**Supplementary material**

**MATERIALS AND Methods**

**Study design**

The PERMIT study was a pooled analysis of real-world data from 44 prospective, retrospective and cross-sectional studies and work groups in which people with focal and generalized epilepsy were treated with PER, full details of which have been published previously (28). These prospective, retrospective and cross-sectional studies were identified by a systematic PubMed literature search, supported by searches of abstracts from key epilepsy congresses from 2012 to December 2019 (28). De-identified individual participant data were pooled together for baseline number of seizures, type of epilepsy/seizures, prior ASMs, dosage, effectiveness at various time points, and adverse events (AEs) (28).

Effectiveness was assessed after 3, 6, and 12 months of PER treatment and at final follow-up (i.e., the last observation of each individual, independent of when it occurred [last observation carried forward]; defined as the ‘last visit’) (28). Safety and tolerability were assessed for the duration of PER treatment (28). Each study included in PERMIT was approved by its own independent ethics committee and letters were sent to these ethics committees to inform them about the PERMIT study; as per current legislation, additional ethics committee approval was not required for participation in PERMIT (28). All participants gave their informed consent prior to inclusion in the studies, according to the protocol. A *post-hoc* subgroup analysis was conducted to assess the effectiveness, safety and tolerability of PER in the subgroup of people with IGE who were included in PERMIT.

**Study population**

Studies included in PERMIT employed broad inclusion/exclusion criteria, to be representative of people with epilepsy (PWE) encountered in clinical practice (28). PWE who initiated PER for the treatment of epilepsy was included (28). PWE were excluded if records contained insufficient data for analysis (28). Duplicate data from PWE included in more than one study were also excluded (28). The current study included all PWE from PERMIT who had IGE.

**Study assessments**

Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised 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 PER initiation), and seizure freedom was defined as no seizures since at least the prior visit (either 3 or 6 months, depending on the timepoint at which seizure freedom was assessed). Since the definition of ‘baseline’ differed between studies included in PERMIT, baseline seizure frequency was standardized as number of seizures per month.

Effectiveness was assessed by seizure type (total seizures, GTCS, myoclonic seizures, absence seizures). Myoclonic-tonic-clonic seizures were included as GTCS. Percentage reduction from baseline in the number of days per month with myoclonic seizures was included as an additional effectiveness assessment. Safety and tolerability were assessed by evaluating AEs, AEs leading to discontinuation, psychiatric AEs, and psychiatric AEs leading to discontinuation. Information relating to PER dosing and use of concomitant ASMs was also evaluated.

**Statistical analysis**

The statistical methodology employed in PERMIT has been reported previously (28). The Full Analysis Set (FAS) included all PWE treated with PER. The Retention Population included PWE from the FAS whose PER status was known at some point during the first 12 months after starting treatment (including those with ongoing PER treatment at 12 months, those who stopped PER prior to 12 months and those lost to follow-up/end of study follow-up prior to 12 months). The Effectiveness Population included PWE from the FAS who had at least one effectiveness measurement available. The Tolerability Population included PWE from the FAS for whom data on AEs were available.

There was great heterogeneity in the objectives of each study included in the pooled analysis and therefore in the information reported. As previously described, PERMIT attempted to combine reported information in the most complete way possible (28). Missing data were not imputed, except in cross-sectional studies, in which the last visit datum was captured to include in the established cut-off points. When an observation timepoint did not match the established cut-off points, the following allocations were made: observations performed between 1.5–4.5 months were allocated to the 3-month visit; those performed between 4.5–9 months were allocated to the 6-month visit; and those performed between 9–15 months were allocated to the 12-month visit. A ‘final’ variable was created in which the last observation of each individual was included, independently of when it occurred (defined as ‘last visit’). No hypothesis was defined, and no systematic review of the individual PWE was considered, due to the heterogeneity of individual samples and the different objectives of each study; therefore, individual studies were not treated as clusters.

Quantitative variables were described as mean, standard deviation (SD), median, minimum and maximum values, together with the number of valid cases and confidence intervals (CIs) or interquartile range (25th percentile to 75th percentile). Qualitative variables were described as absolute frequencies and percentages. Data were not available for all PWE at every timepoint; therefore, for each variable, the total number of PWE for whom the datum in question was available was stated and used as the denominator for frequency analyses. Retention was studied within the first 12 months of follow-up using Kaplan–Meier methodology. 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’s exact test, as appropriate. For quantitative variables, the Student’s 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.

**Supplementary Table S1. 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 who did not receive previous VPA (‘No previous VPA’) and PWE who received previous VPA (‘Previous VPA’) (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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No previous VPA n=116** | **Previous VPA**  **n=172** | **p-value** |
| Total seizures | | | |
| Responder rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 86.6 (71/82)  88.6 (70/79)  88.0 (66/75)  86.5 (90/104) | 81.8 (99/121)  79.5 (93/117)  84.0 (100/119)  79.7 (122/153) | NS  NS  NS  NS |
| Seizure freedom rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 63.4 (52/82)  78.5 (62/79)  68.0 (51/75)  65.4 (68/104) | 58.7 (71/121)  71.8 (84/117)  69.7 (83/119)  62.1 (95/153) | NS  NS  NS  NS |
| Unchanged seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 9.8 (8/82)  5.1 (4/79)  5.3 (4/75)  4.8 (5/104) | 7.4 (9/121)  10.3 (12/116)  8.4 (10/119)  7.9 (12/152) | NS  NS  NS  NS |
| Worsening seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 2.4 (2/82)  2.5 (2/79)  2.7 (2/75)  2.9 (3/104) | 4.1 (5/121)  4.3 (5/116)  1.7 (2/119)  3.3 (5/152) | NS  NS  NS  NS |
| GTCS | | | |
| Responder rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 83.9 (47/56)  87.3 (48/55)  88.2 (45/51)  88.9 (56/63) | 76.8 (73/95)  80.7 (71/88)  90.7 (78/86)  82.1 (87/106) | NS  NS  NS  NS |
| Seizure freedom rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 62.5 (35/56)  76.4 (42/55)  62.7 (32/51)  63.5 (40/63) | 51.6 (49/95)  67.0 (59/88)  65.1 (56/86)  57.5 (61/106) | NS  NS  NS  NS |
| Unchanged seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 10.7 (6/56)  5.5 (3/55)  3.9 (2/51)  3.2 (2/63) | 9.5 (9/95)  9.2 (8/87)  2.3 (2/86)  4.8 (5/105) | NS  NS  NS  NS |
| Worsening seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 3.6 (2/56)  3.6 (2/55)  3.9 (2/51)  3.2 (2/63) | 8.4 (8/95)  3.4 (3/87)  1.2 (1/86)  4.8 (5/105) | NS  NS  NS  NS |
| Myoclonic seizures | | | |
| Responder rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 100.0 (14/14)  100.0 (14/14)  92.9 (13/14)  95.7 (22/23) | 79.5 (31/39)  87.5 (35/40)  87.5 (35/40)  81.1 (43/53) | NS  NS  NS  NS |
| Seizure freedom rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 71.4 (10/14)  100.0 (14/14)  85.7 (12/14)  78.3 (18/23) | 53.8 (21/39)  77.5 (31/40)  77.5 (31/40)  67.9 (36/53) | NS  NS  NS  NS |
| Unchanged seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 0 (0/14)  0 (0/14)  0 (0/14)  0 (0/23) | 7.7 (3/39)  10.0 (4/40)  10.0 (4/40)  17.0 (9/53) | NS  NS  NS  NS |
| Worsening seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 0 (0/14)  0 (0/14)  7.1 (1/14)  4.3 (1/23) | 5.1 (2/39)  2.5 (1/40)  2.5 (1/40)  1.9 (1/53) | NS  NS  NS  NS |
| Absence seizures | | | |
| Responder rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 87.5 (14/16)  100.0 (14/14)  100.0 (15/15)  100.0 (15/15) | 100.0 (15/15)  100.0 (11/11)  100.0 (14/14)  100.0 (18/18) | NS  NP  NP  NP |
| Seizure freedom rate, % (n/N)  Month 3  Month 6  Month 12  Last visit | 75.0 (12/16)  85.7 (12/14)  86.7 (13/15)  86.7 (13/15) | 100.0 (15/15)  100.0 (11/11)  100.0 (13/13)  100.0 (18/18) | NS  NS  NS  NS |
| Unchanged seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 6.3 (1/16)  0 (0/14)  0 (0/15)  0 (0/15) | 0 (0/15)  0 (0/11)  0 (0/14)  0 (0/18) | NS  NP  NP  NP |
| Worsening seizure frequency, % (n/N)  Month 3  Month 6  Month 12  Last visit | 0 (0/16)  0 (0/14)  0 (0/15)  0 (0/15) | 0 (0/15)  0 (0/11)  0 (0/14)  0 (0/18) | NP  NP  NP  NP |

GTCS, generalized tonic-clonic seizures; NP, not possible to perform test for statistical significance; NS, not significant; PWE people with epilepsy; VPA, valproate

**Supplementary Table S2. Summary of safety and tolerability in (A) the ‘No previous VPA’ and ‘Previous VPA’ subgroups and (B) the subgroups of PWE with ‘GE with GTCS only’, ‘JME’ and ‘Absence epilepsy’ (Tolerability Population)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **A** | **No previous VPA** | | **Previous VPA** | | **p-value** |
| Number of PWE | N=115 | | N=172 | |  |
| PWE with any AE, n (%) | 42 (36.5) | | 81 (47.1) | | NSa |
| Most frequently reported AEsb, n (%)  Irritability  Dizziness/vertigo  Somnolence | 10 (8.7)  12 (10.4)  5 (4.3) | | 17 (9.9)  16 (9.3)  13 (7.6) | | -  -  - |
| PWE with AEs leading to discontinuation,n (%) | 20 (17.4) | | 42 (24.4) | | NSa |
| Most frequently reported AEsc in PWE who discontinued, n (%)  Irritability  Dizziness/vertigo  Nausea/vomiting  Somnolence  Depression  Weight increased | 3 (2.6)  2 (1.7)  2 (1.7)  1 (0.9)  0  0 | | 6 (3.5)  4 (2.3)  1 (0.6)  2 (1.2)  2 (1.2)  2 (1.2) | | -  -  -  -  -  - |
| PWE with any psychiatric AE, n (%) | 10 (10.9)d | | 21 (13.0)e | | NSa |
| PWE with psychiatric AEs who discontinuedf, n (%) | 4 (4.0)g | | 15 (9.1)h | | NSa |
| **B** | **GE with GTCS only** | **JME** | | **Absence epilepsy** | **p-value** |
| Number of PWE | N=77 | N=96 | | N=40 |  |
| PWE with any AE, n (%) | 40 (51.9) | 39 (40.6) | | 16 (40.0) | NSa |
| Most frequently reported AEsb, n (%)  Irritability  Dizziness/vertigo  Somnolence  Fatigue  Nausea/vomiting | 10 (13.0)  8 (10.4)  6 (7.8)  2 (2.6)  4 (5.2) | 11 (11.5)  7 (7.3)  6 (6.3)  6 (6.3)  0 | | 5 (12.5)  2 (5.0)  5 (12.5)  0  0 | -  -  -  - |
| PWE with AEs leading to discontinuation,n (%) | 10 (14.3)i | 9 (11.0)j | | 5 (13.2)k | NSa |
| Most frequently reported AEsl in PWE who discontinued, n (%)  Irritability  Dizziness/vertigo  Nausea/vomiting  Anxiety  Depression  Somnolence  Psychosis | 2 (2.9)i  2 (2.9)i  3 (4.3)i  2 (2.9)i  0i  0i  0i | 3 (3.7)j  2 (2.4)j  0j  0j  1 (1.2)j  2 (2.4)j  0j | | 3 (7.9)k  0k  0k  0k  1 (2.6)k  0k  1 (2.6)k | -  -  -  -  -  - |
| PWE with any psychiatric AE, n (%) | 17 (22.1) | 22 (22.9) | | 10 (25.0) | NSa |
| PWE with psychiatric AEs who discontinuedf, n (%) | 7 (9.6)m | 6 (6.5)n | | 5 (12.5) | NSa |

aChi-squared test; b≥5% of PWE; c≥1% of PWE; dN=92; eN=161; fThese PWE had psychiatric AEs but it was not possible to determine if it was these AEs that led to discontinuation; gN=100; hN=165; iN=70; jN=82; kN=38; l≥2% of PWE; mN=73; nN=93. AE, adverse event; NS, not significant; GE, generalized epilepsy; GTCS, generalized tonic-clonic seizures; JME, juvenile myoclonic epilepsy; PWE, people with epilepsy; VPA, valproate.

**Supplementary Figure S1. Kaplan–Meier curve for retention (12 months; Retention Population)**

Chart, line chart

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