Perampanel as First Adjunctive Treatment in Patients with Focal-Onset Seizures in the FAME Study: *Post hoc* Analyses of Dose-Related Efficacy, Safety and Clinical Factors Associated with Response

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Background and Purpose: Perampanel is approved for the adjunctive treatment of focal-onset seizures (FOS) with or without secondary generalized seizures. The FAME (Fycompa® as first Add-on to Monotherapy in patients with Epilepsy; NCT02726074) study evaluated the efficacy and safety of perampanel added to monotherapy in patients with FOS with or without secondary generalized seizures (SGS). *Post hoc* analyses of the FAME study assessed potential predictors of response and an in-depth evaluation of the safety and efficacy of perampanel.

Methods: Efficacy was assessed by reduction of total seizure frequency by ≥50%, ≥75% or 100%, and safety by incidence of treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation. Univariate and multivariate logistic regression analyses for treatment response were performed.

Results: Most patients (82/85) received perampanel doses of 4-8 mg/day during maintenance therapy and the highest efficacy rates were achieved with 4 mg/day, irrespective of efficacy outcome. Doses of 4 or 6 mg/day in patients with FOS with SGS (n=16) produced comparable efficacy outcomes. In multivariate analysis, total perampanel dose was predictive of 50% and 75% response rates; longer total perampanel administration period with 50% response; and concomitant non-anti-seizure medication with a 100% response. Patients developed a TEAE more frequently during the 12-week titration period (60.2%) than the 24-week maintenance period (28.4%), including dizziness (45.5% vs. 9.1%), somnolence (10.2% vs. 0%), and headache (4.5% vs. 3.4%).

Conclusions: *Post hoc* analyses show that even low doses of perampanel may be effective and TEAEs are usually self-limited or well-tolerated. **(2022;12:6-12)**

Key words: Perampanel, AMPA receptor, Seizures, focal, Seizures, generalized

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Introduction

Perampanel (Fycompa®; Eisai Co., Ltd., Tokyo, Japan) is a non-competitive, selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist which has been approved in the United States, Europe, and South Korea for the adjunctive treatment of focal-onset (partial-onset) seizures with or without secondary generalized seizures (focal to bilateral tonic-clonic seizures). In South Korea, perampanel was further approved in 2015 as adjunctive therapy for patients with primary generalized tonic-clonic seizures.[1-3] The efficacy and safety of perampanel was demonstrated in pivotal clinical trials of patients with refractory focal-onset seizures[4-6] or drug-resistant, primary generalized tonic-clonic seizures in idiopathic generalized epilepsy.[7] Epileptic seizures, including secondary generalized seizures, are often refractory and have been associated with increased mortality rates from sudden unexpected death in epilepsy and other seizure-re-

lated complications.[8,9] Consequently, it is important to achieve seizure control in patients with drug-resistant seizures.

The FAME (Fycompa® as first Add-on to Monotherapy in patients with Epilepsy) study was an open-label, prospective phase IV study which evaluated the efficacy and safety of perampanel added to monotherapy in South Korean patients with focal-onset seizures with or without secondary generalized seizures. The study consisted of a dose-escalated titration period followed by a 24-week maintenance phase.[3] There is an increasing focus on personalized medicine in epilepsy and identifying potential predictors of treatment response that may help to guide clinicians when prescribing an appropriate anti-seizure drug.[10] We report *post hoc* analyses of the FAME study to assess the safety and efficacy of perampanel including by dose, treatment period, baseline characteristics and disease subset (secondary generalized seizures).

Methods

Study design

FAME (NCT02726074) was a single-arm, multicenter, open-label, phase IV study of perampanel added to monotherapy in patients aged ≥12 years with focal-onset seizures with or without secondary generalized seizures conducted in South Korea. Full methodology details have been published previously.[3] Briefly, perampanel was incrementally increased during a 12-week titration to ≤12 mg/day followed by a 24-week maintenance period.[3]

Outcomes

Efficacy endpoints were 50%, 75%, or 100% response rates defined as the proportion of patients achieving respective ≥50%, ≥75%, or 100% reductions in seizure frequency from baseline during the maintenance period; and median percentage reduction in seizure frequency per 28 days from baseline. Patients with secondary generalized seizures were stratified by low-dose (4 and 6 mg) maintenance perampanel and the proportion of patients achieving a 100% response was evaluated.

Safety data were assessed in the overall population during the titration and maintenance periods. Safety assessments included monitoring of treatment-emergent adverse events (TEAEs), and TEAEs leading to discontinuation. The most common TEAEs were defined as those reported by >5 patients during the titration period.

Statistical analyses

All analyses were *post hoc* and no adjustments were made for multiple comparisons. The full analysis set (FAS) included all patients who received ≥1 dose of perampanel and were included in at least one efficacy assessment. The safety analysis set included all patients who received one or more dose of perampanel and were included in at least one safety assessment.[3]

Univariate and multivariate analyses

Univariate and multivariate analyses were conducted both using logistic regression to determine odds ratio (OR) and 95% confidence interval (CI) for patients in the FAS who achieved a 50%, 75%, or 100% response during the maintenance period. Variables which were assessed individually in univariate analyses were: sex, age, body mass index, epilepsy prevalence period, baseline seizure frequency, history of disease, comorbidities, previous medication(s), concomitant non-anti-seizure medication(s), total perampanel administration period, and total perampanel dose. These variables were included for multivariate analysis.

Results

In the FAME study, the safety analysis set comprised 102 patients with focal-onset seizures with/without focal to bilateral tonic-clonic seizure, and the FAS consisted of 85 patients. The mean±standard deviation (SD) age of patients in the FAS was 42.3±14.1 years, and most were female (57.6%). The number of years since diagnosis of epilepsy was 10.9±9.3 years, and the mean frequency of focal-onset seizures per 28 days was 4.1±7.7.[3]

Post hoc analysis of outcomes by perampanel dose are shown in Table 1. In the FAS, most patients (96.5%) received perampanel doses of 4 mg/day (n=43), 6 mg/day (n=27), or 8 mg/day (n=12) during maintenance therapy, with higher doses (10 or 12 mg/day) administered to three patients. Attainment of a 50% response rate was achieved in the 4, 6, and 8 mg/day dose groups by 93.0%, 81.5%, and 50.0% of patients, respectively; a 75% response rate by 81.4%, 74.1%, and 50.0%, respectively; and a 100% response rate by 60.5%, 44.4%, and 16.7%, respectively.

In patients with focal-onset seizures with secondary generalized seizures (n=16) who received perampanel 4 mg/day (n=8) or 6 mg/day (n=8), 50% and 75% response rates were achieved by seven patients in each dose group (87.5%). The number of patients

achieving 100% response rates (seizure-free) in the 4 and 6 mg/day groups was seven (87.5%) and five (62.5%), respectively.

Univariate analysis for clinical factors associated with response

In univariate logistic regression analyses, factors significantly associated with achievement of a 50% response rate were lower frequencies of focal-onset seizures (with or without focal to bilateral tonic-clonic seizure) (p=0.0443) or complex focal-onset impaired awareness seizures at baseline (p=0.0490), concomitant non-anti-seizure medication (p=0.0091), and total perampanel dose (p=0.0067). Concomitant non-anti-seizure medication was also significantly associated with 75% (p=0.0094) and 100% response rates (p=0.0143). In addition, factors significantly associated with a 100% response rate were: older age (p=0.026), lower frequency of focal-onset seizures (with or without secondary generalized seizure) (p=0.0058) and complex focal-onset seizures (p=0.0204) at baseline (Table 2).

Multivariate analysis

In multivariate analysis, factors significantly associated with a 50% response rate were: longer total perampanel administration period (p=0.0121) and total perampanel dose (p=0.0084); with a 75%

Table 1. Efficacy outcomes by perampanel dose during maintenance therapy (full analysis set; n=85)

	4 mg/day (n=43)	6 mg/day (n=27)	8 mg/day (n=12)	10 mg/day (n=2)	12 mg/day (n=1)
50% response rate	40 (93.0)	22 (81.5)	6 (50.0)	0 (0.0)	0 (0.0)
75% response rate	35 (81.4)	20 (74.1)	6 (50.0)	0 (0.0)	0 (0.0)
100% response rate	26 (60.5)	12 (44.4)	2 (16.7)	0 (0.0)	0 (0.0)
Percentage reduction in seizure frequency per 28 days	100.0 (100.0-106.7)*	91.9 (100.0-85.5)	45.8 (100.0-1457.3)	-13.0 (37.4-63.3)	14.3 (14.3-14.3)

Values are presented as number (%) or median (range).
*n=42.

Table 2. Univariate analysis of clinical factors associated with 50%, 75%, and 100% responses to perampanel treatment (full analysis set; n=85)

Variable	50% response			75% response			100% response		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Sex, male vs. female	0.79	0.27-2.29	0.661	1.32	0.50-3.49	0.5706	0.83	0.35-1.98	0.679
Older age, ≥65 years	1.03	0.99-1.07	0.1984	1.02	0.98-1.05	0.3274	1.04	1.00-1.07	0.026†
Age group, ≥65 vs. <65 years	0.79	0.09-7.22	0.8327	0.49	0.05-4.40	0.5217	0.42	0.07-2.42	0.3306
BMI (kg/m^2)	1.05	0.91-1.22	0.4979	1.08	0.94-1.23	0.2787	1.10	0.97-1.24	0.1386
Epilepsy prevalence period (years)	1.05	0.98-1.12	0.1959	1.03	0.97-1.08	0.3843	1.02	0.98-1.07	0.3174
Baseline frequency (number/28 days)									
Focal-onset seizures with/without SGS	0.94	0.88-1.00	0.0443	0.95	0.90-1.01	0.1249	0.55	0.36-0.84	0.0058†
Focal-onset aware non-motor seizures	1.04	0.44-2.44	0.9332	1.20	0.50-2.85	0.6855	0.98	0.51-1.90	0.9529
Focal-onset aware motor seizures	1.09	0.78-1.53	0.5992	1.10	0.81-1.50	0.5227	0.86	0.58-1.27	0.4430
Focal-onset impaired awareness seizures	0.85	0.72-1.00	0.0490†	0.87	0.74-1.01	0.0743	0.66	0.47-0.94	0.0204†
Focal to bilateral tonic-clonic seizures	2.39	0.45-12.61	0.3036	3.81	0.68-21.40	0.1285	0.90	0.55-1.45	0.6538
Past history of disease, Y vs. N	1.23	0.39-3.90	0.7295	0.75	0.28-2.03	0.5754	1.19	0.48-2.95	0.7035
Comorbidity, Y vs. N	1.28	0.42-3.88	0.6584	1.49	0.55-3.99	0.4327	1.81	0.75-4.35	0.1851
Previous medication, Y vs. N	2.89	0.85-9.76	0.0877	1.70	0.63-4.55	0.2937	1.81	0.76-4.33	0.1803
Concomitant medication*, Y vs. N	5.91	1.55-22.48	0.0091†	4.04	1.41-11.59	0.0094†	3.02	1.25-7.32	0.0143†
Total administration period (days)	1.02	1.00-1.04	0.0577	1.01	1.00-1.03	0.1609	1.03	0.99-1.07	0.1084
Total dosage (mg)	1.00	1.00-1.00	0.0067†	1.00	1.00-1.00	0.0647	1.00	1.00-1.00	0.1179

OR, odds ratio; CI, confidence interval; BMI, body mass index; SGS, secondary generalized seizures; Y, yes; N, no.
*Includes non-antiepileptic medications.
†p-values <0.05.

response rate: total perampanel dose (p=0.0373); and with a 100% response: concomitant medication including non-anti-seizure medications (p=0.0421) (Table 3).

Safety

In the FAME study, 77 (75.5%) of 102 patients reported 138 TEAEs

Table 3. Multivariate analysis of clinical factors associated with 50%, 75%, and 100% responses to perampanel treatment (full analysis set; n=85)

Variable	50% response			75% response			100% response		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Sex, male vs. female	0.60	0.11-3.38	0.5601	1.09	0.30-3.95	0.9002	0.36	0.10-1.27	0.1128
Older age, ≥65 years	0.96	0.90-1.03	0.2773	0.98	0.93-1.03	0.5007	1.01	0.96-1.05	0.8505
Age group, ≥65 vs. <65 years	0.99	0.79-1.25	0.9567	1.03	0.87-1.23	0.7349	1.09	0.92-1.30	0.3222
BMI (kg/m^2)	1.11	0.95-1.28	0.1796	1.03	0.96-1.11	0.4042	1.05	0.98-1.13	0.1947
Baseline frequency (number/28 days)									
Focal-onset seizures with/without SGS	1.27	0.21-7.64	0.7908	2.61	0.38-17.76	0.3258	0.45	0.17-1.21	0.1128
Simple focal seizures without motor signs	0.55	0.07-4.56	0.5788	0.45	0.05-3.80	0.4597	1.29	0.39-4.31	0.6815
Simple focal seizures with motor signs	0.79	0.13-4.79	0.8006	0.42	0.06-2.88	0.3783	1.74	0.59-5.14	0.3192
Complex focal seizures	0.67	0.11-3.97	0.6604	0.35	0.05-2.37	0.2845	0.90	0.36-2.28	0.8294
History of disease, Y vs. N	0.90	0.14-5.64	0.9129	0.52	0.14-1.94	0.3290	1.08	0.28-4.10	0.9095
Comorbidity, Y vs. N	1.10	0.16-7.44	0.9262	2.03	0.48-8.52	0.3327	4.21	0.95-18.69	0.0587
Previous medication, Y vs. N	3.47	0.18-65.63	0.4065	0.38	0.05-2.88	0.3493	0.23	0.03-1.51	0.1243
Concomitant medication*, Y vs. N	4.27	0.33-55.98	0.2690	4.64	0.65-33.24	0.1266	6.77	1.07-42.78	0.0421†
Total administration period (days)	1.04	1.01-1.07	0.0121†	1.02	1.00-1.05	0.0677	1.03	1.00-1.07	0.0538
Total dosage (mg)	1.00	0.99-1.00	0.0084†	1.00	1.00-1.00	0.0373	1.00	1.00-1.00	0.1442

OR, odds ratio; CI, confidence interval; BMI, body mass index; SGS, secondary generalized seizures; Y, yes; N, no.
*Includes non-antiepileptic medications.
†p-values <0.05.

Table 4. Common TEAEs (≥2 patients in any dose group) by dose in the titration and maintenance periods (safety analysis set; n=88)

	4 mg/day (n=45)	6 mg/day (n=28)	8 mg/day (n=12)	10 mg/day (n=2)	12 mg/day (n=1)	Total (n=88)*
Titration period						
Patients with any TEAE	33 (73.3)	12 (42.9)	7 (58.3)	1 (50.0)	0 (0.0)	53 (60.2)
Common TEAEs						
Dizziness	22 (48.9)	10 (35.7)	7 (58.3)	1 (50.0)	0 (0.0)	40 (45.5)
Somnolence	3 (6.7)	4 (14.3)	2 (16.7)	0 (0.0)	0 (0.0)	9 (10.2)
Headache	3 (6.7)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.5)
Dysarthria	2 (4.4)	1 (3.6)	1 (8.3)	0 (0.0)	0 (0.0)	4 (4.5)
TEAEs leading to discontinuation	3 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)
Maintenance period						
Patients with any TEAE	9 (20.0)	12 (42.9)	3 (25.0)	0 (0.0)	1 (100.0)	25 (28.4)
Common TEAEs						
Dizziness	3 (6.7)	3 (10.7)	2 (16.7)	0 (0.0)	0 (0.0)	8 (9.1)
Headache	1 (2.2)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)
Anger	1 (2.2)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	2 (2.3)
TEAEs leading to discontinuation	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)

Values are presented as number (%).
TEAE, treatment-emergent adverse event.
*No dosage information was available for 14 patients in the safety analysis set.

Table 5. Common TEAEs (≥2 patients) and their recovery status (safety analysis set; n=102)

Preferred term	Events/ patients	Week of TEAE onset	Dose reduction due to TEAE event	Discontinuation due to TEAE event	Recovery status by TEAE event			Final dose (mg/day)
					Patients in recovery	Patients recovered	Patients not recovered	
Dizziness	50/48	4.5±2.8	13 (26.0)	9 (18.0)	3 (6.3)	44 (91.7)	1 (2.1)	5.3±1.7 (4.0; 4-10)
Somnolence	9/9	3.4±1.9	2 (22.2)	0 (0.0)	1 (11.1)	8 (88.9)	0 (0.0)	5.8±1.6 (6.0; 4-8)
Headache	6/6	3.0±3.2	1 (16.7)	2 (33.3)	0 (0.0)	6 (100.0)	0 (0.0)	4.5±1.0 (4; 4-6)
Dysarthria	5/5	5.6±3.0	2 (40.0)	1 (20.0)	0 (0.0)	5 (100.0)	0 (0.0)	5.5±1.9 (4; 4-8)
Edema	2/2	6.0±1.4	1 (50.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	4.0±0.0 (4; NA)
Fatigue	2/2	4.5±0.7	1 (50.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	4.0±0.0 (4; NA)
Memory impairment	2/2	3.5±0.7	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	4.0±0.0 (4; NA)
Seizure	2/2	4.5±4.9	0 (0.0)	1 (50.0)	0.0 (0.0)	2 (100.0)	0 (0.0)	6.0±0.0 (6; NA)

Values are presented as mean±standard deviation (mode; range) or number (%) unless otherwise indicated.
TEAE, treatment-emergent adverse event; NA, not applicable.

throughout the study period.[3] *Post hoc* analysis of common TEAEs in the titration and maintenance periods and by dose (4-12 mg/day) are summarized in Table 4. Mean±SD age in the 4, 6, 8, 10, and 12 mg/day groups was 46.0±14.1 years, 39.1±13.5 years, 36±11.0 years, 38.5±23.3 years and 50 years (SD, not applicable), respectively; and the respective number of females subjects in each group was 26 (57.8%), 17 (60.7%), 8 (66.7%), 0 (0%), and 0 (0%). Most TEAEs were reported in the titration period: in 53 patients (60.2%) compared with 25 (28.4%) in the maintenance period. Rates of TEAEs leading to discontinuation in the titration and maintenance periods were 3.4% and 1.1%, respectively.

Common TEAEs in the titration period were dizziness (n=40; 45.5%), somnolence (n=9; 10.2%), headache (n=4; 4.5%), and dysarthria (n=4; 4.5%). Rates of TEAEs by perampanel dose in the titration period were comparable: rates for dizziness, the most common TEAE, in the 4, 6, and 8 mg/day dose groups were 48.9%, 35.7%, and 58.3%, respectively. In the maintenance period, common TEAEs were dizziness (n=8; 9.1%), headache (n=3; 3.4%) and anger (n=2; 2.3%) and were comparable between doses (Table 4).

Recovery status of patients with common TEAEs (occurrence in ≥2 patients) experienced during the study is shown in Table 5. With the exception of one case of dizziness (2.1%), patients with TEAEs were recovering or had recovered.

There was no clear association between age or the presence of comorbidities at baseline and occurrence of the most common TEAEs (≥2 patients). However, more female than male subjects experienced dizziness (32 vs. 16; 66.7% vs. 33.3%), somnolence (7 vs. 2; 77.8% vs. 22.2%), headache (6 vs. 0; 100% vs. 0%), and dysarthria (4 vs. 1; 80% vs. 20%), although the total number of patients for somnolence, headache and dysarthria was low (Table 6).

Table 6. Common TEAEs (≥2 patients) during the study and their association with age and sex (safety analysis set; n=102)

TEAE	Age (years)	Female
Dizziness (n=48)	40.6±13.6	32 (66.7)
Somnolence (n=9)	39.7±13.9	7 (77.8)
Headache (n=6)	33.0±11.0	6 (100.0)
Dysarthria (n=5)	37.6±18.1	4 (80.0)
Edema (n=2)	30.5±6.4	2 (100.0)
Fatigue (n=2)	58.0±14.1	0 (0.0)
Memory impairment (n=2)	44.0±18.4	1 (50.0)
Seizure (n=2)	22.0±2.8	1 (50.0)

Values are presented as mean±standard deviation or number (%).
TEAE, treatment-emergent adverse event.

Discussion

The FAME study open-label, phase IV study showed that perampanel added to monotherapy was effective and well tolerated in patients with focal-onset seizures, with or without secondary generalized seizures.[3] *Post hoc* analyses of patients enrolled in the FAME study, reported here, enable a detailed examination of the efficacy and safety of perampanel. In the FAME study, seizure reductions of 50%, 75%, and 100% were achieved by 80.0%, 71.8%, and 47.1% of patients, respectively, during the maintenance period.[3] In this *post hoc* analysis, most patients (82/85) received doses of 4-8 mg/day during maintenance therapy and the highest efficacy rates were achieved with 4 mg/day, irrespective of efficacy outcome (50%, 75%, or 100% response rates, or percentage reduction in seizure

frequency per 28 days). Comparable efficacy outcomes were found for comparisons of 4 mg/day and 6 mg/day perampanel in patients with focal-onset seizures with secondary generalized seizure, although the small sample size (n=16) precludes any firm conclusions.

Predictors of 50%, 75%, and 100% response rates were identified by univariate and multivariate analyses. In univariate analyses, concomitant non-anti-seizure medication was significantly associated with 50%, 75%, and 100% response rates. Predictors of 50% and 100% response also included a lower seizure frequency at baseline (focal-onset seizures with/without secondary generalized seizure or complex focal-onset seizure). In addition, a total perampanel dose was significantly associated with a 50% response rate and older age with a 100% response rate. In multivariate analysis, total perampanel dose was predictive of 50% and 75% response rates; longer total perampanel administration period with 50% response rate; and concomitant medication including non-anti-seizure medications with a 100% response rate. In a pharmacokinetic/pharmacodynamic study of perampanel (2-12 mg) in patients with pharmacoresistant focal-onset seizures enrolled in three phase III clinical trials,[4-6] seizure frequency decreased proportionately with increased predicted perampanel average steady-state plasma concentrations.[11] However, in this study, a lower perampanel dose during maintenance therapy was associated with superior efficacy compared to higher doses. This is likely to be because, in the prospective FAME study, the perampanel dose was increased every 2-week if patients could tolerate their current dose during the titration period and patients entered the maintenance phase at their last dose in the titration period. Low patient numbers at higher perampanel doses (10 and 12 mg/day) should be taken into account when interpreting these safety and efficacy data.

Across phase III studies, perampanel was associated with a relatively low incidence of serious AEs, especially at low doses, and most TEAEs were mild or moderate in intensity.[12] In logistic analyses, higher exposure to perampanel was significantly associated with increased probability of AEs. Commonly reported AEs were dizziness (32.9%), somnolence (21.7%), fatigue (13.9%), irritability (12.3%), gait disturbance (9.1%), weight increase (6.1%), and dysarthria (4.5%).[11] In the FAME study, the most common AEs were dizziness (50.0%), somnolence (9.8%), and headache (8.8%).[3] This *post hoc* analysis showed that over two-fold more TEAEs developed in the titration period than in the maintenance phase. Dizziness (48.9%), somnolence (6.7%), and headache (6.7%), were the most common TEAEs in the titration period, whereas dizziness (6.7%), headache (2.2%), and anger (2.2%) were most reported in the maintenance period. With the exception of one case with dizziness, AEs were resolved or resolving. Some TEAEs were experienced by a higher proportion of female than male patients notably dizziness (66.7% vs. 33.3%). Somnolence, headache and dysarthria also showed this trend, but patient numbers were low. Additional data from real-world studies may clarify whether some TEAEs are more prevalent in women. Other baseline characteristics (age and presence of comorbidities) showed no clear association with the occurrence of common TEAEs.

In a 2-year real-world Austrian study of perampanel with refractory focal epilepsy with the same inclusion criteria for age (≥12 years) as the FAME study, the most common AE was dizziness (experienced by a third of 122 patients), but frequently resolved following a slight dose reduction.[13] Overall, 34 patients withdrew due to AEs, mainly due to dizziness (n=20) or fatigue (n=11). Perampanel improved seizure control (with a 50-100% reduction in seizures) in 42% of patients.[13] A Korean multicenter retrospective observational study of 220 children and adolescents (aged 4-20 years) with epilepsy treated with add-on perampanel found that 40% experienced AEs commonly somnolence (42.1%), dizziness (21.6%), ataxia (20.5%), and violence (20.5%). Most were of mild severity and resolved after dose reduction or perampanel discontinuation. The overall response rate was 44%, including 18% who were seizure-free. A favorable treatment response was associated with low baseline seizure frequency, small number of concomitant anti-seizure drugs, and the absence of intellectual disability.[14]

Limitations of the *post hoc* analyses reported here reflect those associated with the original FAME study[3] which had an open-label non-comparative design with limited generalizability to wider geographic populations because it was conducted only in South Korean patients and included a relatively small overall study population. The current *post hoc* analyses evaluated relatively small subgroups from the original FAME study and this further compounds the sample size limitation. However, despite these limitations, the current analyses provide data which support the clinical profile of add-on perampanel in patients with focal-onset seizures.

In conclusion, *post hoc* analyses of the FAME study confirm the efficacy and safety of perampanel in patients with focal-onset seizures. Results show that even low doses of perampanel may be effective and TEAEs are usually self-limited or well-tolerated.

Conflict of Interest

Ji Woong Lee and Min Young Kim are employees of Eisai Korea Inc. All other authors have no conflict of interest to declare.

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