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First add-on perampanel for focal-onset seizures: An open-label, prospective study

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Objectives: This study aimed to determine the efficacy and safety of perampanel added to monotherapy in patients with focal-onset seizures, with or without secondarily generalized tonic-clonic seizures.

Materials & Methods: In this multicentre, open-label trial, enrolled patients were treated with perampanel monotherapy. During a 12-week titration period, perampanel was incrementally increased by 2 mg/d over ≥2-week intervals. Patients then entered a 24-week maintenance period. The primary objective was to investigate the 50% responder rate in total seizure frequency, with 75% and 100% responder rates as secondary objectives. Treatment-emergent adverse events (TEAEs) and adverse drug reactions were recorded. A post hoc analysis was performed to investigate the effect of titration speed and different concomitant AEDs on the efficacy and safety of perampanel.

Results: Of the 85 patients analysed, seizure reductions of 50%, 75% and 100% were observed in 80.0% (95% confidence interval [CI]: 69.9-87.9), 71.8% (95% CI: 61.0-81.0) and 47.1% (95% CI: 36.1-58.2) during the maintenance period, respectively. The 50%, 75% and 100% response rates in patients with secondarily generalized tonic-clonic seizures were 87.5% (95% CI: 61.7-98.5), 87.5% (95% CI: 61.7-98.5) and 75.0% (95% CI: 47.6-92.7), respectively. The most common TEAEs were dizziness (50.0%), somnolence (9.8%) and headache (8.8%). The efficacy outcomes and safety profile of perampanel were more favourable with slow titration and relatively consistent when stratified by concomitant AEDs.

Conclusions: Perampanel was effective and well tolerated as a first add-on to monotherapy in patients with focal-onset seizures, with or without secondarily generalized seizures.

KEYWORDS

AMPA receptor, drug resistance, epilepsy, focal seizures, generalised tonic-clonic seizures

Ji Hyun Kim and Dong Wook Kim are joint first authors.

Trial registration: NCT02726074

1 | INTRODUCTION

In general, epilepsy treatment guidelines recommend the use of anti-epileptic drugs (AEDs) after a second epileptic seizure is observed.[1,2] Although monotherapy with a single AED is the first-line treatment option, adjunctive treatment is often required to produce seizure freedom.[3] There is a need for add-on therapies that compliment AEDs, have a broad-spectrum anti-seizure effect, and do not induce or inhibit the pharmacokinetic properties of other AEDs.[4,5]

Perampanel is a selective and non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor antagonist.[6-9] Clinical trials have shown that perampanel is an effective and safe treatment option that significantly improves seizure control in patients with focal-onset seizures.[10-13] In 2012, perampanel was approved by the European Medicines Agency and the United States Food and Drug Administration with the indication as an adjunctive therapy for focal-onset seizures in patients with or without secondarily generalized seizures.[14] Furthermore, the South Korean Ministry of Food and Drug Safety approved perampanel in 2015 for the same indication but with an additional indication as an adjunctive therapy for primary generalized tonic-clonic seizures in patients with epilepsy.

At present, there are limited data on the efficacy and safety of perampanel as a first add-on therapy, as previous clinical trials have generally only included patients who were receiving two or more concomitant AEDs at baseline. When considering the novel mode of action of perampanel, it is of interest to determine whether there are any synergistic effects with combination therapy, which can be best demonstrated in a study investigating perampanel as a first add-on therapy to monotherapy. Therefore, this study aimed to assess the efficacy and safety of perampanel as a first add-on therapy in patients in South Korea with focal-onset seizures, with or without secondarily generalized tonic-clonic seizures.

2 | METHODS

2.1 | Patients

This study included male and female patients aged ≥12 years with a diagnosis of epilepsy with partial-onset seizures (now classified as focal-onset seizures), with or without secondarily generalized tonic-clonic seizures, according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981)[15]; and patients who required add-on therapy after failure to control seizures with AED monotherapy. During the 8 weeks prior to Week 0, patients must have had ≥2 focal-onset seizures and the interval between those seizures must have been >24 hours. The main exclusion criteria were a history of Lennox-Gastaut syndrome, the presence of nonmotor simple focal seizures only, the presence of primary generalized epilepsies or seizures such as absences and/or myoclonic epilepsies, or a history of status epilepticus. Additional exclusion criteria are detailed in the Appendix (supplementary information).

Concomitant AED monotherapy must have been administered at a stable dose for 8 weeks prior to Week 0. Details on standard AEDs that are permitted, as well as prohibited and restricted concomitant drugs, are described in the Appendix S1.

The study protocol was reviewed by the institutional review boards or ethics committees of participating centres for ethical approval, and the study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (2008), the International Conference on Harmonisation of Pharmaceuticals for Human Use and Korea Good Clinical Practice (2014). All patients provided written informed consent prior to trial participation. This trial was registered at ClinicalTrials.gov (NCT02726074).

2.2 | Study design and treatments

This was a multicentre, open-label, single-arm, phase 4 prospective cohort study conducted from January 2016 to April 2017. The study consisted of two treatment periods: a titration period (12 weeks) and a maintenance period (24 weeks; Figure 1).

Patients orally received 2-mg perampanel tablets once daily before bedtime. During the titration period, perampanel was incrementally increased by 2 mg/d over ≥2-week intervals to a maximum of 12 mg/d. However, the presence of permitted enzyme-inducing AEDs (see Appendix S1) that shortened the half-life of perampanel required patients to incrementally increase the dosage by 2 mg/d over ≥1-week intervals. If patients experienced intolerable adverse events (AEs), then dose titration was prohibited until the AEs were resolved, after which dose titration could be resumed if necessary. Patients who could not tolerate 4 mg/d perampanel were discontinued from the study. The final dosage at the end of the titration period was used for the maintenance period; however, if patients experienced intolerable AEs, then the dose could be reduced and subsequently increased if AEs subsided. Similarly, if a patient failed to gain adequate control of their seizures, then the dosage could be increased up to a maximum of 12 mg/d during the maintenance period.

2.3 | Efficacy endpoints

The primary efficacy endpoint was a 50% responder rate, which was defined as patients who had a ≥50% reduction in total seizure frequency during the maintenance period. Secondary efficacy assessments included the 75% responder rate (a ≥75% reduction in total seizure frequency) and the 100% responder rate (seizure-free rate) in total seizures. Furthermore, the efficacy of perampanel for secondarily generalized tonic-clonic seizures was also investigated by assessing the 50%, 75% and 100% responder rates. Nonmotor simple partial seizures were not assessed. Data on seizure frequency were collected in diaries by patients or their legal representatives who were educated by the investigators, using a standardized training program,

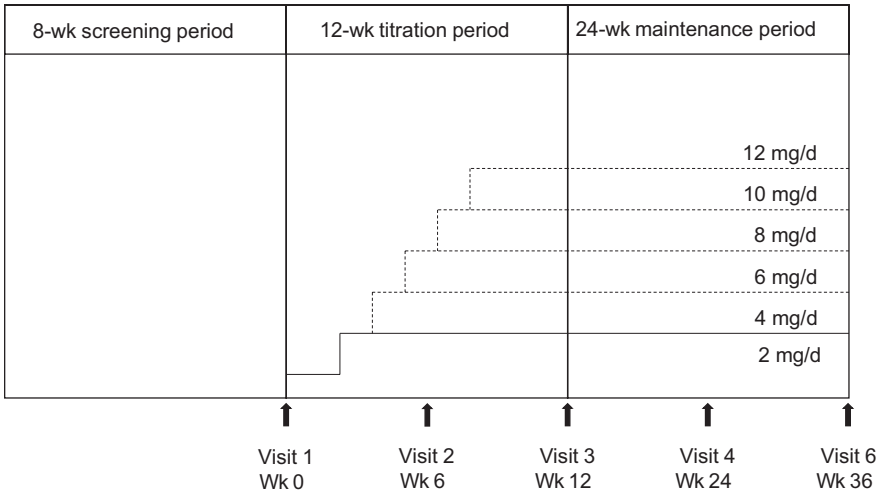


FIGURE 1 Study design

on how to identify a seizure. Baseline data on seizure frequency were collected retrospectively from the 8 weeks prior to the study.

2.4 | Safety endpoints

Safety was assessed by monitoring treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), withdrawal from treatment and clinical laboratory evaluations (haematology, clinical chemistry and urinalysis). AEs were coded by MedDRA Version 21.0 using preferred term and system organ class terminology.

2.5 | Post hoc analyses

Post hoc analyses were performed to determine the effect of perampanel on efficacy and safety endpoints when stratified by titration speed (slow: dosage up-titration performed at ≥2-week intervals; fast: dosage up-titration performed at <2-week intervals) or by the mechanism of action of concomitant AEDs.

2.6 | Statistical methods

The sample size rationale was set using the primary endpoint, the 50% responder rate. Based on the findings of Steinhoff et al[10] who conducted a pooled analysis of three phase 3 studies on adjunctive perampanel, it was assumed that 35.3% of patients would achieve a 50% response in the test group compared with 19.3% of patients in the control group. If the lower limit of the 95% confidence interval (CI) for the 50% responder rate was >19.3%, then 94 patients were required to achieve a power of 90%. When considering a drop-out rate of 10%, the total sample size required was 105 patients.

Efficacy endpoints were analysed using the full analysis set (FAS) comprising patients who received at least one dose of perampanel and were included in at least one efficacy assessment. Efficacy analyses were presented as the proportion of patients who achieved a reduction in seizure frequency and corresponding 95% CIs. The safety analysis set (SAF) comprised patients who received at least one dose of perampanel and were included in at least one safety assessment. Safety analyses were conducted in a descriptive manner and presented with summary statistics. Statistical analysis was performed using SAS® Version 9.4 (SAS Institute).

3 | RESULTS

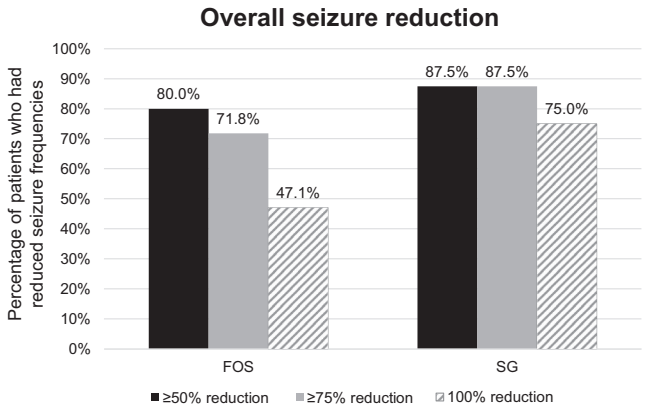
3.1 | Patients

In this study, 106 patients were enrolled, among whom 102 were included in the SAF. The reasons for patient withdrawal were "did not receive any perampanel" (n = 3) and "no safety assessments performed after the study started" owing to loss to follow-up of the patient (n = 1). A further 17 patients were excluded because their primary efficacy outcomes were not evaluated during the maintenance period after perampanel was administered. The reasons for not assessing these patients were as follows: occurrence of an AE (n = 11) and a serious AE (n = 1), withdrawal of consent (n = 2), lost to follow-up (n = 1), investigational drug overdose (n = 1) and protocol violation (n = 1). There were no obvious differences in baseline demographics and characteristics between included and excluded patients. Therefore, 85 patients were included in the FAS, 80 of whom completed the study.

Baseline patient characteristics are shown in Table 1. In the FAS, the mean ± standard deviation (SD) age was 42.3 ± 14.1 years, number of years since an epilepsy diagnosis was 10.9 ± 9.3 years, and frequency of focal-onset seizures was 4.1 ± 7.7 per 28 days.

3.2 | Efficacy outcomes

The proportion of patients who had a reduction in the frequency of focal-onset seizures of ≥50% during the maintenance period was 80.0% (n = 68 [95% CI: 69.9-87.9]) (Figure 2). The proportions of patients who had focal-onset seizure frequency reductions of 75%



Percentage of patients with reduction in seizure frequencies	FOS	SG
≥50% reduction	68/85	14/16
≥75% reduction	61/85	14/16
100% reduction	40/85	12/16

FIGURE 2 Overall reduction in seizure frequency. FOS, focal-onset seizures; SG, secondarily generalized tonic-clonic seizures

and 100% during the maintenance period were 71.8% (n = 61 [95% CI: 61.0-81.0]) and 47.1% (n = 40 [95% CI: 36.1-58.2]), respectively (Figure 2). Overall, the mean ± SD percent change in focal-onset seizure frequency during the maintenance period was −59.6 ± 76.7%.

The percentages of patients who experienced a reduction in the frequency of secondarily generalized tonic-clonic seizures by ≥50%, ≥75% and 100% during the maintenance period were 87.5% (n = 14 [95% CI: 61.7-98.5]), 87.5% (n = 14 [95% CI: 61.7-98.5]) and 75.0% (n = 12 [95% CI: 47.6-92.7]), respectively (Figure 2). The overall mean ± SD percent change in secondarily generalized tonic-clonic seizure frequency during the maintenance period was −82.6 ± 35.1%.

Post hoc analyses showed that, when stratified by titration speed, the proportions of patients in the slow titration group who had 50%, 75% or 100% responder rates were numerically higher than those in the fast titration group (83.1% vs 73.1%, 72.9% vs 69.2% and 49.2% vs 42.3%, respectively) (Table 2). When stratified by the mechanism of action of concomitant AEDs, the proportion of patients with 50% response rates was relatively consistent across the drugs classed as a sodium-channel blocker (79.5% [95% CI: 64.7-90.2]), a synaptic vesicle glycoprotein 2A (SV2A) antagonist (82.4% [95% CI: 65.5-93.2]), or AEDs with multiple mechanisms of action (MoAs) (71.4% [95% CI: 29.0-96.3]) (Table 3). In secondarily generalized tonic-clonic seizures, the 50% response rates were numerically high across the drugs classed as a sodium-channel blocker (88.9% [95% CI: 51.8-99.7]), an SV2A antagonist (83.3% [95% CI: 35.9-99.6]), or AEDs with multiple MoAs (100.0% [95% CI: 2.5-100.0]) (Table S1).

3.3 | Safety outcomes

The incidences of TEAEs and ADRs were 75.5% (138 events in 77 patients) and 55.9% (90 events in 57 patients), respectively. The most common TEAEs reported were dizziness (50.0%), somnolence (9.8%) and headache (8.8%) for the whole study period (Table 4); these common TEAEs were reported in 37.3%, 8.8% and 4.9% of patients, respectively, during the 12-week titration period (Table S2). Most TEAEs were mild in severity (64.7%) and 7.8% (n = 8) of patients reported serious AEs (Table 4). These central nervous system (CNS)-specific TEAEs were consistently observed with 2-8 mg/d perampanel, except for headache, which did not occur at a dosage of 8 mg/d perampanel (Table S3).

When TEAEs were stratified by titration speed, the incidence rate of TEAEs was 82.9% for the fast titration group compared with 70.5% for the slow titration group (Table S4). Somnolence was reported by 13.1% of patients in the slow titration group compared

TABLE 1 Patient characteristics in the full analysis set

	Total N = 85
Age, y	42.3 ± 14.1
Age group, n (%)	
<65 y	79 (92.9)
≥65 y	6 (7.1)
Sex, n (%)	
Male	36 (42.4)
Female	49 (57.6)
Bodyweight, kg	63.3 ± 10.9
Body mass index, kg/m^2	23.3 ± 3.7
Epilepsy duration, y	10.9 ± 9.3
ILAE Classification, n (%)	
Generalized seizures	0 (0.0)
Focal seizures	85 (100.0)
Cause of epilepsy, n (%)	
Head injury/cranial trauma (post-traumatic epilepsy, post-neurosurgery)	7 (8.2)
Stroke (post-stroke epilepsy)	1 (1.2)
Structural brain anomalies or malformations (tuberous sclerosis, etc)	7 (8.2)
Vascular brain anomalies (arteriovenous malformation, etc)	5 (5.9)
Family history of epilepsy	1 (1.2)
Other	9 (10.6)
Unknown	55 (64.7)
Seizure frequency	
Focal-onset seizures frequency	4.1 ± 7.7
Simple focal seizures with motor symptoms	0.8 ± 4.3
Complex focal seizures	2.9 ± 6.8
Complex focal seizures with secondarily generalized seizure	0.3 ± 1.0

Note: Data are presented as mean ± standard deviation unless otherwise stated.

Abbreviations: CNS, central nervous system; ILAE, International League Against Epilepsy.

TABLE 2 Proportion of patients in the full analysis set who had a reduction in the frequency of focal-onset seizures during the maintenance period stratified by titration speed and response rate

Responder rate	Parameter	Reported as	Slow N = 59	Fast N = 26
50% response	Screening period seizure frequency	N	49	19
		Mean ± SD	2.0 ± 2.4	5.8 ± 8.2
	Maintenance period seizure frequency	N	49	19
		Mean ± SD	0.2 ± 0.3	0.4 ± 0.7
	Ratio	N (%)	49 (83.1)	19 (73.1)
		95% CI	71.0-91.6	52.2-88.4
75% response	Screening period seizure frequency	N	43	18
		Mean ± SD	2.1 ± 2.6	5.9 ± 8.4
	Maintenance period seizure frequency	N	43	18
		Mean ± SD	0.1 ± 0.2	0.4 ± 0.7
	Ratio	N (%)	43 (72.9)	18 (69.2)
		95% CI	59.7-83.6	48.2-85.7
100% response	Screening period seizure frequency	N	29	11
		Mean ± SD	1.4 ± 0.7	2.1 ± 1.3
	Maintenance period seizure frequency	N	29	11
		Mean ± SD	0.0 ± 0.0	0.0 ± 0.0
	Ratio	N (%)	29 (49.2)	11 (42.3)
		95% CI	35.9-62.5	23.4-63.1

Note: 95% CIs calculated by the Clopper-Pearson method.

Abbreviations: CI, confidence interval; SD, standard deviation.

TABLE 3 Proportion of patients in the full analysis set who had a frequency reduction in focal-onset seizures stratified by mechanism of action of concomitant anti-epileptic drugs

Response rate	Parameter	Reported as	Sodium-channel blockers N = 44	SV2A Antagonism N = 34	Multiple mechanisms of actions N = 7	Total N = 85
50% Response	Screening period seizure frequency	N	35	28	5	68
		Mean ± SD	2.7 ± 4.6	3.7 ± 5.9	2.2 ± 1.4	3.1 ± 5.0
	Maintenance period seizure frequency	N	35	28	5	68
		Mean ± SD	0.2 ± 0.4	0.3 ± 0.5	0.1 ± 0.2	0.3 ± 0.4
	Ratio	N (%)	35 (79.5)	28 (82.4)	5 (71.4)	68 (80.0)
		95% CI	64.7-90.2	65.5-93.2	29.0-96.3	69.9-87.9
75% Response	Screening period seizure frequency	N	31	25	5	61
		Mean ± SD	2.8 ± 4.9	3.8 ± 6.2	2.2 ± 1.4	3.2 ± 5.3
	Maintenance period seizure frequency	N	31	25	5	61
		Mean ± SD	0.1 ± 0.4	0.3 ± 0.5	0.1 ± 0.2	0.2 ± 0.4
	Ratio	N (%)	31 (70.5)	25 (73.5)	5 (71.4)	61 (71.8)
		95% CI	54.8-83.2	55.6-87.1	29.0-96.3	61.0-81.0
100% Response	Screening period seizure frequency	N	23	14	3	40
		Mean ± SD	1.6 ± 0.9	1.3 ± 0.4	2.7 ± 1.6	1.6 ± 0.9
	Maintenance period seizure frequency	N	23	14	3	40
		Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Ratio	N (%)	23 (52.3)	14 (41.2)	3 (42.9)	40 (47.1)
		95% CI	36.7-67.5	24.7-59.3	9.9-81.6	36.1-58.2

Note: 95% confidence intervals calculated with the Clopper-Pearson method.

Abbreviations: CI, confidence interval; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A.

TABLE 4 Summary of treatment-emergent adverse events in the safety analysis set

System organ class	Preferred term	Total N = 102
Number of patients with TEAEs		**77 (75.5) [138]**
95% CI		66.0-83.5
Severity of TEAEs		
Mild		66 (64.7) [111]
Moderate		16 (15.7) [26]
Severe		1 (1.0) [1]
Number of patients with SAEs		**8 (7.8) [11]**
95% CI		3.5-14.9
Number of patients with TEAEs causing treatment discontinuation		**14 (13.7) [23]**
95% CI		7.7-22.0
Nervous system disorders		**64 (62.7) [95]**
	Dizziness	51 (50.0) [58]
	Somnolence	10 (9.8) [10]
	Headache	9 (8.8) [10]
	Dysarthria	5 (4.9) [5]
	Seizure	4 (3.9) [4]
	Memory impairment	2 (2.0) [2]
	Hypoaesthesia	1 (1.0) [1]
	Lethargy	1 (1.0) [1]
	Paraesthesia	1 (1.0) [1]
	Parkinsonism	1 (1.0) [1]
	Speech disorder	1 (1.0) [1]
	Syncope	1 (1.0) [1]
Psychiatric disorders		**8 (7.8) [9]**
	Anger	2 (2.0) [2]
	Irritability	2 (2.0) [2]
	Confusional state	1 (1.0) [1]
	Depression	1 (1.0) [1]
	Suicidal ideation	1 (1.0) [1]
	Suicide attempt	1 (1.0) [1]
	Tearfulness	1 (1.0) [1]
General disorders and administration site conditions		**7 (6.9) [7]**
	Fatigue	2 (2.0) [2]
	Oedema	2 (2.0) [2]
	Face oedema	1 (1.0) [1]
	Gait disturbance	1 (1.0) [1]
	Perforation	1 (1.0) [1]
Injury, poisoning and procedural complications		**6 (5.9) [6]**
	Clavicle fracture	1 (1.0) [1]
	Contusion	1 (1.0) [1]
	Head injury	1 (1.0) [1]
	Lip injury	1 (1.0) [1]
	Lower limb fracture	1 (1.0) [1]
	Procedural pain	1 (1.0) [1]
Gastrointestinal disorders		**4 (3.9) [4]**
	Dry mouth	1 (1.0) [1]
	Haemorrhoids	1 (1.0) [1]
	Nausea	1 (1.0) [1]
	Pancreatitis acute	1 (1.0) [1]
Respiratory, thoracic and mediastinal disorders		**4 (3.9) [4]**
	Dyspnoea	1 (1.0) [1]
	Epistaxis	1 (1.0) [1]
	Nasal discomfort	1 (1.0) [1]
	Rhinorrhoea	1 (1.0) [1]
Eye disorders		**3 (2.9) [3]**
	Diplopia	1 (1.0) [1]
	Vision blurred	1 (1.0) [1]
	Visual impairment	1 (1.0) [1]
Infections and infestations		**2 (2.0) [2]**
	Furuncle	1 (1.0) [1]
	Nasopharyngitis	1 (1.0) [1]
Musculoskeletal and connective tissue disorders		**2 (2.0) [2]**
	Intervertebral disc disorder	1 (1.0) [1]
	Muscle spasms	1 (1.0) [1]
Skin and subcutaneous tissue disorders		**2 (2.0) [2]**
	Pruritus	2 (2.0) [2]
Blood and lymphatic system disorders		**1 (1.0) [1]**
	Bicytopenia	1 (1.0) [1]
Investigations		**1 (1.0) [1]**
	Weight increased	1 (1.0) [1]
Metabolism and nutrition disorders		**1 (1.0) [1]**
	Diabetes mellitus	1 (1.0) [1]
Vascular disorders		**1 (1.0) [1]**
	Labile hypertension	1 (1.0) [1]

Note: Data are presented as n (%) [number of events]. MedDRA version 21.0. Bold values mean the total number of each details.

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse events.

with 4.9% in the fast titration group. As for other common TEAEs, dizziness was reported by 47.5% and 53.7% of patients in the slow and fast titration groups, respectively; and headache by 6.6% and 12.2% of patients, respectively.

When stratified by the mechanism of action of concomitant AEDs, the incidences of TEAEs observed varied (Table S5). For example, although not statistically tested, fewer incidences of TEAEs such as somnolence or headache were reported in patients administered sodium-channel blockers and SV2A antagonists, but they rarely occurred in patients administered AEDs with multiple different MoAs. Furthermore, the incidence rates of dysarthria and seizures were 10.3% for both in patients administered the SV2A antagonist levetiracetam.

The most commonly reported ADRs were dizziness (44.1%), somnolence (9.8%), dysarthria (4.9%) and headache (4.9%) (Table S6). In addition, anger (n = 2, 2.0%) was reported as an ADR once during the maintenance period (n = 1; 10 mg/d) and once during the follow-up period (n = 1; 4 mg/d). Suicide ideation (n = 1, 1.0%) was reported as an ADR during the titration period when the patient was administered 4 mg/d. Other notable ADRs include bicytopenia (n = 1) and weight increased (n = 1), which were reported during the follow-up period of this study.

Sex (male vs female) and age (continuous variable) had no influence on the incidence of any AE (odds ratio: 0.5 [95% CI: 0.2-1.3] and odds ratio: 1.0 [1.0-1.0], respectively). Sixteen of 79 patients (20.3%) had an increase in weight of 5%-10%, and one patient (1.3%) had an increase of >10%. Some laboratory test changes were also observed, but most were not clinically significant.

4 | DISCUSSION

This study demonstrated that once-daily perampanel as a first add-on treatment to monotherapy was effective and well tolerated in South Korean patients with focal-onset seizures, with or without secondarily generalized tonic-clonic seizures. The responder rates show that first add-on of perampanel is an effective choice for patients with focal-onset seizures. In addition, post hoc analysis suggested that titration speed affects response to treatment with a slower titration speed resulting in numerically higher response rates compared with a faster titration speed. Perampanel was also judged to be well tolerated as most TEAEs were mild in severity and a low percentage of patients discontinued the study.

Perampanel has been extensively evaluated in treatment-resistant patients with perampanel at 8 or 12 mg/d,[16,17] or perampanel at 2, 4 or 8 mg/d.[18] In a pooled analysis of three perampanel clinical trials, it was shown that the majority of patients enrolled were receiving ≥2 concomitant AEDs (two AEDs: 50.7% patients; three AEDs: 35.3% patients).[10] In these clinical trials, the proportions of patients with a 50% responder rate were 28.5%, 35.3% and 35.0% for perampanel administered at 4, 8 and 12 mg/d, respectively.[16-19] Although the designs of these previous clinical trials differed considerably from that of the present study, our results showed that perampanel is much more efficacious in treating patients with partial-onset seizures, which may be because perampanel had been given as a first add-on treatment to monotherapy.

Perampanel also showed good efficacy in reducing seizure frequency of secondarily generalized tonic-clonic seizures. Although only 18.8% of patients have a secondarily generalized tonic-clonic seizure during the screening period, current data suggest that perampanel may also be effective at controlling secondarily generalized tonic-clonic seizures. Perampanel has previously been shown to also be effective at reducing seizure frequency in patients with drug-resistant, primary generalized tonic-clonic seizures.[20] In this study, the 50% seizure responder rate was 64.2% and the median percent change in seizure frequency per 28 days was 76.5%. A pooled analysis of three randomized clinical studies[10] showed that perampanel was also effective in reducing secondarily generalized seizure frequency with 50% response rates of 49.3%, 60.5% and 53.7% for perampanel 4, 8 and 12 mg/d, respectively.

When comparing the safety profile of perampanel against pooled data on perampanel from three phase 3 trials (studies: 304, 305 and 306), there were no new side effects to report.[10,21] The occurrence of CNS-specific AEs (eg dizziness, somnolence and headache) has consistently been reported for other AEDs[22] and in prior studies with perampanel for focal-onset seizures or primary generalized tonic-clonic seizures.[23] In this study, dizziness was reported in 51 patients (50.0%) overall, which may be largely attributable to the study design where the perampanel dose was increased by 2 mg/d over ≥2-week intervals during the 12-week titration period; of note, 38 (37.3%) of these patients reported dizziness during the titration period, but most events were mild in severity (mild, n = 33; moderate, n = 5), and all patients who suffered from dizziness recovered. It is also worth noting that the incidence of dizziness was reduced if the slow titration method was used. The warnings and precautions in the perampanel package insert describe serious behavioural reactions, such as aggression and suicide ideation, as dose-related ADRs.[23] Suicide ideation was reported in one patient currently being administered a concomitant SV2A antagonist (levetiracetam), whereas a suicide attempt was reported in one patient currently being administered a concomitant sodium-channel blocker (lamotrigine). Patient characteristics, including age and sex, did not appear to influence the safety outcomes related to perampanel in this study.

In this study, there were limited numbers of patients currently being administered valproic acid (n = 4), topiramate (n = 2) or zonisamide (n = 1), and thus grouped under "multiple MoAs" for analysis, which makes it difficult to compare efficacy and safety profiles between concomitant AEDs. However, when stratified by the mechanism of action of concomitant AEDs, the 50% and 75% response rates were relatively consistent for AEDs classed as either a sodium-channel blocker (lamotrigine, carbamazepine or oxcarbazepine), an SV2A antagonist (levetiracetam) or AEDs with multiple MoAs (valproic acid or zonisamide). Focal-onset seizure-free rates were modest and relatively consistent across those patients who were

being administered a sodium-channel blocker (52.3%), an SV2A antagonist (41.2%), or AEDs with multiple MoAs (42.9%). When comparing the safety profile stratified by the mechanism of action of concomitant AEDs, the proportion of patients experiencing a TEAE slightly differed, although dizziness was still the most prevalent across all treatment regimes.

Many patients require successive AED drug regimens; however, this is associated with a higher incidence of adverse events and rapidly diminishing seizure-free rates with subsequent AED add-on regimens.[24,25] In previous perampanel clinical trials, most patients in each study cohort were already taking two or three AEDs at baseline, including new-generation AEDs, such as levetiracetam and lamotrigine.[26] In this study, 47.6% of patients were seizure-free with perampanel as a first add-on, which is greater than the 36.7% of patients who were seizure-free after the introduction of a second drug regimen as reported by Brodie et al.[27] The efficacy of perampanel may be owing to its unique mechanism of action, which means that rational polytherapy can be applied when combining perampanel with any underlying AED. Furthermore, first add-on perampanel treatment with slow titration can ensure medication tolerability and has the benefit of being optimally tailored to each patient.

4.1 | Limitations

This study is limited by the inclusion of only Korean patients, the open-label and non-randomized design, the absence of a comparator, and that only a relatively small number of patients were included. However, this phase 4 trial followed a comprehensive clinical development program that was conducted worldwide, with several other studies already indicating the efficacy and safety of perampanel in treatment-refractory patients.

5 | CONCLUSIONS

This phase 4 study demonstrates favourable efficacy and safety profiles for perampanel as a first add-on treatment to monotherapy for focal-onset seizures with or without secondarily generalized tonic-clonic seizures. Post hoc analyses suggested that slow titration of perampanel can improve efficacy and safety, regardless of concomitant AED. Furthermore, perampanel is efficacious in patients with secondarily generalized tonic-clonic seizures, with data suggesting an improved response in these patients. Therefore, perampanel is considered to be an effective broad-spectrum first-line adjunctive therapy for patients with epilepsy in whom AED monotherapy was not effective.

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CONFLICT OF INTEREST

JW Lee and HJ Park are employees of Eisai Korea Inc All other authors have no conflict of interest to declare.

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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 may be found online in the Supporting Information section.

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