Received: 16 December 2024 | Revised: 14 April 2025 | Accepted: 4 May 2025

DOI: 10.1002/epi4.70068

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Real-world use of adjunctive perampanel for focal-onset seizures in Italy: A mirroring clinical practice study of perampanel in adults and adolescents (AMPA)

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Abstract

Objective: The AMPA study (Study 501; NCT04257604) was a multicenter, prospective, 12-month observational study in Italy that evaluated the effectiveness and safety of adjunctive perampanel in patients with focal-onset seizures (FOS), with or without focal to bilateral tonic–clonic seizures (FBTCS).

Methods: Patients aged ≥12 years with insufficiently controlled FOS, with or without FBTCS, receiving 1–3 anti-seizure medications (ASMs) were prescribed adjunctive perampanel per the approved indication. The primary endpoint was the median percent change in total seizure frequency per 28 days from baseline at Month 6. Baseline seizure frequency per 28 days was calculated using seizure diaries and/or medical records of seizures occurring in the 8 weeks prior to the baseline visit while patients were receiving 1–3 ASMs. Treatment-emergent adverse events (TEAEs), including serious TEAEs, were monitored for up to 12 months.

Results: Of the 240 patients enrolled in the study, 234 were included in the Full and Safety Analysis Sets. Median age (minimum, maximum) was 36.0 years (12, 84) and 51.3% ($n = 120/234$) were female. The majority of patients (77.8% [$n = 182/234$]) received ≥2 concomitant ASMs at baseline, with the most common being carbamazepine (33.8% [$n = 79/234$]). The median percent reduction in total

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seizure frequency per 28 days from baseline (95% confidence interval) was 55.4% (46.7%–66.7%) at Month 6. Overall, the retention rate was 57.3% ($n = 134/234$) following 12 months of treatment. During the study, the overall incidence of TEAEs was 56.4% ($n = 132/234$), with the most frequently reported TEAE being dizziness/vertigo (21.8% [$n = 51/234$]). Serious TEAEs were experienced by 6.0% ($n = 14/234$) of patients and no deaths were reported during the 12-month treatment period.

Significance: Data from the AMPA study suggest that adjunctive perampanel is associated with improvement in seizure control and with good retention rates and tolerability in a real-world clinical setting. These findings further support the use of adjunctive perampanel as a suitable treatment option for adolescent and adult patients with epilepsy.

Plain Language Summary: Our study looked at teenage and adult patients with epilepsy in Italy who took the study drug, called perampanel, as well as the epilepsy treatments they had already been prescribed. After 12 months, 134 out of 234 patients were still using perampanel. Patients taking perampanel had fewer seizures than they did before they started taking perampanel. Side effects occurred in 132 patients (most commonly dizziness/vertigo, irritability, and sleepiness) and caused 45 of them to withdraw from the study. Perampanel was a suitable treatment option for teenage and adult patients with epilepsy.

KEYWORDS

adjunctive therapy, anti-seizure medication, epilepsy, focal to bilateral tonic–clonic seizures, low dose, older adults

1 | INTRODUCTION

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor antagonist,[1] is a once-daily oral anti-seizure medication (ASM) approved in >70 countries and territories including the United States (USA), Japan, and other countries in Europe and Asia. In the USA, perampanel is approved as monotherapy or adjunctive therapy for focal-onset seizures (FOS), with or without focal to bilateral tonic–clonic seizures (FBTCS; previously secondarily generalized seizures),[2] in patients aged ≥4 years and as adjunctive therapy of generalized tonic–clonic seizures (GTCS) in patients aged ≥12 years.[3] In the European Union, perampanel is approved for the adjunctive treatment of FOS, with or without FBTCS, in patients aged ≥4 years and for GTCS in patients aged ≥7 years with idiopathic generalized epilepsy (IGE).[4]

The approval of perampanel for FOS was based on results of three randomized, double-blind, placebo-controlled Phase III studies in patients aged ≥12 years,[5–7] and the approval for use for GTCS was based on results

Key points

- Adjunctive perampanel was associated with improved seizure control in patients aged ≥12 years with FOS, with or without FBTCS, in Italy.
- Reductions in seizure frequency were evident after 3 months of treatment and were sustained over the 12-month treatment period.
- Perampanel was well tolerated with >50% of patients remaining on treatment after 12 months in a real-world clinical setting.
- The safety outcomes were consistent with the known safety profile of perampanel reported in randomized controlled trials.
- Adjunctive perampanel may be an appropriate treatment option for adolescent and adult patients with epilepsy.

from another randomized placebo-controlled trial (RCT) in patients with GTCS and IGE.[8] Several observational studies were conducted to monitor the safety of perampanel after marketing authorization, and their clinical outcomes were generally in line with those from the RCTs and their open-label extensions.[9–19] Data from prospectively designed real-world studies complement and expand on data obtained from RCTs by allowing the inclusion of more diverse populations of people with epilepsy.[20] Real-world data on perampanel use from various regions around the world are available[9–11,14,15]; however, real-world evidence from Italy is limited, despite the initial approval for FOS dating back to 2012.[21–26]

A Mirroring clinical practice study of Perampanel in Adults and adolescents (Study 501; AMPA; NCT04257604) was a multicenter, prospective, real-world, observational study which evaluated the effectiveness and safety of adjunctive perampanel in patients with FOS, with or without FBTCS, in Italy. Here, we report the overall effectiveness and safety results, and findings from post hoc subgroup analyses from the AMPA study.

2 | METHODS

2.1 | Study design and patients

AMPA was a multicenter study conducted across 19 study sites in Italy between January 3, 2016, and April 30, 2019. The AMPA study design is shown in Supplementary Figure S1. Patients aged ≥12 years with a diagnosis of FOS, with or without FBTCS, and with no clinically significant psychiatric illness, psychological or behavioral disorders, as specified in Summary of Product Characteristics (SmPC),[4] were included in this study. The protocol and informed consent and case report forms were reviewed and approved by the relevant ethics committees before the study was initiated. The decision to prescribe perampanel, per the approved indication,[4] was made before, and independently of, the physician's decision to include the patient in the study. Since this was an observational study, perampanel dosing and titration were carried out according to the approved SmPC, with treatment initiated at a dose of 2 mg/day, and for the dose to be increased by increments of 2 mg (either weekly or every 2 weeks) based on clinical response and tolerability up to a maximum dose of 12 mg/day.[4] Patients who provided informed consent and met all of the inclusion and none of the exclusion criteria completed the Baseline Visit, during which, baseline seizure frequency per 28 days was calculated using seizure diaries or medical records from a pre-perampanel period of 8 weeks and the number and type of concomitant ASMs the patient was receiving at baseline was recorded. Enzyme-inducing ASMs (EIASMs) included carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenytoin, and phenytoin sodium; all other ASMs were considered non-EIASMs. Treatment with perampanel was not started before the Baseline Visit. Patients were assessed again after 3, 6, and 12 months of treatment (Month 3, Month 6, and Month 12 Treatment Visits, respectively). This follow-up study visit schedule mirrored existing clinical practice (mirrored visits). There were no limitations on concomitant medications. Dose adjustments of concomitant ASMs were permitted according to the treating physician's clinical judgment. Final assessments of participating patients were performed during the Month 12 visit; an early termination visit was scheduled for those who withdrew before the Month 12 visit.

2.2 | Effectiveness and safety assessments

The Intent-to-Treat (ITT) Analysis Set included patients who received ≥1 dose of perampanel, had baseline seizure data, and, where relevant, had post-baseline seizure data; last observation carried forward (LOCF) was used to handle missing data. The Safety Analysis Set included patients who received ≥1 dose of perampanel.

Effectiveness was assessed in the ITT Analysis Set. The primary endpoint was the median percent change in total seizure frequency per 28 days from baseline at Month 6. Baseline seizure frequency per 28 days was calculated using seizure diaries and/or medical records of the number of seizures occurring in the 8 weeks prior to the baseline visit prior to the initiation of perampanel and while patients were receiving 1–3 ASMs. Secondary endpoints included median percent change in the frequency of total seizures per 28 days from baseline at Months 3 and 12, and median percent change in FBTCS frequency from baseline at Months 3, 6, and 12. Other secondary endpoints were 50% and 75% responder rates, seizure-freedom rates at Months 3, 6, and 12, and retention rates at Months 6 and 12. Seizure-freedom rates at Months 3 and 6 were calculated over the previous 3 months, whereas at Month 12 they were calculated over the previous 6 months. Effectiveness was assessed by seizure type, which was based on seizure diaries filled out by patients and "total seizures" included any types of seizures recorded in patients' seizure diaries during the study.

Safety was a secondary endpoint and was assessed in the Safety Analysis Set. Treatment-emergent adverse events (TEAEs), including treatment-related and serious TEAEs, were monitored for up to 12 months. A TEAE was

defined as any adverse event that emerged from the date of the first dose of perampanel to 28 days after the last dose; treatment-related TEAEs included TEAEs that were considered related to treatment or had no known causality. Additional secondary endpoints included mean change in irritability, mean change in Epworth Sleepiness Scale score, and mean change in quality of life (QoL). The irritability in epilepsy questionnaire (I-Epi), a patient-based questionnaire commonly used in clinical and research practice in Italy, was used to assess irritability in adult patients. Other psychiatric symptoms were recorded by the Investigator according to clinical judgment. The self-administered Epworth Sleepiness Scale (ESS) was used to assess the effect of perampanel on sleep and somnolence in adult patients. The 31-item quality-of-life questionnaire (QOLIE-31) was used to assess adult patients' QoL. However, results from the ESS and QOLIE-31 will be reported in a future manuscript.

2.3 | Post hoc analyses

In addition to the planned analyses, a post hoc analysis of patients with FOS only compared with patients with FOS with FBTCS was conducted to further assess the effect of perampanel on different seizure types. A second analysis was done to evaluate the effectiveness and safety of perampanel 4 mg/day as a modal dose. The modal dose represents the most frequent, actual daily perampanel dose received by a patient during the treatment period, and for the longest duration.[27] A third analysis was performed to evaluate the effectiveness and safety of perampanel in patients aged ≥60 years; data were stratified by the number of concomitant ASMs (1, 2, or ≥3) at baseline.

2.4 | Statistical analysis

This was an observational study and therefore no formal sample size calculations were done. Categorical data and continuous variables are presented in this paper along with calculated 95% confidence intervals.

3 | RESULTS

3.1 | Patients

In total, 240 patients with FOS, with or without FBTCS, were enrolled at 19 sites across Italy; 202 of these patients were included in the ITT Analysis Set (Figure 1), and 234 patients were included in the Safety Analysis Set. Overall, 57.7% ($n = 135/234$) of patients completed the study, and

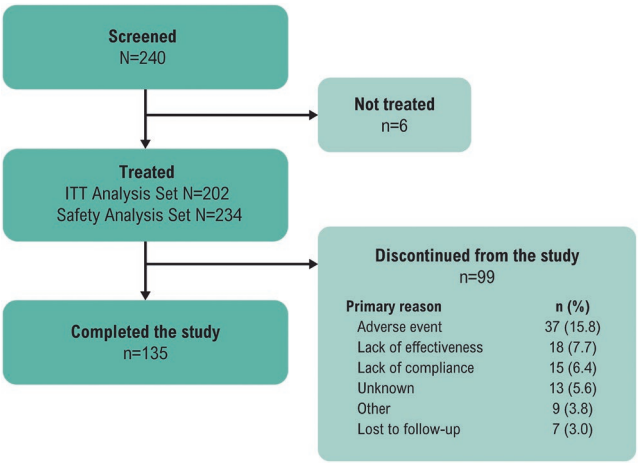

FIGURE 1 Patient disposition. ITT, Intent-to-Treat.

42.3% ($n = 99/234$) discontinued; the most common primary reason for discontinuation was adverse events, occurring in 15.8% ($n = 37/234$) of patients.

Patient demographics and baseline characteristics are presented in Table 1. In the Safety Analysis Set, 38.5% of patients ($n = 90/234$) had FBTCS at baseline. Most patients (77.8% [$n = 182/234$]; Safety Analysis Set) were receiving ≥2 concomitant ASMs at baseline, with the most common being carbamazepine (33.8% [$n = 79/234$]). The mean (standard deviation [SD]) dose of perampanel was 5.9 (2.0) mg/day at Month 3, 6.5 (2.0) mg/day at Month 6, and 6.8 (2.2) mg/day at Month 12. Additionally, 7.7% ($n = 18/234$) of patients received a consistent perampanel dose of 2 mg/day throughout the study, while 92.3% ($n = 216/234$) had at least one dose up titration. Dose up titration occurred in 92% of patients in both groups: those who received non-EIASMs and those who received EIASMs. The mean (SD) modal perampanel dose was 5.8 (2.5) mg/day; the most common modal doses of perampanel received by patients were 4 mg/day (26.5% [$n = 62/234$]), 6 mg/day (25.2% [$n = 59/234$]), and 8 mg/day (24.8% [$n = 58/234$]).

3.2 | Effectiveness outcomes

Perampanel was associated with improvements in seizure control from baseline in patients with FOS, particularly for those with FBTCS. At baseline, the mean (SD) total seizure frequency per 28 days was 14.8 (26.6). In patients with FOS, with or without FBTCS, the median percent reduction in total seizure frequency per 28 days from baseline at Month 6 (95% confidence interval [CI]) was 55.4% (46.7%–66.7%); this increased to 69.2% (58.8%–76.1%) at Month 12. For patients with FBTCS, the median percent reduction in FBTCS frequency per 28 days from baseline was 100.0% at Months 6 and 12 (Figure 2A).

TABLE 1 Baseline demographics and clinical characteristics (Safety Analysis Set).

	Perampanel (*N* = 234)
Age,[a] years	
Mean (SD)	38.6 (16.7)
Median (min, max)	36.0 (12, 84)
Age group, *n* (%)	
12 to <18 years	26 (11.1)
18 to <60 years	177 (75.6)
≥60 years	31 (13.2)
Female, *n* (%)	120 (51.3)
White, *n* (%)	232 (99.1)
Mean (SD) age at epilepsy diagnosis, years	18.3 (14.7)
Mean (SD) time since epilepsy diagnosis, years	20.2 (14.9)
Epilepsy/Epileptic syndrome classification, *n* (%)	
Focal epilepsy of unknown cause	116 (49.6)
Focal structural epilepsy	118 (50.4)
Etiology based on medical history	
Anoxic brain/perinatal ischemic injury	10 (4.3)
Congenital brain injury due to generic, neurocutaneous, or metabolic disease	4 (1.7)
Focal cortical dysplasia, cortical heterotopias	27 (11.5)
Infectious or inflammatory	10 (4.3)
Mesial temporal sclerosis	18 (7.7)
Post-neurosurgery	7 (3.0)
Post-traumatic	6 (2.6)
Vascular, acquired, or congenital	16 (6.8)
Other	20 (8.5)
Number of ASMs at baseline,[b] *n* (%)	
0	2 (0.9)[c]
1	50 (21.4)
2	103 (44.0)
≥3	79 (33.8)
Baseline ASM use, *n* (%)	
EIASMs[d]	131 (56.0)
Non-EIASMs[d]	101 (43.2)
Most common ASMs at baseline (in ≥10% of patients), *n* (%)	
Carbamazepine	79 (33.8)
Levetiracetam	42 (17.9)
Oxcarbazepine	36 (15.4)
Lamotrigine	34 (14.5)
Lacosamide	28 (12.0)

Abbreviations: ASM, anti-seizure medication; EIASM, enzyme-inducing anti-seizure medication; FOS, focal-onset seizures; max, maximum; min, minimum; SD, standard deviation.

[a]Age was calculated on the date of informed consent.

[b]Patients reporting the same ASM more than once were counted only once.

[c]Patients received prior treatment with ASMs but discontinued treatment before the start of this study.

[d]EIASMs include carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenytoin, and phenytoin sodium. All other ASMs are non-EIASMs.

At Month 12, the 50% and 75% responder rates for total seizures were 63.5% and 44.5%, respectively (Figures 2B,C), and the seizure-freedom rate was 18.8% (Figure 2D). For FBTCS, the 50% and 75% responder rates and seizure-freedom rate at Month 12 were numerically higher than those calculated for total seizures (81.3%, 68.8%, and 56.3%, respectively). Following 12 months of treatment, 57.3% (*n* = 134/234; Safety Analysis Set) of patients remained on perampanel (Figure 3).

3.3 | Safety outcomes

The overall incidence of TEAEs was 56.4% (*n* = 132/234). Serious TEAEs were experienced by 6.0% (*n* = 14/234) of patients, and no deaths were reported during the 12-month treatment period (Table 2). Other reported serious TEAEs included events that required hospitalization/prolongation of existing hospitalization (3.4% [*n* = 8/234]), persistent or significant disability or incapacity (0.9% [*n* = 2/234]), and other important medical events (3.4% [*n* = 8/234]). The most commonly reported TEAE and treatment-related TEAE was dizziness/vertigo (21.8% [*n* = 51/234] and 19.7% [*n* = 46/234], respectively), and the most commonly reported behavioral TEAE and treatment-related TEAE was irritability (8.5% [*n* = 20/234] and 7.3% [*n* = 17/234], respectively). Among patients who experienced behavioral TEAEs, 14.0% (*n* = 7/50) had a prior history of behavior disorders, albeit not clinically significant.

Reductions in perampanel dose due to TEAEs occurred in 15.0% of patients (*n* = 35/234). The most commonly reported TEAEs that led to dose reduction were dizziness/vertigo (6.0% [*n* = 14/234]), balance disorder (2.6% [*n* = 6/234]), and somnolence (2.6% [*n* = 6/234]). The mean (SD) perampanel daily dose at the onset of TEAEs that led to dose reductions in these patients was 5.8 (1.9) mg, with the most common doses received being 4 mg (25.7% [*n* = 9/35]), 6 mg (45.7% [*n* = 16/35]), and 8 mg (37.1% [*n* = 13/35]). At TEAE onset, 88.6% (*n* = 31/35) of patients who had their dose reduced received ≥2 concomitant ASMs; 80.0% (*n* = 28/35) received non-EIASMs and 20.0% (*n* = 7/35) received EIASMs.

In total, 19.2% (*n* = 45/234) of patients experienced TEAEs that led to perampanel withdrawal. The most commonly reported TEAEs that led to withdrawal were dizziness/vertigo (6.0% [*n* = 14/234]), somnolence (2.6% [*n* = 6/234]), and behavior disorder (2.6% [*n* = 6/234]). The mean (SD) perampanel daily dose at the onset of TEAEs that led to perampanel withdrawal in these patients was 4.2 (2.1) mg, with the most common doses received being 2 mg (37.8% [*n* = 17/45]), 4 mg (24.4% [*n* = 11/45]), and 6 mg (33.3% [*n* = 15/45]). At TEAE onset, 71.1% (*n* = 32/45) of patients who experienced TEAEs that

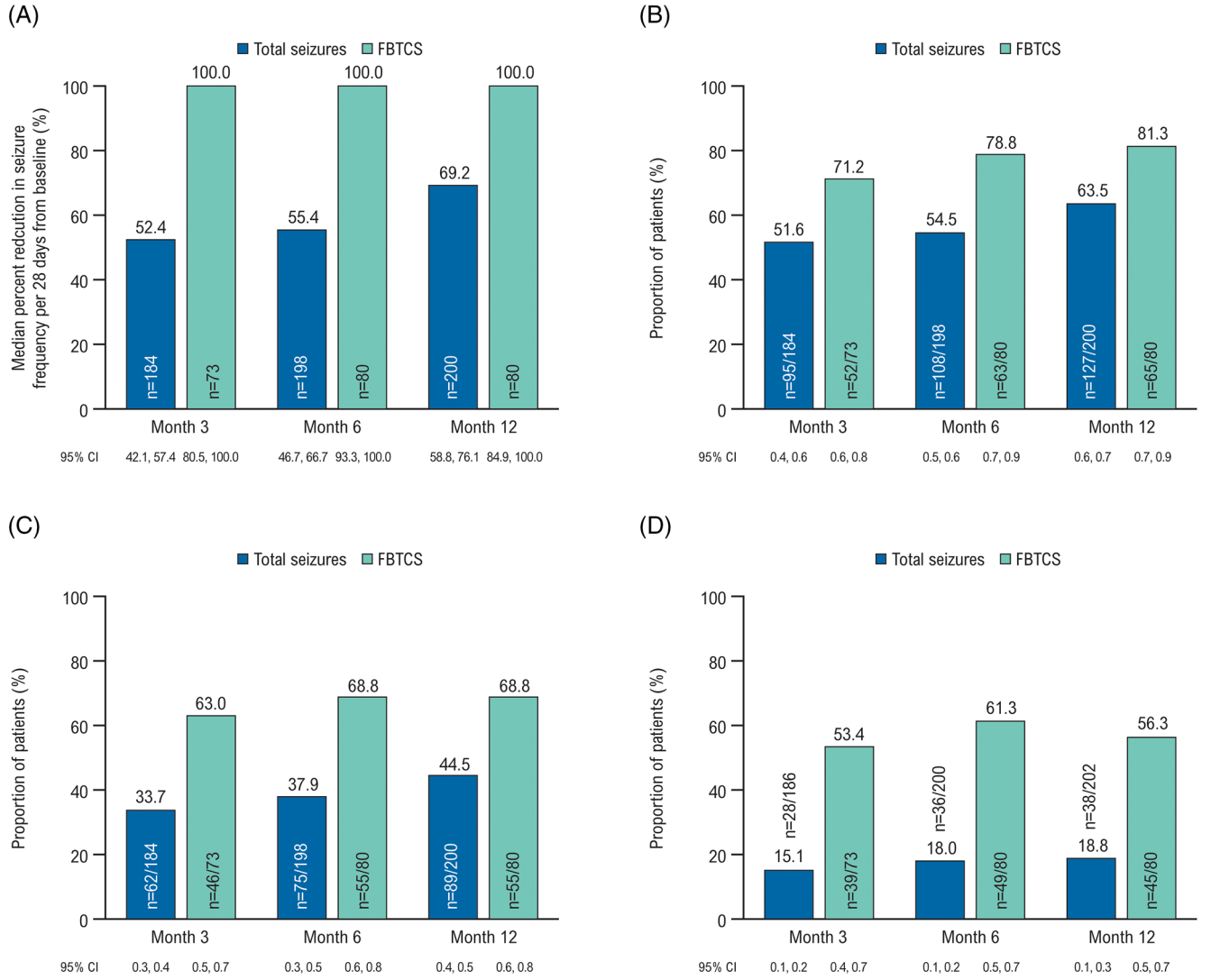

FIGURE 2 (A) Median percent reduction in seizure frequency per 28 days from baseline, (B) 50% responder rates, (C) 75% responder rates, and (D) seizure-freedom rates (ITT Analysis Set; using LOCF analysis). FBTCS, focal to bilateral tonic–clonic seizures; ITT, Intent-to-Treat; LOCF, last observation carried forward.

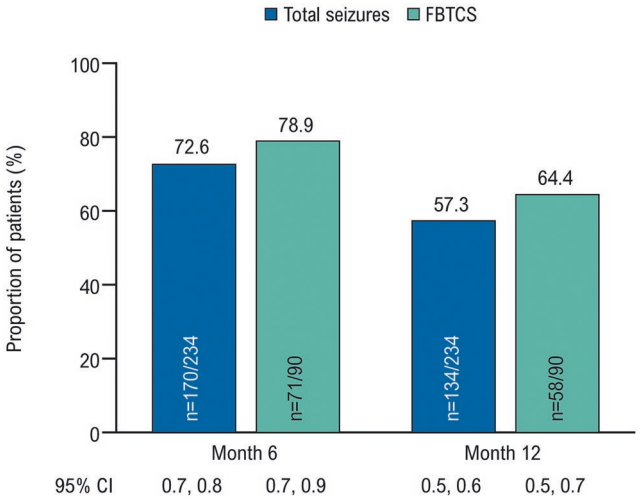

FIGURE 3 Retention rates (Safety Analysis Set). FBTCS, focal to bilateral tonic–clonic seizures.

led to perampanel withdrawal received ≥2 concomitant ASMs; 73.3% ($n = 33/45$) received non-EIASMs and 20.0% ($n = 9/45$) received EIASMs.

3.4 | The effect of perampanel on different seizure types

The clinical outcomes of adjunctive perampanel in patients with FOS versus those with FOS and FBTCS were further assessed in a post hoc analysis. Effectiveness outcomes were assessed in the ITT Analysis Set. Of the 202 patients with FOS in the ITT Analysis Set, 80 were with FBTCS and 122 were without FBTCS. Following 12 months of treatment with perampanel, the median percent reduction in seizure frequency per 28 days from baseline in patients with FBTCS was numerically higher than that in

TABLE 2 Overview of TEAEs and treatment-related TEAEs (Safety Analysis Set).

	Perampanel (*N* = 234)
All TEAEs, *n* (%)	132 (56.4)
Treatment-related TEAEs,[a] *n* (%)	111 (47.4)
Serious TEAEs, *n* (%)	14 (6.0)
Deaths[b]	0 (0.0)
TEAEs leading to perampanel dose adjustment, *n* (%)	88 (37.6)
Withdrawal	45 (19.2)
Dose reduction	35 (15.0)
Pharmacologic therapy	18 (7.7)
Most frequently reported TEAEs (occurring in ≥2% of patients), *n* (%)	
Dizziness/vertigo	51 (21.8)
Irritability	20 (8.5)
Somnolence	19 (8.1)
Behavior disorder	9 (3.8)
Balance disorder	9 (3.8)
Asthenia	5 (2.1)
Most frequently reported treatment-related TEAEs (occurring in ≥2% of patients), *n* (%)	
Dizziness/vertigo	46 (19.7)
Somnolence	19 (8.1)
Irritability	17 (7.3)
Behavior disorder	9 (3.8)
Balance disorder	9 (3.8)

Abbreviation: TEAEs, treatment-emergent adverse events.

[a]Included TEAEs that were considered to be related to the study drug per the investigator's discretion or TEAEs with missing causality.

[b]Includes all subjects with serious TEAEs resulting in death.

patients without FBTCS (73.5% [95% CI, 61.1%–83.5%] vs. 66.1% [95% CI, 49.0%–73.6%]). At Month 12, patients with FBTCS experienced more improvements in seizure control compared with patients without FBTCS. The 50% and 75% responder rates and seizure-freedom rate for patients with FBTCS were 70.0% (*n* = 56/80), 50.0% (*n* = 40/80), and 25.0% (*n* = 20/80), respectively. The 50% and 75% responder rates and seizure-freedom rate for patients without FBTCS were 59.2% (*n* = 71/122), 40.8% (*n* = 49/122), and 14.8% (*n* = 18/122), respectively.

Retention rate was 64.4% (*n* = 58/90; Safety Analysis Set) in patients with FBTCS compared with 52.8% (*n* = 76/144; Safety Analysis Set) in those without FBTCS following 12 months of treatment. The incidences of TEAEs and treatment-related TEAEs were comparable between patients with or without FBTCS (56.7% vs. 56.3% and 47.8% vs. 47.2%, respectively; Safety Analysis Set).

3.5 | The effect of a modal dose of perampanel 4 mg/day

This post hoc analysis included 62 patients from the Safety Analysis Set; among them, 50 patients who had seizure diaries available at baseline and at subsequent visits were included in the effectiveness analysis. Baseline demographics and clinical characteristics of these patients are presented in Table S1. Of the 62 patients included in the Safety Analysis Set, 45.2% (*n* = 28/62) had a history of FBTCS. Most patients (75.8% [*n* = 47/62]) were receiving ≥2 ASMs at baseline, similar to the overall study population. At a modal dose of perampanel 4 mg/day, the median percent reduction in total seizure frequency per 28 days from baseline was 55.6% (95% CI, 39.1%–86.1%) at Month 3, 55.4% (95% CI, 31.7%–90.3%) at Month 6, and 63.9% (95% CI, 31.7%–89.2%) at Month 12 (Figure S2A); the 50% and 75% responder rates and seizure-freedom rates were sustained over the12-month treatment period (Figure S2B–D). The retention rate at Month 12 was 46.8% (*n* = 29/62) (Figure S2E). Over the same treatment period with a modal perampanel dose of 4 mg/day, patients with FOS and FBTCS experienced more improvements in seizure control compared with patients with FOS with or without FBTC (Figure S2A–D). The retention rate at Month 12 for patients with FBTCS was 53.6% (*n* = 15/28) (Figure S2E).

The overall incidence of TEAEs with perampanel 4 mg/day was 50.0% (*n* = 31/62), with the most common TEAE being dizziness/vertigo (17.7% [*n* = 11/62]; Table S2), similar to that reported in the overall study population. Serious TEAEs occurred in 12.9% (*n* = 8/62) of patients and no deaths were reported; other reported serious TEAEs included events that required hospitalization/prolongation of existing hospitalization (4.8% [*n* = 3/62]) and other important medical events (9.7% [*n* = 6/62]).

Furthermore, 16.1% (*n* = 10/62) of patients had a perampanel dose reduction due to TEAEs, and 24.2% (*n* = 15/62) of patients withdrew due to TEAEs. The most commonly reported TEAEs that led to perampanel dose reduction were dizziness/vertigo (50.0% [*n* = 5/10]) and somnolence (20.0% [*n* = 2/10]), while the most commonly reported TEAEs that led to withdrawal from the study were dizziness/vertigo (26.7% [*n* = 4/15]) and behavior disorder (20.0% [*n* = 3/15]).

3.6 | The effect of perampanel in adults aged ≥60 years stratified by the number of concomitant ASMs at baseline

This post hoc analysis included 31 patients aged 60–84 years from the Safety Analysis Set; 23 patients who

had seizure diaries available were included in the effectiveness analysis. Of these patients, 26.1% ($n=6/23$) had FBTCS. Baseline demographics and clinical characteristics, stratified by the number of concomitant ASMs at baseline, are presented in Table S3. Among the 31 patients, two (6.5%) were receiving 1 ASM at baseline, 17 (54.8%) were receiving 2 ASMs, and 12 (38.7%) were receiving ≥3 ASMs. The mean duration of perampanel exposure in older adult patients regardless of baseline ASM was >29 weeks with a mean (SD) perampanel dose of 4.3 (1.5) mg/day (Table S4).

Among the 23 patients with FOS, with or without FBTCS, with effectiveness data, perampanel was associated with a median percent reduction in total seizure frequency per 28 days of 79.5% at Month 12, increasing from 51.6% and 51.7% at Months 3 and 6, respectively (Figure S3A). The 50% and 75% responder rates at Month 12 (59.1% and 54.5%) were numerically higher compared with Months 3 and 6 (Month 3, 50.0% and 35.0%; Month 6, 50.0% and 45.5%; Figure S3B,C) whereas seizure-freedom rates remained unchanged between Months 6 and 12 (21.7% each) but improved compared with Month 3 (10.0%; Figure S3D). At Month 12, the retention rate was 41.9%, decreasing from 48.4% at Month 6 and 71.0% at Month 3, and was comparable between patients regardless of the number of ASMs taken at baseline (Figure S3E).

For older adult patients with FBTCS, the median percent reduction in FBTCS frequency per 28 days from baseline was 90.2% (95% CI, 80.5%–100%) at Month 3, 100.0% (95% CI, 93.3%–100%) at Month 6, and 85.4% (95% CI, 82.7%–100%) at Month 12. The 50% and 75% responder rates at Months 3, 6, and 12 were all 100.0% (Month 3, $n=2/2$; Months 6 and 12, $n=3/3$ each). Seizure-freedom rates were 50.0% ($n=1/2$), 33.3% ($n=1/3$), and 0.0% ($n=0/3$) at Months 3, 6, and 12, respectively. After 12 months, 50.0% ($n=3/6$) of patients with FBTCS remained on perampanel treatment.

The overall incidence of TEAEs in older adult patients was 71.0% ($n=22/31$; Table S5). The most frequently reported TEAE was dizziness/vertigo (22.6% [$n=7/31$]), similar to the overall study population. The incidence of TEAEs and treatment-related TEAEs decreased as the number of concomitant ASMs at baseline increased. Serious TEAEs occurred in 16.1% ($n=5/31$) of patients, and no deaths were reported; other reported serious TEAEs included events that required hospitalization/prolongation of existing hospitalization (12.9% [$n=4/31$]) and other important medical events (6.5% [$n=2/31$]).

Additionally, 22.6% ($n=7/31$) of patients had a perampanel dose reduction due to TEAEs and 41.9% ($n=13/31$) of patients withdrew due to TEAEs. The most frequently reported TEAEs that led to dose reduction were balance disorder and dizziness/vertigo (6.5% [$n=2/31$] each), which were also the most frequently reported TEAEs that led to study withdrawal (dizziness/vertigo, 12.9% [$n=4/31$]; balance disorder, 6.5% [$n=2/31$]).

4 | DISCUSSION

The AMPA study evaluated the effectiveness and safety of adjunctive perampanel in patients with epilepsy for 1 year in a real-world clinical setting across 19 sites in Italy. This study demonstrated that perampanel was associated with improvements in seizure control compared with baseline in patients with FOS, particularly for those with FBTCS; these improvements were evident after 3 months of treatment, and seizure frequency reductions were sustained over the 12-month treatment period. Adjunctive perampanel was well tolerated and safety outcomes were consistent with the known safety profile of perampanel.[3,4] The most common TEAE in the overall AMPA study population was dizziness/vertigo, which reflects previous experience in clinical trials.[6,8,17,18,28] Approximately 42% of patients discontinued from the study; similar rates of discontinuation were seen in other observational studies conducted in the USA, such as the real-world PROVE study (Study 506 [NCT03208660])[29] and the open-label, Phase IV ELEVATE study (Study 410 [NCT03288129]),[30] from which 46.8% and 40.7% of patients discontinued, respectively. Overall, the effectiveness of adjunctive perampanel observed in the AMPA study is in line with that observed in other real-world studies of perampanel conducted in the USA, South Korea, Germany, Italy, Spain, and other countries in Europe.[9–19]

Subgroup analyses were conducted to evaluate the effectiveness and safety of perampanel administered as a modal dose of 4 mg/day, as well as in patients aged ≥60 years. Findings suggest that adjunctive perampanel at a dose of 4 mg/day was effective, with comparable improvement in seizure outcomes to that of the overall study population, including the observed improvements for patients with FBTCS. The effectiveness of adjunctive perampanel at a dose of 4 mg/day in this study was consistent with data from the real-world PROVE study (Study 506 [NCT03208660]) in which a perampanel dose of 4 mg/day was the second most common maximum dose and the most common modal daily dose received by patients.[29] A low perampanel dose of 4 mg/day was well tolerated, and the overall incidence of TEAEs (50.0%) was numerically lower than in the overall study population (56.4%).

The effectiveness of perampanel in patients aged ≥60 years suggested that adjunctive perampanel was associated with improved seizure control, regardless of the number of concomitant ASMs at baseline. Seizure outcomes in

older adult patients were generally comparable with those in the overall study population. Of note, the use of fewer baseline ASMs (2 ASMs vs. ≥3 ASMs) in older adults was generally associated with a numerically greater reduction in seizure frequency; however, the interpretations of these results are limited by the small sample size. One possible explanation for these results is that epilepsy may be more refractory in patients receiving a greater number of concomitant ASMs, although this effect is not unique to older adults.[31–33] In patients aged ≥60 years, adjunctive perampanel was generally well tolerated; however, the overall incidence of TEAEs (71.0%) was higher than that in the overall population (56.4%). These findings are consistent with data in patients aged ≥60 years from Studies 307 (NCT00735397) and 335 (NCT01618695), Phase III open-label extension studies of adjunctive perampanel.[28] These findings were also observed in the PERMIT Extension study,[34] which was a pooled analysis of data from patients included in the PERMIT[19] and PROVE[18] retrospective studies; patients aged ≥65 years had a numerically higher overall incidence of TEAEs than the overall population (55.0% vs. 49.2%, respectively).[34] Similar results were seen in a recent retrospective, observational study conducted in Italy, the PEROC study,[24] where the overall incidence of TEAEs was ~20.0% in the overall patient population[35] compared with 34.9% in patients aged ≥65 years.[24]

Limitations of the AMPA study include those commonly associated with real-world, observational studies, such as the absence of a control group, the lack of blinding, and variation in clinical settings and standards of practice across multicenter studies. These limitations could introduce bias and confounding factors, thus reducing the statistical validity of real-world data.[20] In addition, 56.0% of patients in the AMPA study were receiving concomitant EIASMs, which are known to increase perampanel clearance,[36,37] thus possibly impacting effectiveness outcomes, the onset, duration, and rate of TEAEs reported in this study. Another limitation of this study is the use of the LOCF method for handling missing data. While LOCF is a simple and widely used approach that allows for complete case analysis without requiring complex modeling, it may introduce bias by assuming that a patient's last recorded value remains stable over time or not accounting for delayed treatment effects beyond the last observed time point,[38] even within a 12-month follow-up.

A key strength of the study is the real-world observational design, which is a better reflection of routine clinical practice than RCTs. When compared with RCTs, observational real-world data may have broader applicability and more representative patient populations with common comorbidities. Additionally, the prospective design allowed for greater data accuracy than a retrospective study.

5 | CONCLUSION

The AMPA study was a multicenter, observational, prospective study that evaluated the effectiveness and safety of adjunctive perampanel in patients aged ≥12 years with epilepsy in Italy who needed an additional anti-seizure pharmacotherapy. Overall, data from the AMPA study suggested that adjunctive perampanel was associated with improvement in seizure control, with good retention rates and tolerability in a real-world clinical setting. Further, data from subgroup analyses suggested that a low perampanel dose of 4 mg/day was effective and safe. In patients aged ≥60 years, the effectiveness of adjunctive perampanel was comparable to that in the overall study, although a higher incidence of TEAEs was observed in this subgroup than in the overall AMPA population. Together, these findings provide further support for perampanel as an appropriate treatment option for adolescent and adult patients with insufficiently controlled FOS, with or without FBTCS. Future analyses will assess the impact of adjunctive perampanel treatment on patients' sleep and quality of life in the AMPA study.

AUTHOR CONTRIBUTIONS

Alfredo D'Aniello, Paolo Tinuper, Caterina Cerminara, Francesca Felicia Operto, Giancarlo Di Gennaro, Andrea Pecori, and Leock Y Ngo contributed to the conception and design of the study. Alfredo D'Aniello, Anna Teresa Giallonardo, Paolo Tinuper, Oriano Mecarelli, Umberto Aguglia, Giovanni Assenza, Antonio Gambardella, Maria Paola Canevini, Renato Scifo, Stefano Meletti, Valentina De Giorgis, Roberto Michelucci, Caterina Cerminara, Antonino Romeo, Francesca Felicia Operto, Luciana Tramacere, Giancarlo Di Gennaro, and Alfonso Iudice contributed to patient recruitment and enrollment. Alfredo D'Aniello, Anna Teresa Giallonardo, Paolo Tinuper, Umberto Aguglia, Renato Scifo, Stefano Meletti, Enrica Bonanni, Federico Vigevano, Francesca Felicia Operto, Giancarlo Di Gennaro, and Samantha Goldman contributed to the acquisition of the data. Alfredo D'Aniello, Paolo Tinuper, Federico Vigevano, Francesca Felicia Operto, Giancarlo Di Gennaro, Leock Y Ngo, Anna Patten, Anna Lisa Gentile, and Samantha Goldman conducted the analysis of the data. All authors were involved in data interpretation, reviewing, and approval of the manuscript, and the decision to submit the article for publication.

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ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in Study 501 and their families, as well as all study investigators in the AMPA study group and their teams: Valentina Chiesa, Paola De Liso, Alfonso Iudice, Orazio Spitaleri, Salvatore Striano, Giulia Turchi, Pierangelo Veggiotti, Emilio Russo, and Massimilano Copetti. Medical writing support, under the direction of the authors, was provided by Heyam Hayder, PhD, of CMC Connect, a division of IPG Health Medical Communications, funded by Eisai Inc., in accordance with Good Publication Practice (GPP 2022) guidelines. Study 501 was funded by Eisai s.r.l.

CONFLICT OF INTEREST STATEMENT

Alfredo D'Aniello has participated in pharmaceutical industry-sponsored clinical trials for UCB Pharma, has received speaker's honoraria from Angelini Pharma, Eisai, Neuraxpharm, and UCB Pharma, and has participated in advisory boards for Angelini Pharma. Valentina De Giorgis has received speaker's honoraria from Jazz Pharmaceuticals, Kanso, Nutricia, and Vitaflo, and has participated in consultancy boards for Kanso, Nutricia, and Vitaflo. Oriano Mecarelli has received speaker's honoraria from BIAL Italy and GW Pharmaceuticals and has participated in consultancy/advisory boards for Arvelle Therapeutics Int, Sanofi S.A., and UCB Pharma. Umberto Aguglia has participated in advisory boards for Eisai and has participated in industry-sponsored meetings for Biogen and Ecupharma. Giovanni Assenza has received speaker's honoraria from BIAL, Eisai s.r.l., LivaNova, and Lusofarmaco. Maria Paola Canevini has participated in advisory boards for Eisai, received honoraria towards courses from Ecupharma, Eisai, GW Pharmaceuticals, and UCB Pharma, and participated in an industry-sponsored ILAE meeting for Angelini Pharma. Stefano Meletti has participated in advisory boards for Eisai and received honoraria towards courses from Eisai, GW Pharmaceuticals, and UCB Pharma. Roberto Michelucci has received speaker's honoraria from Eisai. Antonino Romeo has participated in advisory boards for Neuroxpharm, Proveca Ltd., and Kolfarma, and has received speaker's honoraria from UCB Pharma. Luciana Tramacere has participated in advisory boards for Angelini Pharma and Eisai. Giancarlo Di Gennaro has received speaker's honoraria from Angelini Pharma, Eisai, GW Pharmaceuticals, LivaNova, Lusofarmaco, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, and BIAL. Alfonso Iudice has received research grants, speaker's or consultancy fees from Bayer, Biogen, Eisai, GW Pharmaceuticals, Janssen, Merck-Serono, Neuraxpharm, Teva, and UCB Pharma. Leock Y Ngo is a former employee of Eisai Inc. Anna Patten and Samantha Goldman are employees of Eisai Europe Ltd. Anna Lisa Gentile and Andrea Pecori are employees of Eisai s.r.l. Anna Teresa Giallonardo, Paolo Tinuper, Antonio Gambardella, Renato Scifo, Enrica Bonanni, Caterina Cerminara, Federico Vigevano, and Francesca Felicia Operto have no real or apparent conflicts of interest to disclose in relation to this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

How to cite this article: D'Aniello A, Giallonardo AT, Tinuper P, Mecarelli O, Aguglia U, Assenza G, et al. Real-world use of adjunctive perampanel for focal-onset seizures in Italy: A mirroring clinical practice study of perampanel in adults and adolescents (AMPA). Epilepsia Open. 2025;00:1–12. https://doi.org/10.1002/epi4.70068