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ORIGINAL ARTICLE

Efficacy and safety of perampanel as first adjunctive therapy in patients with focal-onset seizures or generalized tonic-clonic seizures in four post-marketing studies across regions

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Abstract

Objective: Early response to anti-seizure medication (ASM) is associated with a favorable prognosis in patients with epilepsy. Research is required to confirm existing data on the clinical use of perampanel as first adjunctive therapy in different patient groups and different regions. Here, we present a post hoc analysis of four post-marketing studies to examine side by side the efficacy and safety of perampanel administered as the first adjunctive ASM across different geographic settings.

Methods: Data from patients receiving first adjunctive perampanel were included in this post hoc analysis from Study 412 (NCT02726074, South Korea), Study 410 (NCT03288129, US), Study 509 (NCT04202159, Germany), and Study 501 (NCT04257604, Italy). Assessments included the median percent reduction from baseline/screening in seizure frequency, seizure-freedom rate, retention rate, and safety.

Results: A total of 170 patients who received first adjunctive perampanel were included in this study, including 102 patients from Study 412, 44 from Study 410, 13 from Study 509, and 11 from Study 501. At the latest time point in each study, 50% responder rates were ≥62.5% (range, 62.5%–100.0%) across seizure types, while seizure-freedom rates ranged from 25.0% to 100.0% (median, 51.6%). Retention rates were ≥61.8% at Month 6 in all studies and ≥54.5% at Month 12 in Studies 410 and 501 where these data were available. Overall, 46.2%–90.9% of patients experienced ≥1 treatment-emergent adverse event (TEAE) and 13.7%–27.3% discontinued perampanel due to TEAE(s). The most common TEAEs reported across each study were dizziness (≤50.0%), somnolence (≤36.4%), and fatigue (≤13.6%).

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Significance: The results from this post hoc analysis demonstrated that perampanel as first adjunctive therapy had a good treatment response with no new safety signals observed. Limitations included the post hoc nature of the analysis and the inability to pool data due to study design differences. Overall, these data support the use of perampanel as an early-line treatment in patients with epilepsy.

Plain Language Summary: This analysis looked at a medicine called perampanel and how well it works for people with epilepsy when it was one of the first medicines added to their regular seizure treatment. Data were collected from four separate studies that were done in South Korea, the United States, Germany, and Italy. Most patients had fewer seizures across all four studies after 6 months of treatment. The most common side effects reported in patients included dizziness and sleepiness. Perampanel worked well when used early during treatment, and most people were able to keep taking perampanel without significant difficulties.

KEYWORDS

anti-seizure medication, first add-on therapy, focal epilepsy, focal-onset seizures, generalized tonic-clonic seizures, perampanel

1 | INTRODUCTION

Early response to anti-seizure medications (ASMs) is associated with a favorable prognosis in patients with epilepsy.[1] Results from a study following a total of 1098 patients with epilepsy for up to 26 years demonstrated that approximately 50% of patients did not achieve seizure freedom with their first ASM.[2] Adjunctive ASMs are prescribed with the aim of improving seizure control[2]; however, ASM polytherapy has been associated with an increased frequency of adverse events vs. ASM monotherapy.[3] Furthermore, patients who fail to achieve seizure freedom with their first ASM may have an increased likelihood of experiencing uncontrolled seizures with each subsequent ASM.[4] Thus, effective early-line treatments with a beneficial balance between efficacy and tolerability are required.

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist is a once-daily, oral ASM for focal-onset seizures (FOS) and generalized tonic-clonic seizures (GTCS).[5,6] Perampanel is approved in over 70 countries and territories globally. In the United States (US) and Korea, perampanel is approved for adjunctive and monotherapy treatment of FOS, with or without focal to bilateral tonic-clonic seizures (FBTCS), in patients aged ≥4 years and is approved for adjunctive treatment of FOS, with or without FBTCS, in patients aged ≥4 years in Europe.[5,7,8] In addition, perampanel is approved for adjunctive treatment of GTCS in patients aged ≥12 years in the US, and in patients aged ≥7 years with idiopathic generalized epilepsy (IGE) in Europe and Korea.

Key points

- This post hoc analysis evaluates perampanel as first adjunctive therapy for epilepsy across different clinical and regional settings.
- Perampanel as first adjunctive therapy had favorable responder rates and was well tolerated across different geographic settings.
- The safety profile of first adjunctive perampanel was consistent with the known safety of perampanel in patients with epilepsy.
- The data reported here support the use of perampanel as an early-line treatment in patients with epilepsy.

A pooled analysis of patients treated with perampanel in routine clinical practice in the PERMIT study demonstrated that fewer previous or concomitant ASMs at baseline were associated with improved seizure control.[9] This was supported by evidence from a post hoc analysis of PERMIT, which suggested that perampanel administered as early-line therapy (one or two previous ASMs) was significantly more effective and better tolerated than when administered as late adjunctive therapy (≥3 previous ASMs).[10] Furthermore, it has been shown

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that perampanel is efficacious and well tolerated as early-line treatment in patients with epilepsy from different geographic regions and across ethnicities based on data from Study 412 (FAME [NCT02726074], South Korea),[11] Study 410 (ELEVATE [NCT03288129], US),[12] interim data from Study 509 (PERPRISE [NCT04202159], Germany),[13] and Study 501 (AMPA [NCT04257604], Italy).[14] However, data are limited regarding the clinical use of perampanel as first adjunctive therapy and further research is required to improve the management of epilepsy in patients.

Here, we present a post hoc analysis of data from Studies 412, 410, 509, and 501 to examine side by side the efficacy and safety of perampanel administered as the first adjunctive ASM across different clinical and regional settings.

2 | METHODS

2.1 | Study design

The key features of each study are shown in Table 1. Briefly, Study 412 was a Phase IV, multicenter, open-label study of perampanel as first adjunctive therapy, consisting of a 12-week titration phase and a 24-week maintenance phase.[11] Study 410 was a Phase IV, multicenter, open-label study of perampanel as monotherapy or first adjunctive therapy, comprising a 13-week titration period, a 39-week maintenance period, and a 4-week follow-up period.[12] Study 509 was a 12-month, multicenter, prospective, non-interventional study which assessed the efficacy and safety of perampanel as the only adjunctive ASM; data from the 6-month interim analysis are presented here.[13] Finally, Study 501 was a 12-month, multicenter, prospective, real-life, observational study assessing adjunctive perampanel.[14] These four studies were selected as the most appropriate data available to answer the research question at the time of data analysis.

2.2 | Patients

Patient populations of studies included in this analysis have been described previously,[11–14] and are summarized in the Methods S1. Briefly, Study 412 assessed patients aged ≥12 years with FOS, with or without FBTCS[11]; Study 410 included patients aged ≥4 years with FOS, with or without FBTCS, or with GTCS[12]; Study 509 assessed patients aged ≥18 years with FBTCS or GTCS due to IGE[13]; and Study 501 included patients aged ≥12 years with insufficiently controlled FOS, with or without FBTCS, who were receiving 1–3 concomitant ASMs (Table 1).

All study protocols were reviewed by the institutional review boards or ethics committees of participating centers for ethical approval and all patients provided written informed consent before trial participation. Each trial was registered at ClinicalTrials.gov (Study 412: NCT02726074; Study 410: NCT03288129; Study 509: NCT04202159; Study 501: NCT04257604).

2.3 | Endpoint assessments

The primary endpoint was the 50% responder rate at 6 months in Study 412; the retention rate at 3, 6, 9, and 12 months in Study 410; and the median percent reduction from baseline in seizure frequency per 28 days at 6 months in Study 501 (Table 1). Secondary and exploratory endpoints across studies included the median percent reduction from baseline in seizure frequency per 28 days, 50% and 75% responder rates, seizure-freedom rates, retention rates, and the incidence of treatment-emergent adverse events (TEAEs; Table 1). Interim endpoints in Study 509 included retention rate, measures of effects on seizure frequency, and TEAEs.

2.4 | Post hoc analysis

In the post hoc analysis reported here, only data from patients receiving perampanel as the first adjunctive therapy were included from each study. Data from each study could not be pooled due to differences in study design and are therefore presented side by side.

Efficacy assessments included 50% responder rates and seizure-freedom rates in all studies, and 75% responder rates in Studies 412, 410, and 501. Safety and tolerability assessments included retention rates, the incidence of TEAEs, serious TEAEs, TEAEs leading to perampanel discontinuation, and the most frequently reported TEAEs in each study.

2.5 | Statistical analysis

Assessments of efficacy were conducted in the full analysis set (FAS; patients who received at least one dose of perampanel and were included in at least one post-dose efficacy assessment) in Studies 412 and 410, the interim analysis set (IAS; the first 100 patients who received at least one dose of perampanel and were projected to complete the 6-month study visit or discontinued treatment before this visit) in Study 509, and in the intent-to-treat (ITT) analysis set (all patients who enrolled in the study) in Study 501. Last observation carried forward (LOCF) type imputation was employed to handle missing data for seizure-related efficacy endpoints in Study 410[12] and Study 501.[14]

Retention rates and safety assessments were based on the safety analysis set (SAS; patients who received at least one dose of perampanel and were included in at least one

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TABLE 1 Overview of studies.

	Study 412 (NCT02726074)[11]	Study 410 (NCT03288129)[12]	Study 509 (NCT04202159)[13]	Study 501 (NCT04257604)[14]
Study type	Phase IV, multicenter, open-label clinical study	Phase IV, multicenter, open-label clinical study	Multicenter, prospective, non-interventional study	Multicenter, prospective, real-life, observational study
Patients	Patients aged ≥12 years with a diagnosis of FOS, with or without FBTCS, who required adjunctive therapy after failure to control seizures with ASM monotherapy	Patients aged ≥4 years with FOS, with or without FBTCS, or with GTCS who were treatment naïve or required adjunctive therapy after failure to control seizures with ASM monotherapy	Patients aged ≥18 years with FBTCS or GTCS due to focal epilepsy or IGE who are receiving perampanel as the only adjunctive therapy to ASM monotherapy or as a substitute for one ASM of a baseline dual therapy	Patients aged ≥12 years with insufficiently controlled FOS, with or without FBTCS, while receiving 1–3 ASMs
Region	South Korea	US	Germany	Italy
Study dates	January 2016–April 2017	August 2017–April 2021	January 2020–March 2023	January 2016–April 2019
Treatment	First adjunctive therapy	Monotherapy or first adjunctive therapy	Adjunctive therapy	Adjunctive therapy
Dosage	4–12 mg/day[a]	4–12 mg/day[b]	Per approved indication	Per approved indication
Objectives	The efficacy and safety of perampanel as first adjunctive therapy in patients with FOS, with or without FBTCS	The efficacy and safety of perampanel as monotherapy or first adjunctive therapy in patients with FOS, with or without FBTCS, or with GTCS	The effectiveness of perampanel as the only adjunctive therapy in patients with FBTCS or GTCS	The effectiveness of adjunctive perampanel in patients with FOS, with or without FBTCS, in a real-life clinical setting
Primary endpoint	50% responder rate for FOS, with or without FBTCS	Retention rate at 3, 6, 9, and 12 months	Retention rate at 12 months	Median percentage change from baseline in all seizure frequency per 28 days at 6 months
Other endpoints	50% responder rate for GTCS, 75% responder rate and seizure-freedom rate for all seizures, and percent change from baseline in all seizure frequency	50% and 75% responder rates, seizure-freedom rate, and median percent change from baseline in all seizure frequency	Retention rate, median percent change in monthly seizure frequency, 50% responder rate, and seizure-freedom rate at 6 months	Retention rate, 50% and 75% responder rates, seizure-freedom rates, and median percent change from baseline in seizure frequency

Abbreviations: ASM, anti-seizure medication; FBTCS, focal to bilateral tonic-clonic seizures; FOS, focal-onset seizures; GTCS, generalized tonic-clonic seizures; IGE, idiopathic generalized epilepsy.

[a]During the titration period, perampanel was initiated at 2 mg/day and incrementally increased by 2 mg/day over weekly intervals for patients receiving non-enzyme-inducing ASMs (or ≥2-week intervals for those receiving enzyme-inducing ASMs) to a maximum of 12 mg/day. The final dosage at the end of the titration period was used for the maintenance period. Patients who could not tolerate 4 mg/day perampanel were discontinued from the study.

[b]During the titration period, perampanel was initiated at 2 mg/day and up-titrated to 4 mg/day at week 3; additional up-titrations by 2 mg/day over ≥2-week intervals to a maximum of 12 mg/day were optional based on clinical response and tolerability. The final dosage at the end of the titration period was used for the maintenance period. Patients who could not tolerate 4 mg/day perampanel were discontinued from the study.

post-dose safety assessment) in Studies 412, 410, and 501 were based on the IAS in Study 509.

3 | RESULTS

3.1 | Patients

Table 2 shows the baseline demographics and clinical characteristics of patients receiving perampanel as first adjunctive therapy from each study. The number of patients who received perampanel as first adjunctive therapy varied between studies: in Study 412, 102 patients received first adjunctive perampanel and were included in the SAS, of whom 85 were included in the FAS; in Study 410, 44 patients were included in the SAS and FAS; 13 patients were included in the IAS in Study 509; and 11 patients were included in the SAS and 8 were included in the ITT analysis set in Study 501. The median (range) age of patients was 39 (20–77) years in Study 412, 36 (12–77) years in Study 410, 49 (25–85) years in Study 509, and 28 (17–78) years in Study 501. The most common ASM at baseline was levetiracetam in Study 412 (40.0%), Study 410 (54.5%), and Study 509 (30.8%),

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TABLE 2 Baseline demographics and clinical characteristics of patients who received perampanel as first adjunctive therapy.

	Study 412 ($N=85$)[a]	Study 410 ($N=44$)[b]	Study 509 ($N=13$)[c]	Study 501 ($N=11$)[d]
Median (range) age, years	39.0 (20–77)	36.0 (12–77)	49.0 (25–85)	28.0 (17–78)
Female, *n* (%)	49 (57.7)	23 (52.3)	7 (53.8)	3 (27.3)
Mean (SD) time since epilepsy diagnosis, years	10.9 (9.3)	7.1 (9.6)	11.2 (14.6)	12.6 (12.5)
Seizure type,[e] *n* (%)				
FOS	85 (100.0)	35 (79.5)	8 (61.5)	11 (100)
FOS with FBTCS	16 (18.8)	21 (47.7)	8 (61.5)	5 (45.5)
GTCS	0 (0.0)	12 (27.3)	4 (30.8)	0 (0.0)
Mean (SD) baseline seizure frequency per 28 days[f]				
FOS	4.1 (7.7)[g]	8.5 (20.5)[h]	1.5 (1.2)	6.0 (7.3)
FBTCS	NR	20.5 (35.8)[h]	0.9 (0.6)	NR
GTCS	NR	0.9 (0.5)[h]	1.8 (1.5)	NR
Total seizures	NR	6.7 (17.2)	NR	6.0 (7.3)
Most common[i] ASMs at baseline, *n* (%)				
Levetiracetam	34 (40.0)	24 (54.5)	4 (30.8)	2 (18.2)
Carbamazepine	20 (23.5)	1 (2.3)	0 (0.0)	5 (45.5)
Oxcarbazepine	17 (20.0)	2 (4.5)	0 (0.0)	0 (0.0)
Lamotrigine	7 (8.2)	6 (13.6)	3 (23.1)	1 (9.1)
Valproic acid	5 (5.9)	3 (6.8)	0 (0.0)	1 (9.1)
Lacosamide	1 (1.2)	3 (6.8)	1 (7.7)	1 (9.1)
Sodium valproate	0 (0.0)	0 (0.0)	4 (30.8)	0 (0.0)

Abbreviations: ASMs, anti-seizure medications; FBTCS, focal to bilateral tonic-clonic seizures; FOS, focal-onset seizures; GTCS, generalized tonic-clonic seizures; NR, not reported; SD, standard deviation.

[a]Full analysis set.

[b]All 44 patients were included in the safety analysis set and full analysis set.

[c]Interim analysis set.

[d]Safety analysis set.

[e]Seizure type at baseline for Studies 412, 509, and 501; history of seizure type for Study 410.

[f]Seizure frequency = (number of seizures/[date of visit 1 - date 8 weeks before visit 1]) × 28 for Study 412; baseline seizure frequency data were collected retrospectively for Study 410; seizure frequency in the 3 months before perampanel initiation for Study 509; baseline seizure frequency per 28 days was calculated based on seizure diaries 8 weeks before perampanel initiation for Study 501.

[g]FOS with or without FBTCS.

[h]Included all types of seizures at baseline rather than the type of seizures recorded during the study.

[i]≥5% of patients from Studies 412 and 410, or ≥2 patients from Studies 509 and 501 (due to the small number of patients).

sodium valproate in Study 509 (30.8%), and carbamazepine in Study 501 (45.5%). The patient disposition of each trial is shown in Figure S1.

3.2 | Perampanel dose and exposure

Median mean daily dose of perampanel during the Maintenance Period of Study 410 or throughout the study period of Study 412, and median modal dose over the treatment period (Studies 509 and 501) ranged from 4.0 to 6.0 mg/day across studies (Table S1). The mean cumulative duration of exposure to perampanel was over 179 days in each study.

3.3 | Efficacy outcomes

The 50% and 75% responder rates and the seizure-freedom rates across studies are summarized in Figure 1. The proportion of patients achieving a 50% response was comparable at each time point within each of the studies (Figure 1A). At the final visit (or interim analysis in Study 509), the 50% responder rates across seizure types were 88.8%–100.0% in Study 412, 75.0%–87.5% in Study 410, 85.7%–100.0% in Study 509, and 62.5%–75.0% in Study 501. The 75% responder rates in patients with FOS varied between studies: 77.6%–84.5% in Study 412; 48.1%–59.3% in Study 410; and 25.0%–50.9% in Study 501 (Figure 1B). Results were similar in patients with FBTCS (Study

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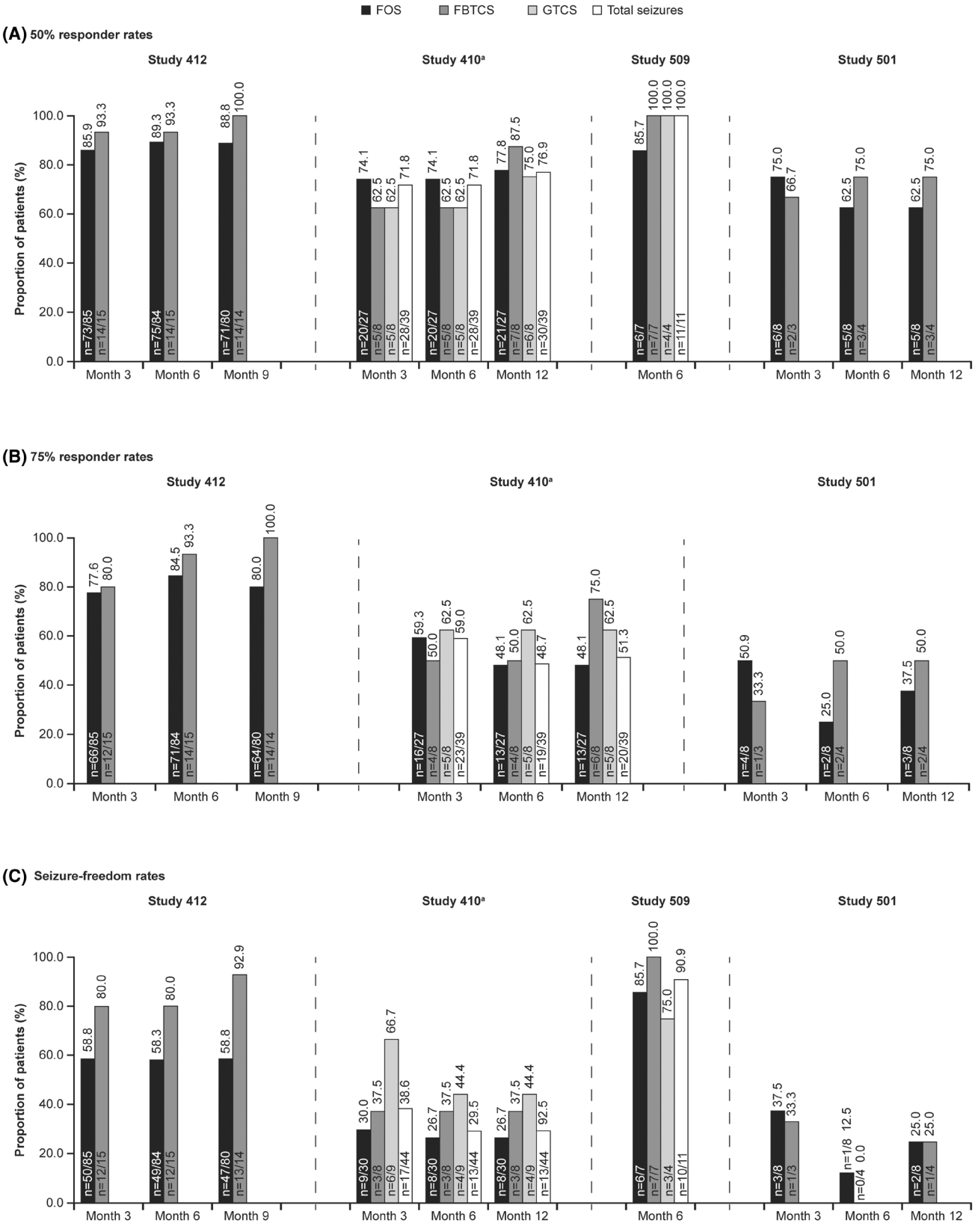

FIGURE 1 (A) 50% responder rates, (B) 75% responder rates, and (C) seizure-freedom rates in patients who received perampanel as first adjunctive therapy. [a]In Study 410, FOS includes patients with FOS only (with or without FBTCS); FBTCS is the subset of FOS only patients who recorded FBTCS during baseline; GTCS includes patients with GTCS only. The "Total" column includes patients with FOS only, GTCS only, and mixed FOS and GTCS; therefore, the total number of patients is greater than the sum of patients with FOS only or GTCS only. FBTCS, focal to bilateral tonic-clonic seizures; FOS, focal-onset seizures; GTCS, generalized tonic-clonic seizures.

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412, 80.0%–100.0%; Study 410, 50.0%–75.0%; Study 501, 33.3%–50.0%) and GTCS (Study 410, 62.5%). The seizure-freedom rates were >58% in patients with FOS and >80% in patients with FBTCS from Study 412 at each time point (Figure 1C). The proportion of patients achieving seizure freedom in Study 410 varied between seizure types but was consistent across time points (FOS, 26.7%–30.0%; FBTCS, 37.5%; GTCS, 44.4%–66.7%). At Month 6, seizure-freedom rates in Study 509 were >75.0% across all seizure types. In Study 501, the seizure-freedom rates were 12.5%–37.5% in patients with FOS and 0.0%–33.3% in patients with FBTCS.

3.4 | Safety outcomes

The percentage of patients who remained on perampanel as first adjunctive therapy at Month 6 was 61.8% in Study 412, 65.9% in Study 410, 92.3% in Study 509, and 72.7% in Study 501 (Figure 2). At Month 12, 59.1% of patients from Study 410 and 54.5% of patients from Study 501 remained on perampanel as first adjunctive therapy.

An overview of safety outcomes across studies is provided in Table 3. Overall, 46.2%–90.9% of patients experienced ≥1 TEAE and 13.7%–27.3% of patients across studies experienced a TEAE which resulted in perampanel

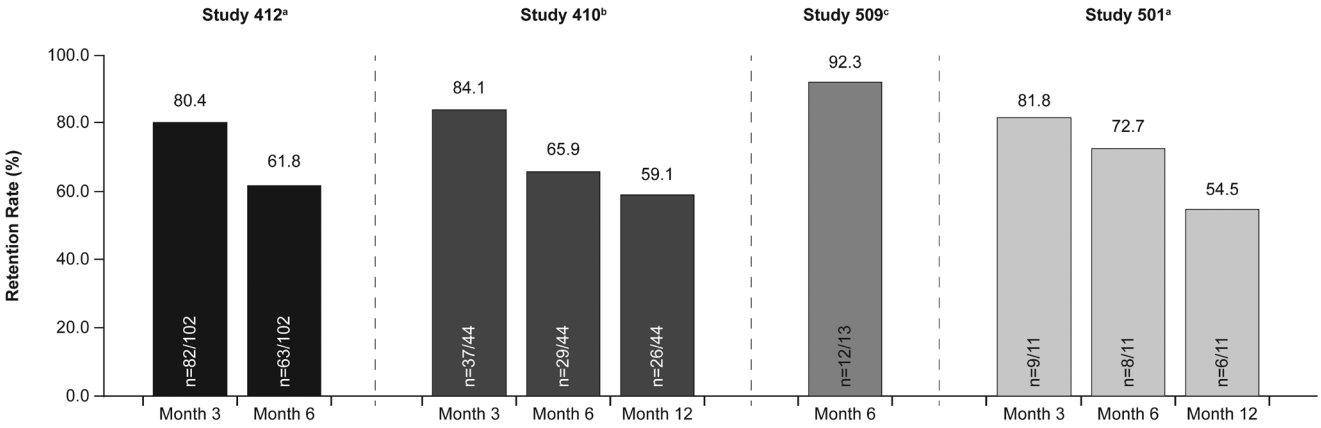

FIGURE 2 Retention rates in patients who received perampanel as first adjunctive therapy. [a]Safety analysis set. [b]All 44 patients were included in the safety analysis set and full analysis set. [c]Interim analysis set.

TABLE 3 Summary of TEAEs in patients who received perampanel as first adjunctive therapy.

	Study 412 (*N* = 102)[a]	Study 410 (*N* = 44)[a]	Study 509 (*N* = 13)[b]	Study 501 (*N* = 11)[a]
TEAEs, *n* (%)	77 (75.5)	40 (90.9)	6 (46.2)	10 (90.9)
Treatment-related TEAEs, *n* (%)	57 (55.9)[c]	27 (61.4)	1 (7.7)	8 (72.7)
Serious TEAEs, *n* (%)	8 (7.8)	3 (6.8)	1 (7.7)	1 (9.1)
TEAEs leading to perampanel discontinuation, *n* (%)	14 (13.7)	8 (18.2)	2 (15.4)	3 (27.3)
Most frequently reported TEAEs,[d] *n* (%)				
Dizziness[e]	51 (50.0)	14 (31.8)	1 (7.7)	3 (27.3)
Fatigue	2 (2.0)	6 (13.6)	1 (7.7)	0 (0.0)
Headache	9 (8.8)	5 (11.4)	0 (0.0)	1 (9.1)
Irritability	2 (2.0)	5 (11.4)	0 (0.0)	0 (0.0)
Somnolence	10 (9.8)	6 (13.6)	0 (0.0)	4 (36.4)
Vomiting	0 (0.0)	5 (11.4)	0 (0.0)	0 (0.0)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Safety analysis set.

[b]Interim analysis set.

[c]Adverse drug reactions, irrespective of causality to perampanel treatment, were reported in Study 412.

[d]TEAEs that occurred in ≥5% of patients from Study 412 or ≥10% of patients from Study 410; patients with >1 TEAE in the same category are only counted once in that category.

[e]Data for dizziness and vertigo have been combined for Study 501 because the Italian term "vertigine" translates to both "vertigo" and "dizziness" in English.

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discontinuation. The most common TEAEs reported across each study were dizziness (up to 50.0% of patients), somnolence (up to 36.4% of patients), fatigue (up to 13.6% of patients), headache (up to 11.4% of patients), irritability (up to 11.4% of patients), and vomiting (up to 11.4% of patients).

Serious TEAEs were reported in 6.8%–9.1% of patients across studies. One death, caused by sudden unexpected death in epilepsy, was reported in Study 410, but this was not considered to be related to perampanel; no deaths were reported in any other study.

4 | DISCUSSION

This post hoc analysis of Studies 412, 410, 509, and 501 demonstrated that treatment with perampanel as first adjunctive therapy was effective in reducing seizure frequency, with 50% responder rates ≥62.5% across seizure types in each of the four studies. In addition, perampanel as first adjunctive therapy also demonstrated favorable 75% responder rates at the latest time point in each study, ranging from 37.5% to 100.0%; while seizure-freedom rates ranged from 25.0% to 100.0%. First adjunctive perampanel was well tolerated in all studies, with retention rates >61% at Month 6. No new safety signals were observed. Overall, the results presented here suggest that perampanel may be an effective early-line ASM for the treatment of epilepsy.

The efficacy findings in this post hoc analysis were generally consistent with those in other real-world studies that evaluated perampanel as early-line adjunctive therapy in patients with epilepsy.[15–18] In these real-world studies, retention rates ranged from 67.0% to 90.5%; 50% responder rates ranged from 50.4% to 85.7%; and seizure-freedom rates ranged from 20.4% to 71.4%. Our results were also in line with PERMIT, a global pooled-analysis study evaluating the effectiveness and tolerability of perampanel in routine clinical care.[9] The 12-month retention rate in the PERMIT study was 64.2%, the 50% responder rate was 58.3%, and the seizure-freedom rate was 23.2%.[9] However, PERMIT included studies conducted in 17 countries in Europe, Asia, North America, the Middle East, and Australia, whereas in this post hoc analysis, we present a more homogeneous data set.

The safety of early-line perampanel treatment reported here is consistent with the known safety profile of perampanel in patients with epilepsy[5]; no new safety signals emerged and ≤27.3% of patients discontinued treatment due to TEAEs. It is important to note that this analysis was not powered to detect new safety signals. The frequency of treatment-related TEAEs varied by study, because these studies were conducted in four different countries and treating physicians could have distinctive criteria to assess the causality of TEAEs. Incidences of serious TEAEs were similar across studies, with 6.8–9.1% of patients reporting serious TEAEs. In addition, the incidences of TEAEs reported in this post hoc analysis were in line with those reported previously for perampanel as adjunctive therapy (30.1%–91.8%), with the highest incidence of TEAEs in this analysis being 72.7% in Study 501.[9,15–21] With this in mind, it is important to highlight the need to balance efficacy with tolerability for each patient when considering perampanel as a first adjunctive ASM.

Of note, research has found that cytochrome P450 3A4 (CYP3A4) polymorphism is related to ethnicity, with higher instances in people of non-European descent.[22] Polymorphic differences in CYP3A4 lead to altered drug metabolism and resultant differences in efficacy and tolerability.[22] Perampanel undergoes metabolism primarily via CYP3A4/5, and also has a weak inhibitory effect on CYP3A4 resulting in decreased midazolam concentrations (a CYP3A4 substrate).[5,23] A study of Korean participants found that the most common CYP3A4 variant in Asian populations was CYP3A4*18, with further research finding that this variant did not significantly affect midazolam disposition.[24] Together, these findings could indicate that the most common CYP3A4 variant in Asian populations may not have an impact on perampanel metabolism, as the CYP3A4*18 variant did not affect the metabolism of midazolam.[24] This is in line with the results presented here; results from Study 412 (South Korea) were comparable with those from Studies 410, 509, and 501 (US, Germany, Italy, respectively). In support of the findings of this analysis, results from subgroup analyses of the PERMIT study demonstrated that perampanel as early-line treatment was more effective and better tolerated than perampanel administered as late adjunctive therapy in patients with focal and/or generalized epilepsy.[25] Similarly, these findings are also supported by a multicenter survey of clinical experiences of adjunctive perampanel in Austria and Germany, which demonstrated better tolerability in patients with one or two baseline ASMs compared with those on more than two baseline ASMs, and a subgroup analysis of the PERPRISE study, which showed higher retention rates and better seizure outcomes with early-use perampanel (one or two prior ASMs) compared with late-use perampanel (≥5 prior ASMs).[13,26] Taken together, these data illustrate the importance of administering perampanel as early-line therapy, particularly because early response to ASM therapy is associated with a favorable prognosis in patients with epilepsy.[1]

Given the clinical benefit of perampanel as first adjunctive therapy observed in this post hoc analysis, it is

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also relevant to examine how the dosing regimen used in these studies compares with the approved indications and clinical practice guidelines.

In Europe, the recommended perampanel maintenance dose as an adjunctive therapy for patients aged ≥12 years with FOS is 4–8 mg/day (maximum 12 mg/day); for children aged 4–11 years, the recommended maintenance dose varies by weight (≥30 kg, 4–8 mg/day; 20–<30 kg, 4–6 mg/day; <20 kg, 2–4 mg/day).[7] For patients aged ≥7 years with GTCS, the recommended perampanel maintenance dose as an adjunctive therapy is up to 8 mg/day for those aged ≥12 years; the recommended maintenance dose for children aged 4–11 years also varies by weight and has similar ranges to those for patients with FOS.[7] In Korea, the recommended perampanel maintenance dose for patients aged ≥4 years with FOS is 4–8 mg/day (maximum 12 mg/day), both as monotherapy and adjunctive therapy; for patients aged ≥7 years with GTCS, the recommended maintenance dose as adjunctive therapy is 8 mg/day.[8] In the US, the recommended perampanel maintenance dose for patients aged ≥4 years with FOS as monotherapy or adjunctive therapy is 8–12 mg/day (maximum 12 mg/day), and for patients aged ≥12 years with GTCS as adjunctive therapy is 8 mg/day.[5] In the current post hoc analysis, the median daily dose of perampanel was ≤6 mg/day across studies. In addition, the dosing observed in Studies 412, 410, 509, and 501 was lower than that seen in the pivotal Phase III studies of adjunctive perampanel (8 or 12 mg/day).[19,20]

5 | LIMITATIONS

This post hoc analysis has several limitations, such as the small sample sizes (especially the patient populations of Studies 509 interim analysis and 501), the nonrandomized study designs, and the LOCF method, which was used to handle missing data in Studies 410 and 501. Although LOCF is a commonly used technique that enables complete case analysis without the need for complex modeling, it can introduce certain biases[27]; for example, this technique assumes that a patient's last recorded value remains unchanged over time and does not account for any changes in treatment effect beyond the last observed time point.

Another limitation is that the data were reported side by side and could not be pooled due to differences in study designs, which limits the ability to interpret and generalize the findings across studies. In addition, Studies 412, 410, 509, and 501 were mostly conducted in local countries and over different time periods (January 2016 to March 2023) rather than a controlled, global study conducted in parallel in these countries. The standard of care/clinical practice may be different in each country and may have evolved over this time within a single country. Furthermore, safety monitoring approaches could vary substantially across geographic regions or clinical practice settings, leading to inconsistent reporting; thus, incidences of TEAEs, and the potential heterogeneity in safety reporting may render cross-study comparisons of safety data inappropriate. Further analysis of the association between perampanel in combination with specific ASMs or groups stratified by enzyme-inducing or enzyme-inhibiting ASMs would be beneficial, but due to data limitations, it was not possible within the scope of this analysis.

6 | CONCLUSION

The results of post hoc analyses demonstrated that perampanel as first adjunctive therapy had favorable responder rates with no new safety signals across studies conducted in a range of clinical and regional settings. Overall, these data add further evidence to support the use of perampanel as an early-line treatment in patients with various seizure types (FOS, FBTCS, and GTCS).

AUTHOR CONTRIBUTIONS

Stefano Meletti was involved in data acquisition, interpretation of the study data, and the conceptual design of the study. Vineet Punia was involved in the acquisition, analysis, and interpretation of the study data. Amitabh Dash, Anna Lisa Gentile, Samantha Goldman, Tobias Goldmann, and Leock Y. Ngo were involved in the analysis and interpretation of the study data. Ricardo Sáinz-Fuertes provided clinical input and was involved in the interpretation of the study data. Anna Patten and Dinesh Kumar provided statistical support for the analyses. Bernhard J. Steinhoff was involved in the data acquisition and conceptual design of the study. All authors contributed to and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

Stefano Meletti has received speaker honoraria from Eisai, Jazz Pharmaceuticals, and UCB Pharma; and has served as a paid consultant for Jazz Pharmaceuticals and UCB Pharma. Vineet Punia has carried out consultancy and/or been on an advisory board for Catalyst Pharmaceuticals, Eisai Inc., Ovid Therapeutics, and UNEEG. Amitabh Dash is an employee of Eisai Singapore Pte. Ltd. Anna Lisa Gentile is an employee of Eisai S.r.l. Ricardo Sáinz-Fuertes, Samantha Goldman, and Anna Patten are employees of Eisai Europe Ltd. Tobias Goldmann is an employee of Eisai GmbH. Dinesh Kumar is an employee of Eisai Inc. Leock Y. Ngo is a former employee of Eisai Inc. Bernhard J. Steinhoff has received speaker honoraria from Angelini, Desitin, Eisai, Medscape, Paladin Labs, Tabuk Pharmaceuticals, Teva, and UCB Pharma, and has served as a paid consultant for Angelini, B. Braun Melsungen, Precisis, Roche Diagnostics, and UCB Pharma. 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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REFERENCES

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
2. Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012;78:1548–54.
3. Ayalew MB, Muche EA. Patient reported adverse events among epileptic patients taking antiepileptic drugs. SAGE Open Med. 2018;6:2050312118772471.
4. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
5. Food and Drug Administration (FDA). FYCOMPA® Prescribing Information. https://www.fycompa.com/media/media/Files/Fycompa/Fycompa_Prescribing_Information.pdf
6. Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. Epilepsia. 2015;56:12–27.
7. European Medicines Agency (EMA). FYCOMPA® Annex I: Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/fycompa-epar-product-information_en.pdf
8. Ministry of Food and Drug Safety - Republic of Korea. FYCOMPA® Prescribing Information. http://www.eisaikorea.com/
9. Villanueva V, D'Souza W, Goji H, Kim DW, Liguori C, McMurray R, et al. PERMIT study: a global pooled analysis study of the effectiveness and tolerability of perampanel in routine clinical practice. J Neurol. 2022;269:1957–77.
10. Liguori C, Santamarina E, Strzelczyk A, Rodríguez-Uranga JJ, Shankar R, Rodríguez-Osorio X, et al. Perampanel outcomes at different stages of treatment in people with focal and generalized epilepsy treated in clinical practice: evidence from the PERMIT study. Front Neurol. 2023;14:1120150.
11. Kim JH, Kim DW, Lee SK, Seo DW, Lee JW, Park HJ, et al. First add-on perampanel for focal-onset seizures: an open-label, prospective study. Acta Neurol Scand. 2020;141:132–40.
12. Punia V, Klein P, Mihaylova T, Biton V, Samad O, Ngo LY, et al. Perampanel as monotherapy or first adjunctive therapy in pediatric and adult patients with epilepsy: the first United States-based phase IV open-label ELEVATE study. J Neurol. 2024;271:4587–98.
13. Steinhoff BJ, Goldmann T, Kockelmann E, Winter Y. PERPRISE: a prospective non-interventional study of PERampanel as only adjunctive treatment in patients with PRImary or SEcondarily generalized tonic-clonic seizures: first interim analysis. Epilepsia Open. 2024;9(3):926–39.
14. 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;10:1074–85.
15. Abril Jaramillo J, Estévez María JC, Girón Úbeda JM, Vega López Ó, Calzado Rivas ME, Pérez Díaz H, et al. Effectiveness and safety of perampanel as early add-on treatment in patients with epilepsy and focal seizures in the routine clinical practice: Spain prospective study (PERADON). Epilepsy Behav. 2020;102:106655.
16. Santamarina E, Bertol V, Garayoa V, Garcia-Gomara MJ, Garamendi-Ruiz I, Giner P, et al. Efficacy and tolerability of perampanel as a first add-on therapy with different anti-seizure drugs. Seizure. 2020;83:48–56.
17. Rea R, Traini E, Renna R, Pagliuca F, Pezzella M, Pagliuca M. Efficacy and impact on cognitive functions and quality of life of

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perampanel as first add-on therapy in patients with epilepsy: a retrospective study. Epilepsy Behav. 2019;98:139–44.
18. Canas N, Félix C, Silva V, Arraiolos A, Fernandez-Llimos F. Comparative 12-month retention rate, effectiveness and tolerability of perampanel when used as a first add-on or a late add-on treatment in patients with focal epilepsies: the COM-PER study. Seizure. 2021;86:109–15.
19. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79:589–96.
20. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54:117–25.
21. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78:1408–15.
22. Guttman Y, Nudel A, Kerem Z. Polymorphism in cytochrome P450 3A4 is ethnicity related. Front Genet. 2019;10:224.
23. Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta Neurol Scand Suppl. 2013;127:19–24.
24. Lee SJ, Lee SS, Jeong HE, Shon JH, Ryu JY, Sunwoo YE, et al. The CYP3A4*18 allele, the most frequent coding variant in asian populations, does not significantly affect the midazolam disposition in heterozygous individuals. Drug Metab Dispos. 2007;35:2095–101.
25. Santamarina E, Abril-Jaramillo J, Rodriguez-Osorio X, Yamamoto T, McMurray R, Trinka E, et al. Perampanel as early add-on therapy for epilepsy patients with focal-onset and generalized-onset seizures treated in clinical practice. 75th annual meeting of the American Epilepsy Society, Chicago, IL, USA. 3.213 ed2021.
26. Steinhoff BJ, Hamer H, Trinka E, Schulze-Bonhage A, Bien C, Mayer T, et al. A multicenter survey of clinical experiences with perampanel in real life in Germany and Austria. Epilepsy Res. 2014;108:986–8.
27. Mavridis D, Salanti G, Furukawa TA, Cipriani A, Chaimani A, White IR. Allowing for uncertainty due to missing and LOCF imputed outcomes in meta-analysis. Stat Med. 2019;38:720–37.

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