Perampanel in Real-World Clinical Care of Patients with Epilepsy at Carle Foundation Hospital, Urbana, Illinois: a Regional Comparison of Results from PROVE Study 506

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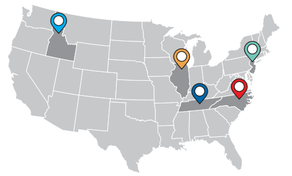
RATIONALE

- Real-world retrospective studies can provide information on the effectiveness, safety, tolerability, and characteristics of a drug or device, outside the relative confines of a clinical efficacy study
- Perampanel is a once-daily oral anti-seizure drug (ASD) for partial-onset seizures (POS) and primary generalized tonic-clonic (PGTC) seizures[1,2]
  - In the US, perampanel is approved for the treatment of POS (adjunctive and monotherapy) in patients 4 years of age and above, and as adjunctive treatment of PGTC seizures in patients 12 years of age and above[1]
- There are limited data on the real-world use of perampanel in the US as an ASD in routine clinical care in patients with epilepsy, and such data may help to inform patient management
- The PROVE Study (Perampanel Real-world Evidence; NCT03208660; Study 506) was a multicenter, non-interventional, retrospective Phase IV study designed to assess the retention rate, dosing experience, efficacy, and safety of perampanel when administered to patients with epilepsy during routine clinical care
- Here, we report results from an analysis of the PROVE Study to compare outcomes for patients who received perampanel at a single study site, the Carle Foundation Hospital in Urbana, Illinois, US (Site #1001), and patients who received perampanel across all other study sites
  - Four further PROVE Study site analyses are being presented at this meeting (Posters 1.306, 3.308, 3.315, and 3.316; Figure 1)
  - Additional posters presented at this meeting report results from the PROVE Study for: the overall population (Poster 1.312); adult patients (aged ≥18 years; Poster 1.311); adolescent patients (aged 12 to <18 years; Poster 2.209); older pediatric patients (aged 4 to <12 years; Poster 3.303); younger pediatric patients (aged <4 years; Poster 1.313); effect of enzyme-inducing ASDs (EIASDs; Poster 3.301); and perampanel monotherapy (Poster 1.304)

Figure 1. Map of site-specific analyses of the PROVE Study presented at the 73rd Annual Meeting of the American Epilepsy Society, Baltimore, MD, USA, December 6–10, 2019



Scan QR code to view analyses of other US-regional sites

- The Carle Foundation Hospital in Urbana, Illinois, US (known as Site #1001)
- The Idaho Comprehensive Epilepsy Center in Boise, Idaho, US (known as Site #1003)
- Le Bonheur Children's Hospital in Memphis, Tennessee, US (known as Site #1007)
- Northeast Regional Epilepsy Group in Hackensack, New Jersey, US (known as Site #1009)
- Duke University Medical Center in Durham, North Carolina, US (known as Site #1023)

METHODS

- The PROVE Study included patients with a diagnosis of epilepsy who initiated perampanel treatment after January 1, 2014. The study was ongoing over a 2-year period, completed on March 15, 2019, and was conducted at sites across the US
  - Site #1001 was selected for comparison with all other sites as one of the top 5 centers with the greatest number of enrolled patients
- Patients attended their usual epilepsy clinic and were prescribed perampanel on the basis of the treating clinician's recommendation
- Data were obtained from medical records of patients treated with perampanel and, where available, included:
  - ASD history
  - Seizure frequency from seizure diaries or investigator assessment of therapeutic response
  - Perampanel titration and dosage data
  - Safety data including treatment-emergent adverse events (TEAEs) and serious TEAEs
- The Safety Analysis Set included patients with a diagnosis of epilepsy who received perampanel at any time after January 1, 2014 and for whom safety information was obtained
- The Full Analysis Set included all patients with a diagnosis of epilepsy who received perampanel at any time after January 1, 2014 and for whom seizure frequency data were recorded
- This analysis assessed the following endpoints in patients who received perampanel at Site #1001 and across all other sites:
  - The primary efficacy endpoint was the retention rate (proportion of patients in the Safety Analysis Set remaining on perampanel at 3, 6, 12, 18, and 24 months following treatment initiation)
  - Secondary efficacy endpoints, assessed in the Full Analysis Set, included:
    - Median percent change in seizure frequency per 28 days from baseline
    - 50% and 75% responder rates and seizure-freedom rates (proportion of patients with a ≥50%, ≥75%, or 100% reduction, respectively, in seizure frequency per 28 days from baseline)
  - The proportion of patients who had an improvement, no change/stable, or a worsening of seizures (based on the investigator's impression of seizure effect as assessed at the end of treatment) was assessed in the Safety Analysis Set
  - Secondary safety endpoints, assessed in the Safety Analysis Set, included:
    - Maximum and average perampanel dose
    - Incidence of TEAEs

Statistical analysis

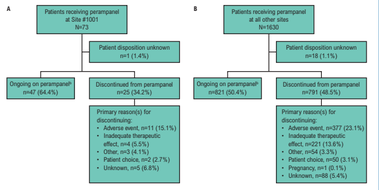
- Retention rates at 24 months, proportion of patients who had improvement in seizures, and the incidence of TEAEs between Site #1001 and all other sites were compared using a χ^2-test

RESULTS

Patients

- Of 1703 patients in the final Safety Analysis Set, 73 (4.3%) patients received perampanel at Site #1001 and 1630 (95.7%) patients received perampanel at all other sites
- Patient disposition for patients receiving perampanel at Site #1001 and across all other sites is outlined in Figures 2A and 2B, respectively

Figure 2. Patient disposition for patients (A) at the Carle Foundation Hospital (Site #1001) and (B) across all other sites[a]



[a]All enrolled and treated patients
[b]At time of date of data collection. This will occur at different time points on treatment for different patients

- Patient demographic and clinical characteristics during baseline for the Safety Analysis Set are shown in Table 1
- Most patients received 1–3 concomitant ASDs during baseline (Site #1001, n=63 [86.3%]; all other sites, n=1258 [77.2%]; taken at date of first dose of perampanel); the most common concomitant ASDs at Site #1001 were levetiracetam (n=28 [38.9%]), clobazam (n=20 [27.8%]), and lamotrigine (n=18 [25.0%]), and across all other sites were levetiracetam (n=552 [34.4%]), lacosamide (n=456 [28.4%]), and clobazam (n=387 [24.1%])
  - A total of 25 (34.7%) patients at Site #1001 and 330 (20.6%) patients at all other sites were receiving concomitant EIASDs; the most common were oxcarbazepine (n=6 [8.3%] and n=157 [9.8%], respectively), carbamazepine (n=11 [15.3%] and n=79 [4.9%], respectively), and phenytoin (n=8 [11.1%] and n=59 [3.7%], respectively)

OVERVIEW

- There are limited data available on the real-world use of perampanel as an anti-seizure drug in routine clinical care of patients with epilepsy
- The PROVE Study (Perampanel Real-world Evidence; NCT03208660) was a retrospective Phase IV study of patients with epilepsy who initiated perampanel after January 1, 2014. Here, we report results from the final analysis of the PROVE Study to assess differences in retention rates, dosing experience, efficacy, and safety between patients at a single study site, the Carle Foundation Hospital in Urbana, Illinois, US (Site #1001), and patients across all other study sites
- Following 24 months of perampanel treatment during routine clinical care, 65.5% (n=36/55) of patients at Site #1001 remained on perampanel
- These data indicate that perampanel is generally well tolerated during routine clinical care, with favorable retention rates for up to 2 years in patients with epilepsy, when administered at Site #1001 and across all other sites

Table 1. Patient demographics and baseline characteristics at the Carle Foundation Hospital (Site #1001) and across all other sites (Safety Analysis Set)

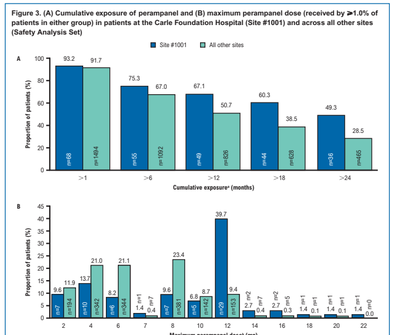
	Perampanel (N=1703)	
	Site #1001 (N=73)	All other sites (N=1630)
Age,[a] years		
Mean (SD)	30.8 (12.5)	28.4 (16.7)
Median (min, max)	31.0 (3, 59)	25.0 (1, 84)
Female, n (%)	37 (50.7)	861 (52.8)
Race,[b] n (%)		
Caucasian	63 (86.3)	1168 (71.7)
Black or African American	5 (6.8)	171 (10.5)
Asian	2 (2.7)	39 (2.4)
Other[c]	3 (4.1)	251 (15.4)
Mean (SD) age at epilepsy diagnosis, years	14.1 (12.9)	13.8 (15.5)
Time since diagnosis, years		
Mean (SD)	16.9 (12.3)	15.6 (13.2)
Median (min, max)	16.5 (0, 47)	12.0 (0, 65)
ILAE classification, n (%)		
Partial-onset	31 (42.5)	818 (50.2)
Idiopathic generalized epilepsy	17 (23.3)	273 (16.7)
Other	4 (5.5)	271 (16.6)
Unknown	21 (28.8)	268 (16.4)
Number of concomitant ASDs,[d] n (%)		
0	2 (2.7)	164 (10.1)
1	18 (24.7)	314 (19.3)
2	27 (37.0)	564 (34.6)
3	18 (24.7)	380 (23.3)
>3	8 (11.0)	208 (12.8)

[a]Age at perampanel treatment initiation
[b]Percentages are based on the total number of patients with non-missing data (Site #1001, n=73; all other sites, n=1629)
[c]Includes Arabic, Hispanic, Indian, Kuwaiti, Latino, Middle Eastern, Native American, and unknown
[d]ASDs being administered during baseline (taken at date of first dose of perampanel; rescue medications not included)
ASD, anti-seizure drug; ILAE, International League Against Epilepsy; max, maximum; min, minimum; SD, standard deviation

Dosage and exposure

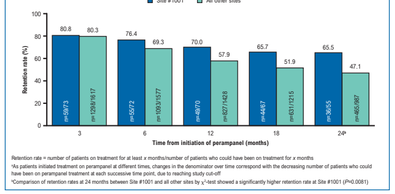
- Perampanel dose titration occurred weekly (Site #1001, n=0 [0.0%]; all other sites, n=379 [23.3%]), every 2 weeks (Site #1001, n=45 [61.6%]; all other sites, n=357 [21.9%]), every 3 weeks (Site #1001, n=1 [1.4%]; all other sites, n=17 [1.0%]), and other (Site #1001, n=16 [21.9%]; all other sites, n=415 [25.5%])
  - Examples of 'other' titration rates were: no titration, as needed/as medically necessary, irregular/variable, and every 4 weeks
- The overall mean (standard deviation [SD], range) cumulative duration of exposure to perampanel was 23.1 (16.5, 0.0–58.3) months at Site #1001 and 17.1 (15.7, 0.0–77.1) months at all other sites
  - The proportions of patients with >1, >6, >12, >18, and >24 months of perampanel exposure are shown in Figure 3A
- Mean (SD, range) maximum perampanel doses were 9.3 (4.5, 2–22) mg/day for patients at Site #1001 and 6.5 (3.1, 0–20) mg/day for patients across all other sites (Figure 3B)
- Most common modal daily doses of perampanel at Site #1001 were 12 mg (n=18 [24.7%]) and 2 mg (n=7 [9.6%]), and across all other sites were 4 mg (n=327 [20.1%]), 6 mg (n=295 [18.1%]), and 8 mg (n=267 [16.4%])

Figure 3. (A) Cumulative exposure of perampanel and (B) maximum perampanel dose (received by ≥1.0% of patients in either group) in patients at the Carle Foundation Hospital (Site #1001) and across all other sites (Safety Analysis Set)



[a]Patients were counted in each applicable exposure category
[b]Data for maximum perampanel dose were missing for 1 patient at Site #1001 and 7 patients at all other sites

Figure 4. Retention rates over 24 months following initiation of perampanel treatment at the Carle Foundation Hospital (Site #1001) and across all other sites (Safety Analysis Set)[a]

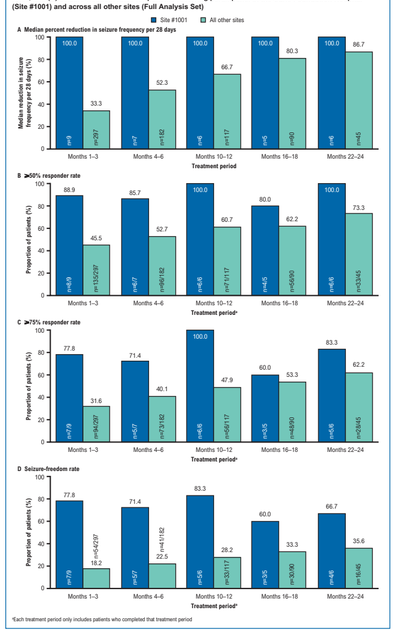


Retention rate = number of patients on treatment for at least x months/number of patients who could have been on treatment for x months
[a]As patients initiated treatment on perampanel at different times, changes in the denominator over time correspond with the decreasing number of patients who could have been on perampanel treatment at each successive time point, due to reaching study cut-off
[b]Comparison of retention rates at 24 months between Site #1001 and all other sites by χ^2-test showed a significantly higher retention rate at Site #1001 (P=0.0081)

Efficacy outcomes

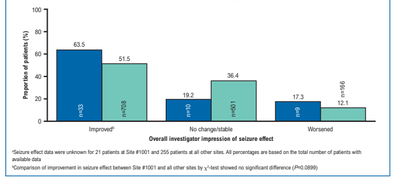
- Retention rates for patients at Site #1001 and patients at all other sites are shown in Figure 4
  - Following 24 months of perampanel treatment during routine clinical care, 36/55 (65.5%) patients at Site #1001 and 465/987 (47.1%) patients across all other sites remained on perampanel (Site #1001 vs all other sites, P<0.01)
- During Months 10–12 and Months 22–24, median percent reductions in seizure frequency per 28 days were: 100.0% (n=6) and 100.0% (n=6), respectively, for patients at Site #1001; and 66.7% (n=117) and 86.7% (n=45), respectively, for patients across all other sites (Figure 5A)
  - Fifty-percent responder rates, 75% responder rates, and seizure-freedom rates are also presented in Figure 5B–D
- Improvements in seizure effect, based on overall investigator impression as assessed at the end of treatment, were reported in 63.5% (n=33/52) of patients at Site #1001 and 51.5% (n=708/1375) of patients across all other sites (Site #1001 vs all other sites, P=0.0899; Figure 6)

Figure 5. (A) Median percent reduction in seizure frequency, (B) 50% responder rates, (C) 75% responder rates, and (D) seizure-freedom rates for patients receiving perampanel at the Carle Foundation Hospital (Site #1001) and across all other sites (Full Analysis Set)



[a]Each treatment period only includes patients who completed that treatment period

Figure 6. Proportion of patients with improvement, no change/stable, or worsening of seizures based on overall investigator impression of seizure effect as assessed at the end of treatment for patients receiving perampanel at the Carle Foundation Hospital (Site #1001) and across all other sites (Safety Analysis Set)[a]



[a]Seizure effect data were unknown for 21 patients at Site #1001 and 255 patients at all other sites. All percentages are based on the total number of patients with available data
[b]Comparison of improvement in seizure effect between Site #1001 and all other sites by χ^2-test showed no significant difference (P=0.0899)

Table 2. Summary of TEAEs and most common TEAEs (occurring in ≥5% of patients in either group) at the Carle Foundation Hospital (Site #1001) and across all other sites (Safety Analysis Set)

	Perampanel (N=1703)	
	Site #1001 (N=73)	All other sites (N=1630)
TEAE, n (%)	50 (68.5)	654 (40.1)
Serious TEAEs, n (%)	3 (4.1)	76 (4.7)
Deaths	0 (0.0)	15 (0.9)
TEAEs leading to perampanel discontinuation, n (%)	12 (6.4)	402 (24.7)
TEAEs occurring in ≥5% of patients in either group,[a] n (%)		
Dizziness	20 (27.4)	105 (6.4)
Aggression	6 (8.2)	84 (5.2)
Fatigue	8 (11.0)	46 (2.8)
Somnolence	5 (6.8)	49 (3.0)
Anger	6 (8.2)	32 (2.0)
Agitation	4 (5.5)	31 (1.9)
Insomnia	4 (5.5)	15 (0.9)

For each row category, a patient with >2 TEAEs in that category is counted only once; a TEAE is defined as an adverse event that 1) emerges during treatment, having been absent at Pretreatment, or 2) re-emerges during perampanel treatment, having been present at Pretreatment, but ceased prior to treatment initiation
[a]Preferred term based on MedDRA version 21.1
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

CONCLUSIONS

- This analysis of the PROVE Study demonstrates significantly higher retention rates on perampanel at 24 months for patients at Site #1001 than for patients across all other sites (65.5% vs 47.1%; P<0.01)
- Despite small patient numbers, perampanel was shown to be efficacious at Site #1001 and across all other sites; however, a greater frequency of TEAEs was observed at Site #1001 than across all other sites (68.5% vs 40.1%; P<0.0001)
- Limitations include those associated with real-world, retrospective, observational studies, such as the lack of placebo control arm and blinding
  - A specific limitation of this analysis was the low number of patients at Site #1001 included in the Full Analysis Set (n=9)
- The recent approval of perampanel monotherapy for POS and potential for earlier perampanel use may affect regional variability
  - Additional analyses are planned to further investigate outcomes of real-world use of perampanel between specific PROVE Study sites to assess whether regional differences do indeed exist

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DISCLOSURES

[Dr Huesmann: please could you provide your disclosure information?]

Anna Patten is an employee of Eisai Ltd.

Manoj Malhotra is an employee of Eisai Inc.

ACKNOWLEDGMENTS

Medical writing support, under the direction of the authors, was provided by Patrick Griffin, MSc, on behalf of CMC AFFINITY, a division of McCann Health Medical Communications Ltd., Macclesfield, UK, funded by Eisai Inc., in accordance with Good Publication Practice (GPP3) guidelines.

PROVE Study 506 was funded by Eisai Inc.

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