PER monotherapy. The mean (SD) number of concomitant ASMs used at the time of PER initiation was 1.4 (1.0).

In the vascular aetiology subgroup, 59.3% were male, the median age was 61.0 years, and the median duration of epilepsy was 4.0 years; learning disability and psychiatric comorbidity were present in 9.5% and 31.2% of individuals, respectively (Table 2). The mean number of previous ASMs (including concomitant ASMs) was 2.6. Nearly all individuals (97.8%) had only focal seizures at baseline (two individuals [2.2%] had only generalised seizures). The mean (SD) PER dose was 3.5 (1.7) mg/day (median, 4.0 mg/day; IQR, 2–4 mg/day; $n=33$) at treatment initiation and 5.1 (2.1) mg/day (median, 4.0 mg/day; IQR, 4–6 mg/day; $n=87$) at the last visit. PER was given as monotherapy in 31.5% (29/92) of individuals at baseline and in 4.4% (2/45) at the last visit. The mean (SD) number of concomitant ASMs used at the time of PER initiation was 1.1 (1.0).

In the TBI aetiology subgroup, 78.1% were male, the median age was 43.0 years and the median duration of epilepsy was 17.0 years; learning disability and psychiatric comorbidity were present in 20.8% and 24.6% of individuals, respectively (Table 2). The mean number of previous ASMs (including concomitant ASMs) was 3.9. Nearly all individuals (98.6%)

Table 2 Demographic and baseline characteristics for the structural aetiology subgroups (tumour, vascular and TBI aetiologies; FAS)

Characteristic	Tumour aetiology *N* = 127	Vascular aetiology *N* = 93	TBI aetiology *N* = 73
Sex			
N[a]	126	91	73
Male, *n* (%)	68 (54.0)	54 (59.3)	57 (78.1)
Female, *n* (%)	58 (46.0)	37 (40.7)	16 (21.9)
Age, years			
N[a]	127	93	73
Mean (SD)	46.3 (17.0)	58.3 (21.6)	44.9 (16.0)
Median (range)	46.0 (11.0—85.0)	61.0 (8.0–97.0)	43.0 (13.0–86.0)
Age category			
N[a]	127	93	73
< 12 years, *n* (%)	1 (0.8)	1 (1.1)	0
≥ 12 to < 18 years, *n* (%)	6 (4.7)	3 (3.2)	2 (2.7)
≥ 18 to < 65 years, *n* (%)	98 (77.2)	47 (50.5)	59 (80.8)
≥ 65 years, *n* (%)	22 (17.3)	42 (45.2)	12 (16.4)
Age at epilepsy onset, years			
N[a]	84	87	68
Mean (SD)	37.4 (21.3)	51.0 (25.0)	27.4 (20.2)
Median (range)	36.0 (1.0—83.0)	56.0 (1.0–97.0)	22.5 (0–85.0)
Duration of epilepsy, years			
N[a]	84	87	68
Mean (SD)	9.6 (11.1)	8.6 (10.0)	17.5 (12.6)
Median (range)	6.5 (0—49.0)	4.0 (0–43.0)	17.0 (0–50.0)
Presence of learning disability			
N[a]	36	42	24
Yes, *n* (%)	2 (5.6)	4 (9.5)	5 (20.8)
No, *n* (%)	34 (94.4)	38 (90.5)	19 (79.2)
Presence of psychiatric comorbidity			
N[a]	69	77	65
Yes, *n* (%)	11 (15.9)	24 (31.2)	16 (24.6)
No, *n* (%)	58 (84.1)	53 (68.8)	49 (75.4)

Table 2 continued

Characteristic	Tumour aetiology *N* = 127	Vascular aetiology *N* = 93	TBI aetiology *N* = 73
Most frequent types of psychiatric comorbidity[b]			
N[a]	69	77	65
Depression, *n* (%)	1 (1.4)	12 (15.6)	4 (6.2)
Anxiety, *n* (%)	5 (7.2)	9 (11.7)	4 (6.2)
Seizure type			
N[a]	122	93	70
Focal only	121 (99.2)	91 (97.8)	69 (98.6)
Generalised only	0	2 (2.2)	1 (1.4)
Both focal and generalised	1 (0.8)	0	0
Number of previous ASMs[c]			
N[a]	108	87	68
Mean (SD)	2.9 (2.7)	2.6 (2.9)	3.9 (2.5)
Median (range)	2.0 (0−16.0)	2.0 (0–18.0)	3.0 (1–10.0)
Number of previous ASMs[c]			
N[a]	87	87	68
0, *n* (%)	1 (0.9)	4 (4.6)	0
1, *n* (%)	31 (28.7)	36 (41.4)	14 (20.6)
2, *n* (%)	35 (32.4)	22 (25.3)	13 (19.1)
3, *n* (%)	15 (13.9)	8 (9.2)	8 (11.8)
4, *n* (%)	10 (9.3)	2 (2.3)	6 (8.8)
5, *n* (%)	4 (3.7)	3 (3.4)	8 (11.8)
6, *n* (%)	6 (5.6)	3 (3.4)	9 (13.2)
7, *n* (%)	0	6 (6.9)	5 (7.4)
8, *n* (%)	1 (0.9)	0	1 (1.5)
9, *n* (%)	1 (0.9)	0	1 (1.5)
≥ 10, *n* (%)	4 (4.6)	3 (3.4)	3 (4.4)
Most frequently used[d] previous ASMs[c]			
N[a]	96	57	57
Levetiracetam, *n* (%)	65 (67.7)	29 (50.9)	34 (59.6)
Valproate, *n* (%)	35 (36.5)	14 (24.6)	25 (43.9)
Lamotrigine, *n* (%)	26 (27.1)	13 (22.8)	12 (21.1)

Table 2 continued

Characteristic	Tumour aetiology *N* = 127	Vascular aetiology *N* = 93	TBI aetiology *N* = 73
Topiramate, *n* (%)	6 (6.3)	5 (8.8)	22 (38.6)
Oxcarbazepine, *n* (%)	11 (11.5)	7 (12.3)	19 (33.3)
Carbamazepine, *n* (%)	19 (19.8)	8 (14.0)	26 (45.6)
Lacosamide, *n* (%)	26 (27.1)	12 (21.1)	9 (15.8)
Clobazam, *n* (%)	8 (8.3)	4 (7.0)	11 (19.3)
Zonisamide, *n* (%)	13 (13.5)	4 (7.0)	11 (19.3)
Clonazepam, *n* (%)	14 (14.6)	7 (12.3)	14 (24.6)
Phenytoin, *n* (%)	10 (10.4)	4 (7.0)	13 (22.8)
Phenobarbital, *n* (%)	8 (8.3)	3 (5.3)	8 (14.0)
Number of concomitant ASMs			
N[a]	110	92	73
Mean (SD)	1.4 (1.0)	1.1 (1.0)	2.1 (1.5)
Median (range)	1.0 (0—5.0)	1.0 (0–4.0)	2.0 (0–7.0)
Number of concomitant ASMs			
N[a]	110	92	73
0, *n* (%)	18 (16.4)	29 (31.5)	7 (9.6)
1, *n* (%)	46 (41.8)	41 (44.6)	22 (30.1)
2, *n* (%)	32 (29.1)	12 (13.0)	17 (23.3)
3, *n* (%)	13 (11.8)	7 (7.6)	18 (24.7)
4, *n* (%)	0	3 (3.3)	4 (5.5)
≥ 5, *n* (%)	3 (0.9)	0	5 (6.8)
Most frequently used[d] concomitant ASMs			
N[a]	110	89	72
Levetiracetam, *n* (%)	37 (34.3)	20 (22.5)	24 (33.3)
Lamotrigine, *n* (%)	20 (18.5)	11 (12.4)	10 (13.9)
Lacosamide, *n* (%)	15 (13.9)	8 (9.0)	12 (16.7)
Valproate, *n* (%)	25 (23.1)	11 (12.4)	20 (27.8)
Carbamazepine, *n* (%)	16 (14.8)	6 (6.7)	13 (18.1)
Zonisamide, *n* (%)	7 (6.5)	1 (1.1)	9 (12.5)
Clobazam, *n* (%)	3 (2.8)	2 (2.2)	10 (13.9)
Topiramate, *n* (%)	1 (0.9)	5 (5.6)	10 (13.9)

Table 2 continued

Characteristic	Tumour aetiology *N* = 127	Vascular aetiology *N* = 93	TBI aetiology *N* = 73
Oxcarbazepine, *n* (%)	6 (5.6)	6 (6.7)	9 (12.5)
Clonazepam, *n* (%)	5 (4.6)	5 (5.6)	12 (16.7)

ASM antiseizure medication, *FAS* full analysis set, *SD* standard deviation, *TBI* traumatic brain injury

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

[b]≥ 5% of people in any group

[c]Including concomitant ASMs

[d]≥ 10% of people in any group

had only focal seizures at baseline (one individual [1.4%] had only generalised seizures). The mean (SD) PER dose was 2.8 (1.6) mg/day (median, 2.0 mg/day; IQR, 2–4 mg/day; $n = 47$) at treatment initiation and 5.1 (2.3) mg/day (median, 4.0 mg/day; IQR, 4–6 mg/day; $n = 68$) at the last visit. PER was given as monotherapy in 9.6% (7/73) of individuals at baseline and 3.3% (1/30) at the last visit. The mean (SD) number of concomitant ASMs used at the time of PER initiation was 2.1 (1.5).

Retention

Retention rates at 3, 6 and 12 months were, respectively, 86.5% (109/126), 78.7% (96/122) and 65.6% (63/96) in the tumour aetiology subgroup, 92.1% (82/89), 82.8% (72/87) and 71.4% (55/77) in the vascular aetiology subgroup, and 94.5% (69/73), 88.4% (61/69) and 68.3% (41/60) in the TBI aetiology subgroup. Retention rates at 12 months did not differ significantly between the three subgroups (Fig. 6). The mean (95% CI) time under PER treatment over 12 months in the tumour, vascular and TBI aetiology subgroups were 11.2 (10.3−12.0) months, 11.4 (10.4−12.4) and 10.2 (9.5−11.0) months, respectively. The most common reasons for discontinuation over 12 months (≥ 5% of population) were AEs and lack of efficacy in all three subgroups (tumour aetiology, 15.6% [AEs] and 5.2% [lack of efficacy]; vascular aetiology, 16.9% and 6.5%; TBI aetiology, 16.7% and 8.3%).

Effectiveness

In the tumour aetiology subgroup, the monthly frequency of total and focal seizures decreased significantly from a median of 3.0 (mean [SD], 7.2 [12.1]; range, 0.2–60; $n = 85$) at baseline to 0.5 (mean [SD], 2.3 [5.0]; range, 0.0–20.0; $n = 67$) at the last visit ($|Z| = 5.36$; $p < 0.001$), representing a median (mean) reduction from baseline of 88.9% (53.7%). Responder rates (only available for focal seizures) at 12 months and the last visit were 71.2% and 66.7%, respectively, and the corresponding seizure freedom rates were 38.3% and 33.6%, respectively (Fig. 7a). At the last visit, focal seizure worsening was reported for 6.8% of individuals.

In the vascular aetiology subgroup, the monthly frequency of total seizures decreased significantly from a median of 1.3 (mean [SD], 6.6 [29.7]; range, 0.3–240.0; $n = 65$) at baseline to 0.2 (mean [SD], 1.0 [2.0]; range, 0.0–11.7; $n = 58$) at the last visit ($|Z| = 5.50$; $p < 0.001$), representing a median (mean) reduction from baseline of 84.5% (60.7%). The monthly frequency of focal seizures decreased significantly from a median of 1.3 (mean [SD], 2.5 [2.7]; range, 0.3–12.0; $n = 63$) at baseline to 0.2 (mean [SD], 1.0 [2.0]; range, 0.0–11.7; $n = 57$) at the last visit ($|Z| = 5.42$; $p < 0.001$), representing a median (mean) reduction from baseline of 85.7% (60.5%). Data were not available for generalised seizures. Responder rates (only available for focal seizures) at 12 months and the last visit were 80.4% and 70.1%, respectively, and the corresponding seizure freedom rates

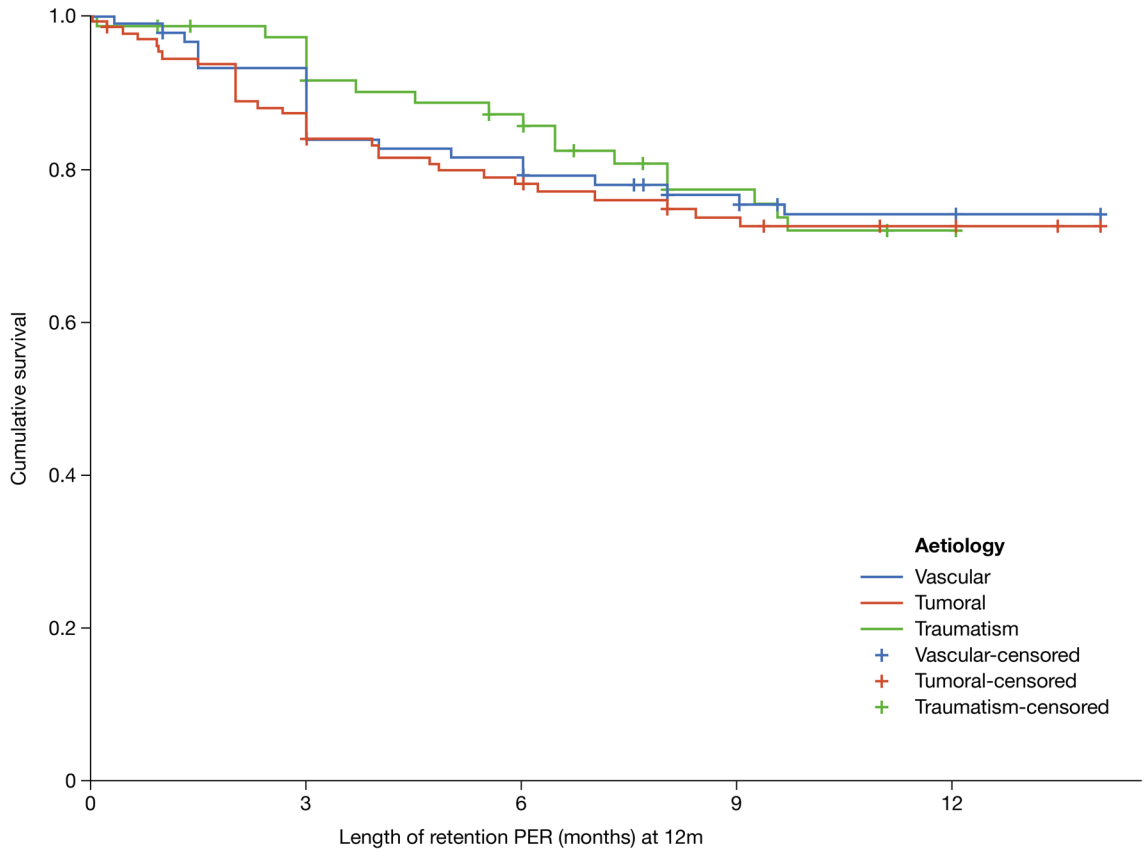


Fig. 6 Kaplan–Meier plot for retention on PER treatment over 12 months in the three structural aetiology subgroups (tumour, vascular and TBI aetiologies; retention population). No statistically significant differences were observed between aetiologies ($p = 0.906$; log rank test). *PER* perampanel, *TBI* traumatic brain injury

were 51.7% and 49.4%, respectively (Fig. 7b). Focal seizure worsening was reported for 6.9% of individuals at the last visit.

In the TBI aetiology subgroup, the monthly frequency of total and focal seizures decreased significantly from a median of 1.3 (mean [SD], 4.9 [8.6]; range, 0.3–43.3; $n = 46$) at baseline to 0.2 (mean [SD], 3.0 [11.7]; range, 0.0–72.0; $n = 43$) at the last visit ($|Z| = 4.47$; $p < 0.001$), representing a median (mean) reduction from baseline of 85.3% (55.2%). Responder rates (only available for focal seizures) at 12 months and the last visit were 87.2% and 80.4%, respectively, and the corresponding seizure freedom rates were 37.5% and 42.1%, respectively (Fig. 7c). At the last visit, 5.4% of individuals had focal seizure worsening.

Responder and seizure freedom rates at the last visit did not differ significantly between the three subgroups.

Safety and Tolerability

In the tumour aetiology subgroup, AEs were experienced by 36.2% of individuals and the most frequently reported AEs (≥5% of subgroup) were dizziness/vertigo (13.8%), somnolence (9.5%) and irritability (6.9%) (Table 3). Overall, 15.6% of individuals discontinued because of AEs over 12 months. Psychiatric AEs were experienced by 13.9% of individuals and 8.8% of those who discontinued because of AEs had psychiatric AEs. In total, 33.3% (4/12) of individuals who experienced psychiatric AEs and 37.5% (3/8) of

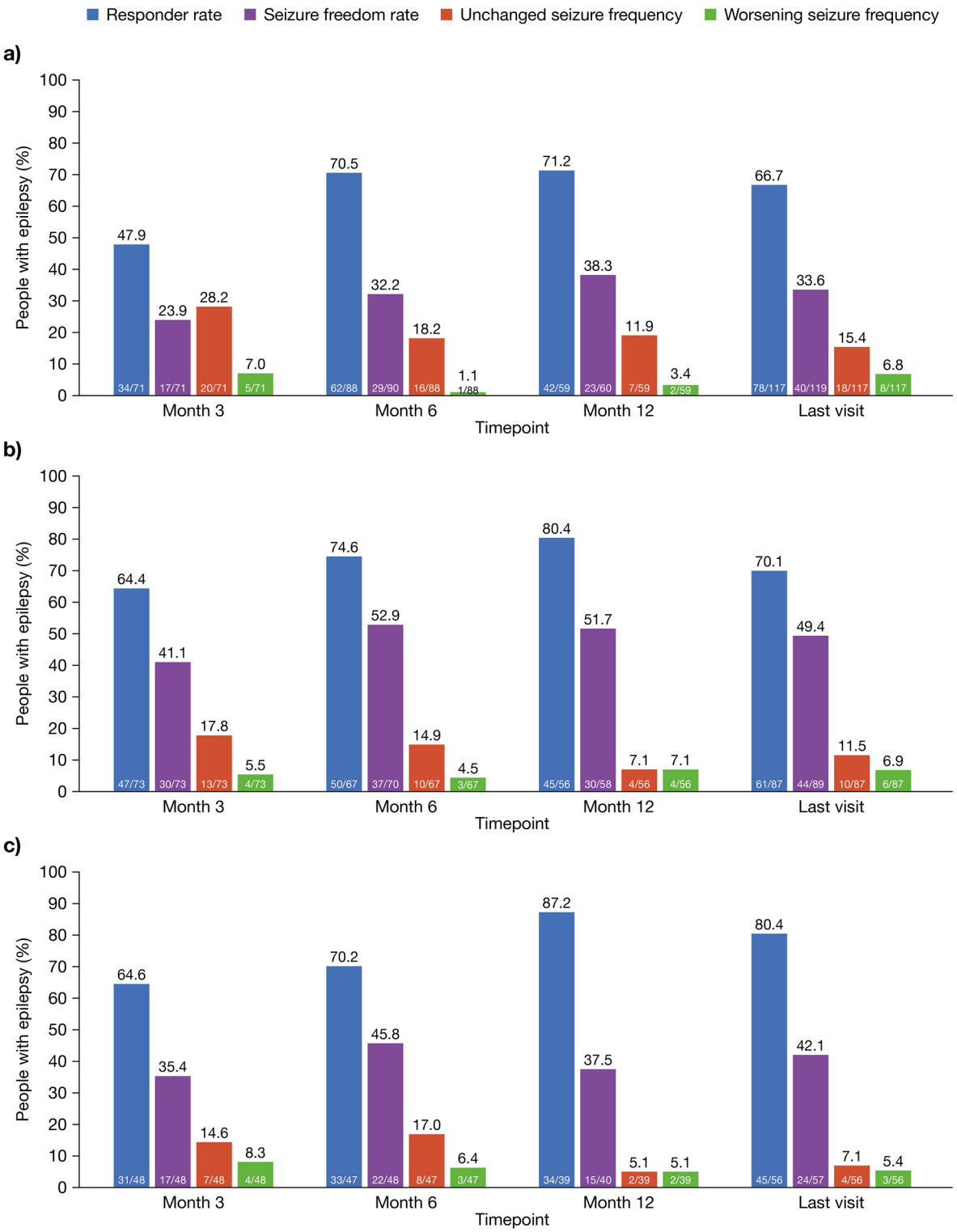


Fig. 7 Responder rate, seizure freedom rate and the proportions of individuals with unchanged and worsening seizure frequency for focal seizures at 3, 6 and 12 months and the last visit in **a** tumour aetiology subgroup, **b** vascular aetiology subgroup, **c** TBI aetiology subgroup (effectiveness population). *TBI* traumatic brain injury

Table 3 Summary of AEs in the structural aetiology subgroups (tumour, vascular and TBI aetiology; tolerability population)

Characteristic	Tumour aetiology $N=127$	Vascular aetiology $N=93$	TBI aetiology $N=73$
People with any AE			
N[a]	116	91	71
n (%)	42 (36.2)	42 (46.2)	34 (47.9)
Most frequently reported AEs,[b] n (%)			
N[a]	116	91	71
Dizziness/vertigo	16 (13.8)	15 (16.5)	9 (12.7)
Somnolence	11 (9.5)	15 (16.5)	11 (15.5)
Irritability	8 (6.9)	13 (14.3)	9 (12.7)
Sedation	4 (3.4)	0	0
Behavioural disorders	1 (0.9)	1 (1.1)	1 (1.4)
Fatigue	2 (1.7)	1 (1.1)	1 (1.4)
Instability/ataxia	2 (1.7)	7 (7.7)	5 (7.0)
Aggression/aggressiveness	3 (2.6)	1 (1.1)	1 (1.4)
Mood disturbance	0	0	1 (1.4)
Weight increased	0	0	1 (1.4)
Headache	0	2 (2.2)	0
Depression	2 (1.7)	6 (6.6)	1 (1.4)
Anxiety	2 (1.7)	1 (1.1)	4 (5.6)
Psychosis	0	2 (2.2)	0
Attempted autolysis	0	1 (1.1)	0
Confusion	0	1 (1.1)	0
Hallucinations/delusions	0	1 (1.1)	0
Memory disturbance	0	1 (1.1)	2 (2.8)
Nausea/vomiting	0	0	2 (2.8)
Malaise general	0	0	3 (4.2)
Speech disturbance	1 (0.9)	0	1 (1.4)
Disturbance in attention/concentration	0	0	1 (1.4)
People with AEs leading to discontinuation over 12 months			
N[a]	96	77	60
n (%)	15 (15.6)	14 (18.2)	12 (20.0)

Table 3 continued

Characteristic	Tumour aetiology $N = 127$	Vascular aetiology $N = 93$	TBI aetiology $N = 73$
Most frequent AEs[c] in people who discontinued over 12 months, *n* (%)			
N[a]	96	77	60
Dizziness/vertigo	7 (7.3)	6 (7.8)	5 (8.3)
Sedation	4 (4.2)	0	0
Behavioural disorders	1 (1)	1 (1.3)	1 (1.7)
Irritability	4 (4.2)	5 (6.5)	6 (10.0)
Somnolence	2 (2.1)	5 (6.5)	2 (3.3)
Instability/ataxia	1 (1)	4 (5.2)	3 (5.0)
Aggression/aggressiveness	3 (3.1)	0	1 (1.7)
Fatigue	0	1 (1.3)	0
Depression	0	2 (2.6)	1 (1.7)
Headache	0	0	0
Anxiety	0	0	1 (1.7)
Bradypsychia	1 (1.0)	0	0
Drooling	1 (1.0)	0	0
Joint pain	1 (1.0)	0	0
Personality disorder	1 (1.0)	0	0
Speech disturbance	1 (1.0)	0	0
Memory disturbance	0	1 (1.3)	1 (1.7)
Disturbance in attention/concentration	0	0	1 (1.7)
People with any psychiatric AE, *n* (%)			
N[a]	115	91	71
n (%)	16 (13.9)	18 (19.8)	15 (21.1)
People with psychiatric AEs who discontinued[d]			
N[b]	114	88	71
n (%)	10 (8.8)	7 (8.0)	8 (11.3)

AE adverse event, *TBI* traumatic brain injury

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

[b]≥ 1% in any group

[c]≥ 0.5% in any group

[d]These people had psychiatric AEs but it was not possible to determine if it was these AEs that led to discontinuation

those who discontinued with psychiatric AEs had psychiatric comorbidities at baseline. The mean (SD) PER dose in individuals who discontinued with psychiatric AEs was 5.6 (2.6) mg/day (median, 4; range, 2–10).

In the vascular aetiology subgroup, AEs were experienced by 46.2% of individuals and the most frequently reported AEs (≥ 5% of subgroup) were dizziness/vertigo (16.5%), somnolence (16.5%), irritability (14.3%), instability/ataxia (7.7%) and depression (6.6%) (Table 3). Over 12 months, 18.2% of individuals discontinued because of AEs. Psychiatric AEs were experienced by 19.8% of individuals and 8.0% of those who discontinued because of AEs had psychiatric AEs. Overall, 46.7% (7/15) of individuals who experienced psychiatric AEs and 80.0% (4/5) of those who discontinued with psychiatric AEs had psychiatric comorbidities at baseline. The mean (SD) PER dose in individuals who discontinued with psychiatric AEs was 4.9 (1.9) mg/day (median, 4; range, 2–10).

In the TBI aetiology subgroup, AEs were experienced by 47.9% of individuals and led to discontinuation of 20.0% over 12 months (Table 3). The most frequently reported AEs (≥ 5% of subgroup) were somnolence (15.5%), dizziness/vertigo (12.7%), irritability (12.7%), instability/ataxia (7.0%) and anxiety (5.6%). Psychiatric AEs were reported by 21.1% of individuals and 11.3% of those who discontinued because of AEs had psychiatric AEs. In total, 36.4% (4/11) of individuals who experienced psychiatric AEs and 60.0% (3/5) of those who discontinued with psychiatric AEs had psychiatric comorbidities at baseline. The mean (SD) PER dose in those who discontinued with psychiatric AEs was 5.1 (2.3) mg/day (median, 4; range, 2–12).

The incidence of AEs and the rate of discontinuation due to AEs did not differ significantly between the three subgroups.

DISCUSSION

This post hoc analysis of data from over 5500 people with epilepsy included in the PERMIT Extension study demonstrated that PER was effective and generally well tolerated when used to treat individuals with wide range of epilepsy aetiologies in everyday clinical practice. Retention, which is considered to reflect the overall effectiveness and tolerability of ASMs in clinical practice [25], differed significantly between the aetiology subgroups, being highest in the genetic aetiology subgroup and lowest in the immune aetiology subgroup. The types of AEs reported across the aetiology subgroups were consistent with PER's known safety profile [11, 12], with no idiosyncratic AEs emerging for specific aetiologies. Psychiatric AEs were generally more common in individuals with pre-existing psychiatric comorbidity and clinicians should be aware of this when treating such patients with PER.

As shown previously [20, 26–29], PER was particularly effective in individuals with a presumed genetic aetiology, with almost 50% of this subgroup achieving seizure freedom (total seizures) after 12 months of PER treatment. Among the aetiology subtypes, this subgroup experienced the highest seizure freedom and responder rates. In addition, the incidence of AEs and the rate of discontinuation due to AEs were lowest in the genetic aetiology subgroup. These findings are consistent with those of a multicentre project based on the framework of the Network for Therapy in Rare Epilepsies (NETRE), conducted in 137 individuals with 79 different aetiologies, which demonstrated that PER was efficacious and well tolerated in individuals with a range of rare genetic epilepsies (including mutations in *SCN1A*, *GNAO1*, *PIGA*, *PCDH19*, *SYNGAP1*, *CDKL5*, *NEU1*, and *POLG*), indicating that PER may have a targeted effect related to glutamate transmission [30]. Unlike the other aetiology subgroups, the majority of individuals in the genetic aetiology subgroup had only generalised seizures, and, as previously reported [26], the majority of these individuals had IGEs, which are thought to have a more favourable prognosis than other types of epilepsy [31]. Further research is therefore required to determine the effects of PER in individuals with other types of genetic epilepsies, which may be associated with more severe seizure outcomes.

Structural aetiology was the most common type of aetiology in the current study, representing over a third of the study population. This type of aetiology refers to abnormalities visible on structural neuroimaging that are likely to be the cause of an individual's seizures [1]. Such abnormalities may be acquired (e.g. following a stroke, trauma, or infection) or genetic (e.g. malformations of cortical development) [1], and consequently encompass a variety of aetiologies. The large size of the structural aetiology subgroup in the current study allowed meaningful subanalyses to be conducted for the subgroups of individuals who had tumour, vascular and TBI-related aetiologies. However, no significant between-group differences were observed for these three subcategories of structural aetiology. In a retrospective analysis of 62 children with newly diagnosed focal epilepsy who were treated with PER monotherapy at a single centre in China, the responder rate (≥ 50% seizure frequency reduction) in 14 children diagnosed with structural aetiology was 50.0% after 6 months [32]. In the current study, the structural aetiology subgroup had a median age of 42.0 years and only 4.3% were initially treated with PER as monotherapy, indicating a more treatment-resistant population (mean number of previous ASMs, 5.9). Nevertheless, after 6 months, the responder rate (total and focal seizures) was 45.9% and 15.7% of individuals were seizure free. Several studies have assessed the use of PER in the treatment of people with tumour aetiology in the clinical practice setting [33–39], and these have also been included in systematic reviews [40, 41]. Over a follow-up duration of 6–12 months, responder rates ranged from 67% to 88%, seizure freedom rates from 25% to 50%, and the incidence of AEs from 18% to 52% [36–39]. The findings of the current study are consistent with these reports: 6-month responder and seizure freedom rates (for focal seizures) were 70.5% and 32.2%, respectively, and corresponding rates at 12 months were 71.2% and 38.3%, respectively; the incidence of AEs in the tumour aetiology subgroup was 36.2%. Glutamatergic mechanisms (including excessive glutamate release, glutamate receptor activation and altered expression of glutamate transporters) are thought to play a central role in both brain tumour pathophysiology and epileptogenesis [41–44], and there is evidence suggesting a bidirectional association between brain tumours and tumour-associated epilepsy, whereby tumour growth may cause seizures, which in turn promote tumour progression [41]. Preclinical studies (in vitro and animal models) have indicated that PER (an AMPA receptor antagonist that selectively inhibits glutamate receptors on postsynaptic membranes [3]) may possess antitumour and neuroprotective activity [45–50]. However, similar effects have been demonstrated for other ASMs in preclinical models [48, 51, 52], and further research is therefore required to assess whether the preclinical effects of PER translate into the clinical setting.

Infectious aetiology is one that directly results from a known infection in which seizures are a core symptom of the disorder (e.g. cerebral toxoplasmosis, cerebral malaria, neurocysticercosis, tuberculosis, HIV), as opposed to seizures occurring within the context of an acute infection, such as meningitis [1]. As such, this cause of epilepsy is preventable. Worldwide, it represents the most common type of aetiology [1], although, in PERMIT Extension (which largely comprised individuals from Europe and North America), it represented only 1.7% of the study population. The presence of psychiatric comorbidity and learning disability at baseline were highest in this subgroup. Although the reasons for this are not clear, it might be related to the presence of large lesions in the brain caused by the infection.

In the current study, individuals with an immune aetiology were the least likely to respond to PER treatment and achieve seizure freedom, and also experienced the highest incidence of AEs and were the most likely to discontinue because of AEs. Both innate and adaptive immunity may be involved in epilepsy [53, 54] and a wide range of immune-mediated epilepsies have been identified, although the proportion of individuals with immune-mediated epilepsy is low overall (4–8%) [55–57]. ASMs are often unsuccessful in controlling seizures in immune-mediated epilepsy [58, 59], and PER may therefore be at least as effective as other ASMs in this

setting. Treatment should target the underlying cause of immune system dysregulation and early diagnosis of the cause of immune-mediated seizures is required in order to ensure that appropriate treatment is initiated as soon as possible; for example, it is important to identify acute symptomatic seizures secondary to autoimmune encephalitis, since this has well-defined diagnostic criteria and requires early treatment with immunotherapy, including first-line treatment with high-dose intravenous corticosteroids, with or without intravenous immunoglobulins or plasma exchange [59]. Novel immunomodulatory treatment options are emerging, targeting specific components of the immune system (such as immune cells or cytokines), which may allow individualised treatment of immune-mediated epilepsies in the future, providing that the specific aetiology is identified early [59].

The large size of PERMIT Extension allowed meaningful subgroup analyses to be conducted. Further strengths of the study were its relatively long duration, in comparison with clinical trials, and that it was conducted under routine clinical practice conditions. The study was limited in being a post hoc analysis of a pooled analysis, which itself had limitations, as previously reported [23], such as the fact that data were not available for all individuals at every timepoint. In addition, aetiology diagnosis relied on the judgment of the treating clinicians, which may have been incorrect or inconsistent, and, as a result of the limited numbers of specific aetiologies reported, only broader groups of aetiology could be analysed. A further limitation was that the unknown aetiology subgroup included individuals for whom information on aetiology was missing, in addition to those categorised as having unknown aetiology, and could therefore not be assessed as a 'pure' unknown aetiology subgroup. Finally, despite the large study population, sample sizes for some outcome assessments were too small to draw reliable conclusions.

CONCLUSION

This study demonstrated that PER was effective and generally well tolerated when used to treat individuals with a range of epilepsy aetiologies in clinical practice. Variability in the effectiveness and tolerability of PER across the aetiology subgroups indicates that PER may be particularly useful for individuals with specific epilepsy aetiologies. Such evidence requires confirmation in other studies but may allow the future facilitation of individualised treatment approaches.

ACKNOWLEDGEMENTS

Medical Writing and Editorial Assistance Editorial assistance in the preparation of this article was provided by John Scopes and Eliana D'Araio of m*X*m Medical Communications. Support for this assistance was funded by Eisai Europe Ltd. Patricia Santagueda provided statistical analysis.

Authorship All authors whose names appear on this paper made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agree to be accountable for all aspects of the work.

Author Contributions. Adam Strzelczyk, Marta Maschio, Max C. Pensel, Antonietta Coppola, Satoru Takahashi, Shuichi Izumoto, Eugen Trinka, Sheri Cappucci, Ricardo Sainz-Fuertes, and Vicente Villanueva: contributed equally to the drafting and critical review of the manuscript. Vicente Villanueva: responsible for data extraction and analysis with a statistician's support. All authors contributed to the article and approved the submitted version.

Funding. This work was supported by Eisai Europe Ltd. The Rapid Service Fee was funded by Eisai Europe Ltd.

Data Availability. The datasets generated during and/or analysed during the current study

are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Adam Strzelczyk reports personal fees and grants from Angelini Pharma, Bicodex, Desitin Arzneimittel, Eisai, Jazz Pharmaceuticals, Precisis, Takeda, UCB Pharma, and UNEEG medical. Marta Maschio has no conflict of interest. Max C. Pensel has no conflict of interest. Antonietta Coppola has received speaker fees from Eisai and consultancy fees from GW Pharmaceuticals/Jazz Pharmaceuticals, UCB and Bial-Portela & C^{a}. Satoru Takahashi has no conflict of interest. Shuichi Izumoto has no conflict of interest. Eugen Trinka reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Bial-Portela & C^{a}, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, and Actavis. His institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Österreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. Sheri Cappucci is an employee of Eisai. Ricardo Sainz-Fuertes is an employee of Eisai. Vicente Villanueva has participated in advisory boards and symposia organised by Angelini, Bial, Biocodex, Eisai Inc, Jazz Pharmaceuticals, Novartis, Takeda, UCB and Xenon.

Ethical Approval. Each study in PERMIT was approved by its own independent ethics committee, and all committees were notified about PERMIT. Further approval was not required for participation in PERMIT, as per current legislation. In PROVE, the study protocol was approved by institutional review boards or independent ethics committees at each site. PROVE was conducted under a waiver of consent, due to its retrospective design, which was approved by the ethics committees at each site, and no sites requiring consent were included in the study. All studies included in this article were approved by the appropriate ethics committees and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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