■ Original article

Epileptic Disord 2022; 24 (5): 813-821

Epileptic Disorders

Real-world evaluation of perampanel effectiveness in Japanese adolescents with epilepsy

Yushi Inoue[1], Kenta Sumitomo[2], Kazuhiro Matsutani[2], Mika Ishii[2]

[1] National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan
[2] Clinical Planning and Development Department, Medical Headquarters, Eisai Co., Ltd., Tokyo, Japan

Received February 22, 2022;
Accepted May 03, 2022

ABSTRACT

Objective. Real-world data from adolescents treated with perampanel in a routine clinical setting are lacking in Japan. We evaluated the safety and efficacy of perampanel for adolescent patients (aged 12-17 years) with drug-resistant, refractory epilepsy in real-world settings.

Methods. This was a large-scale, prospective, observational post-marketing study, with a 104-week observation period. Safety was assessed by monitoring adverse effects (adverse drug reactions). For efficacy assessments, seizure frequency was compared between the four weeks immediately prior to the last observation and the four weeks before the commencement of perampanel.

Results. In total, 519 patients were enrolled; 505 and 484 patients were included in the safety and efficacy analysis sets, respectively. The mean age was 14.4 years. The mean daily dose of perampanel was 4.4 mg/day. The main reasons for discontinuation at 104 weeks were adverse events (48.4%) and inadequate efficacy (46.8%). The retention rate at 104 weeks was 50.5%. Adverse effect and severe adverse effect incidences were 42.2% and 1.8%, respectively. The most common adverse effects were somnolence (13.5%), irritability (8.5%), dizziness (5.1%), and agitation (4.8%). There were significant differences in the occurrence of adverse effects between the initial titration interval of <2 weeks and 2-4 weeks (odds ratio=0.441, p=0.029) and 4-8 weeks (odds ratio=0.462, p=0.027). The median percent change in seizure frequency at the last observation carried forward was −50.0 for focal aware seizures with motor signs, −73.3 for focal aware seizures without motor signs, −28.6 for focal impaired awareness seizures, −62.6 for focal to bilateral tonic-clonic seizures, and −20.0 for generalized tonic-clonic seizures.

Significance. In adolescent patients, perampanel was well tolerated and efficacious in reducing seizure frequency. No unexpected safety issues were observed, and slow titration may reduce the incidence of adverse effects.

Key words: efficacy, safety, perampanel, post-marketing study, long-term outcome

• **Correspondence:**
Yushi Inoue
National Epilepsy Center,
NHO Shizuoka Institute
of Epilepsy and Neurological
Disorders,
886 Urushiyama,
Aoi-ku, Shizuoka 420-8688,
Japan
<yshinoue@gmail.com>

doi:10.1684/epd.2022.1454

The anti-seizure medication (ASM) perampanel is an orally administered, selective, and non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors used to treat epilepsy [1-3]. In Japan, perampanel is approved as monotherapy and adjunctive therapy for the treatment of focal seizures (including focal to bilateral tonic-clonic

seizures [FBTCS]) in patients aged ≥four years, and as adjunctive therapy for the treatment of generalized tonic-clonic seizures (GTCS) in patients aged ≥12 years who have failed to respond adequately to other ASMs [4].

We previously reported on the actual use of perampanel in adult patients in Japan in a real-world setting [5]. Perampanel was effective in reducing seizure frequency and was safe, especially in older patients. The efficacy and tolerability profiles of perampanel in Asian adult patients appears to be similar to that in non-Asian populations [6, 7]. Data for paediatric and adolescent patients were collected in randomized trials [8-12] and real-world data are also available [13-16]; however, there is a scarcity of information from large samples of adolescents treated in routine clinical settings in Asia. Therefore, we conducted a large-scale, prospective, observational, post-marketing study (PMS) to evaluate the safety and efficacy of perampanel in adolescent patients (aged 12-17 years) with drug-resistant, refractory epilepsy in real-world settings in Japan.

Methods

Study design and patients

Patients treated with perampanel in Japan were prospectively enrolled in accordance with the Good Post-marketing Surveillance Practice (GPSP) ordinance. The treatment regimen was not mandated but was determined at the physician's discretion, according to routine practice; details of the treatment regimen used were collected for evaluation. Based on the Japanese package insert [4], perampanel should be started at 2 mg orally once daily at bedtime for adults and adolescents aged ≥12 years, and then titrated in 2-mg increments at intervals of ≥one week. The approved maintenance dose is 4-8 mg once daily in the absence of concomitant ASMs that accelerate the metabolism of this product, or 8-12 mg once daily in the presence of such concomitant drugs.

A total of 142 clinical departments at 141 institutions across Japan participated, with enrolment occurring between August 1st, 2016 and March 31st, 2019. Patients were registered using a central system utilizing Electronic Data Capture. The study observation period comprised the 104 weeks after the first treatment. If treatment was withdrawn during the observation period, the follow-up period comprised the four weeks after withdrawal.

As the GPSP Ordinance does not require patient consent, it was not mandatory for this study. This study was registered at ClinicalTrials.gov under the identifier number, NCT03059381.

Eligible participants were individuals aged 12-17 years with drug-resistant, refractory epilepsy. Patients had either focal seizures with or without FBTCS or primary GTCS. FBTCS or GTCS were defined according to the 2017 International League Against Epilepsy classification of epileptic seizures [17]. The only exclusion criterion was a history of prior perampanel administration.

Outcome measures

The following patient and treatment data were collected: patient background information (sex, age, epilepsy classification, disease duration, and comorbid conditions); the daily dose of perampanel administered, the administration period, and reasons for withdrawal; and retention rates at 104 weeks. Safety was assessed by monitoring adverse effects (adverse drug reactions; *i.e.*, treatment-emergent adverse events for which a causal relationship with perampanel could not be ruled out) during the observation period. Adverse effects were categorized using the Medical Dictionary for Regulatory Activities version 24.0. Current seizures and seizure-related events (*e.g.*, abnormal EEG, computed tomography, or MRI findings, and falls due to seizures) were not considered adverse effects. For patients who received ≥one increased dose of perampanel within eight weeks, safety outcomes were evaluated in subgroups of <2 weeks, 2-4 weeks, and 4-8 weeks, according to the initial perampanel dose escalation interval. The dose of perampanel was determined at the physician's discretion.

For efficacy assessments, seizure frequency during the four weeks immediately prior to the last observation was compared with the frequency during the four weeks before the start of perampanel use (baseline). The last observation carried forward (LOCF) approach was used and the data collected at the last efficacy assessment during the observation period were included. The 50% responder rate (the percentage of patients who achieved a 50% or greater reduction in seizure frequency), 100% responder rate (the percentage of patients who achieved seizure-free status during the four weeks prior to the last observation), and the median percent reduction in seizure frequency from baseline for focal aware seizures (FAS) with motor seizures, FAS without motor seizures, focal impaired awareness seizures (FIAS), FBTCS, and GTCS were also evaluated.

Statistical methods

The target sample size was set at 500 patients; this was based on the calculation that 300 patients would be

required to detect at least one adverse effect with a frequency of 1% and a 95% confidence interval (CI), and assuming a withdrawal rate within the 52-week observation period of 40%. Thus, we planned to collect data from 500 patients to ensure that approximately 300 patients would complete the 52-week observation period.

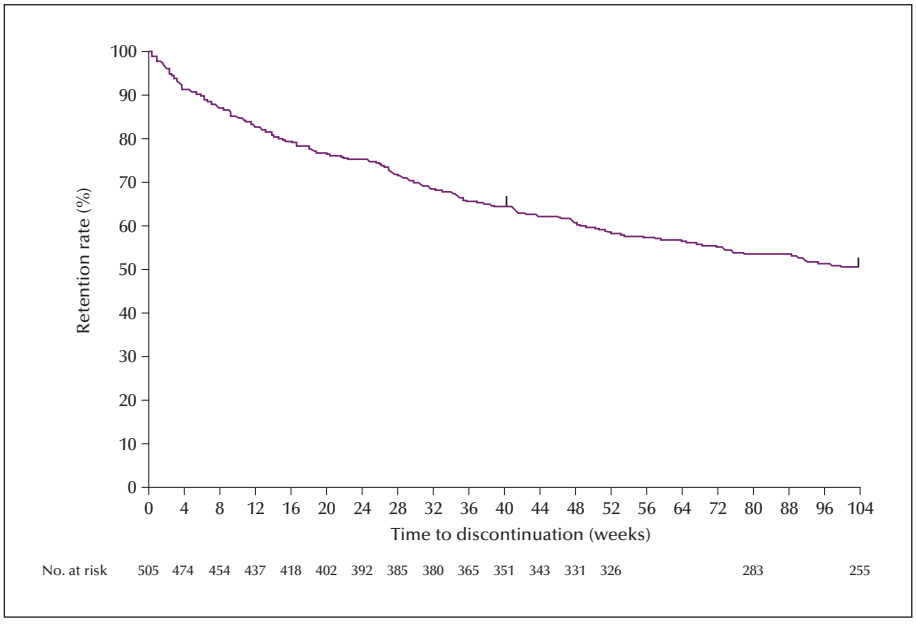
Patient characteristics were recorded using descriptive statistics; data are shown as mean values with standard deviations (SD) or the median percent change (min, max). The perampanel retention rate was estimated using the Kaplan–Meier method. To investigate factors that could potentially affect safety, we calculated and compared the incidences of adverse effects in terms of patient background. We used multivariable logistic regression analysis to investigate the relationships between the incidence of adverse effects and each factor. For the efficacy analyses, we calculated the 50% and 100% responder rates for each type of seizure; patients without a specific type of seizure at baseline were excluded from these analyses. To investigate the factors that could affect efficacy, we calculated the percentage change in seizure frequency according to patient background, and multivariate logistic regression was performed. All tests were two-sided and we applied a significance level of <5%. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

During the registration period, a total of 519 patients were enrolled. Data were not received for 12 patients; thus, the baseline patient population comprised 507 patients (*supplementary figure 1*). The safety analysis set included 505 patients after two individuals were excluded (one lacked evaluable data and one was found to have a protocol violation). The efficacy analysis set included 484 patients; 21 patients were excluded from perampanel use due to seizure types other than FAS (including FBTCS) or GTCS within one year before the start of administration, no concomitant ASM, lack of evaluable data, and unapproved dose/dosage of perampanel (over 12 mg).

Table 1 shows the characteristics of the patients included in the safety and efficacy analyses. Within the safety analysis set, the mean ± SD age was 14.4 ± 1.7 years. A total of 415/505 patients (82.2%) had a disease duration of ≥five years, with the majority having FAS (including FBTCS; 361/505 [71.5%]). The majority of patients were taking ≥two oral ASMs (425/504 [84.3%]). Psychiatric symptoms within two years prior to the study were observed in 70 (13.9%) patients, with aggression being the most frequent (43/70 [61.4%]). There were no patients with a history of suicide-related behaviour.



■ **Figure 1.** Perampanel retention rates (safety analysis set) calculated using the Kaplan–Meier method.

▼ **Table 1.** Patient baseline characteristics.

	Safety analysis set (*n*=505)	Efficacy analysis set (*n*=484)
Male	300 (59.4)	287 (59.3)
Female	205 (40.6)	197 (40.7)
Age (years), mean ± SD	14.4 ± 1.7	14.3 ± 1.7
Body weight (kg), mean ± SD	42.1 ± 16.2 (*n*=411)	42.0 ± 16.3 (*n*=394)
Body mass index (kg/m^2)		
<15.0	69 (13.7)	66 (13.6)
≥15.0 to <20.0	141 (27.9)	136 (28.1)
≥20.0	128 (25.3)	121 (25.0)
Unknown	167 (33.1)	161 (33.3)
Seizure type at baseline[a,b]		
FAS with or without FBTCS	361 (71.5)	356 (73.6)
GTCS	79 (15.6)	79 (16.3)
Other (including other seizure types, seizure frequency unknown, or no seizure reported)	78 (15.4)	62 (12.8)
Epilepsy type[b]		
Focal epilepsy	384 (76.0)	374 (77.3)
Generalized epilepsy	107 (21.2)	97 (20.0)
Combined epilepsy	14 (2.8)	13 (2.7)
Unknown epilepsy	5 (1.0)	5 (1.0)
Aetiology[b]		
Structural	171 (33.9)	164 (33.9)
Neurodevelopmental malformation[c]	86 (50.3)	81 (49.4)
Perinatal events[c]	43 (25.1)	43 (26.2)
Cerebrovascular disorder[c]	18 (10.5)	18 (11.0)
Brain tumour[c]	14 (8.2)	12 (7.3)
Trauma[c]	7 (4.1)	7 (4.3)
Degenerative disorder[c]	3 (1.8)	3 (1.8)
Other[c]	4 (2.3)	4 (2.4)
Genetic	70 (13.9)	64 (13.2)
Infection	39 (7.7)	38 (7.9)
Metabolic	4 (0.8)	3 (0.6)
Immune	7 (1.4)	5 (1.0)
Unknown	232 (45.9)	227 (46.9)
Disease duration (years)		
<5	88 (17.4)	85 (17.6)
≥5	415 (82.2)	397 (82.0)
Unknown	2 (0.4)	2 (0.4)
Presence of psychiatric symptoms within 2 years prior to the study	70 (13.9)	67 (13.8)
Aggression[b,d]	43 (61.4)	41 (61.2)
Depression[b,d]	6 (8.6)	6 (9.0)
Other[b,d]	26 (37.1)	25 (37.3)

▼ **Table 1.** Patient baseline characteristics (*continued*).

	Safety analysis set (*n*=505)	Efficacy analysis set (*n*=484)
Presence of developmental or cognitive impairment		
Yes	379 (75.0)	361 (74.6)
Unknown	5 (1.0)	5 (1.0)
Concomitant use of enzyme-inducer ASM		
No	363 (71.9)	345 (71.3)
Yes	142 (28.1)	139 (28.7)
Use of concomitant oral ASM at baseline	504 (99.8)	484 (100.0)
Number of concomitant oral ASMs[d,e]		
1	79 (15.7)	76 (15.7)
2	143 (28.4)	138 (28.5)
≥3	282 (56.0)	270 (55.8)

Data are n (%) unless otherwise stated.
[a]Aggregated by the presence or absence of seizures in the four weeks prior to the start of treatment.
[b]Duplicates were allowed.
[c]Tabulation of participants for which the response was "yes" for structural aetiology.
[d]Tabulation of participants for which the response was "yes".
[e]Drugs with the same generic name were counted as a single drug.
ASM: anti-seizure medication; FAS: focal aware seizures; FBTCS: focal to bilateral tonic-clonic seizures; GTCS: generalized tonic-clonic seizure: SD, standard deviation.

Treatment and retention rates

For the majority of patients, there was no change in the number of concomitant oral ASMs at the last observation point (or at the end of treatment in patients who discontinued the study) compared with baseline (*supplementary table 1*). The mean ± SD daily dose of perampanel in the safety analysis set was 4.4 ± 2.3 mg/day, with a maximum dose of 5.9 ± 3.0 mg/day. The retention rate for perampanel is shown in *figure 1*. At 52 weeks, the retention rate in the safety analysis set was 326/505 (64.6%); at 104 weeks, the retention rate was 255/505 (50.5%). The main reasons for discontinuation at 104 weeks were adverse events (48.4%) and inadequate efficacy (46.8%).

Safety

The incidence of adverse effects was 213/505 (42.2%) overall, of which 9/505 (1.8%) were severe (*table 2*). The most commonly occurring adverse effects were somnolence (68/505 [13.5%]), irritability (43/505 [8.5%]), dizziness (26/505 [5.1%]), and agitation (24/505 [4.8%]). Among these events, the only serious adverse effect occurring in >one patient was somnolence (2/505 [0.4%]). Among 213 patients with adverse effects, adverse effects were observed in 99 patients (46.5%) within eight weeks after starting perampanel and in 124 patients (58.2%) within 12 weeks after starting perampanel.

An analysis of adverse effects by dosing showed significant differences according to the titration interval (*figure 2*). There was a significant difference in the occurrence rate of adverse effects between the initial titration interval of <2 weeks and 2-4 weeks (OR=0.441, *p*=0.029) and between the initial titration interval of <2 weeks and 4-8 weeks (OR=0.462, *p*=0.027). Among the adverse effects, those classified as psychiatric disorders were observed significantly less frequently in patients with an initial titration interval of 2-4 weeks (OR=0.391, *p*=0.017) and 4-8 weeks (OR=0.321, *p*=0.001) compared with <2 weeks. A multivariate analysis showed that the presence of psychiatric symptoms was the only independent factor associated with the occurrence of adverse effects in the patient sample (OR=2.581, 95% CI: 1.467-4.542, *p*=0.001).

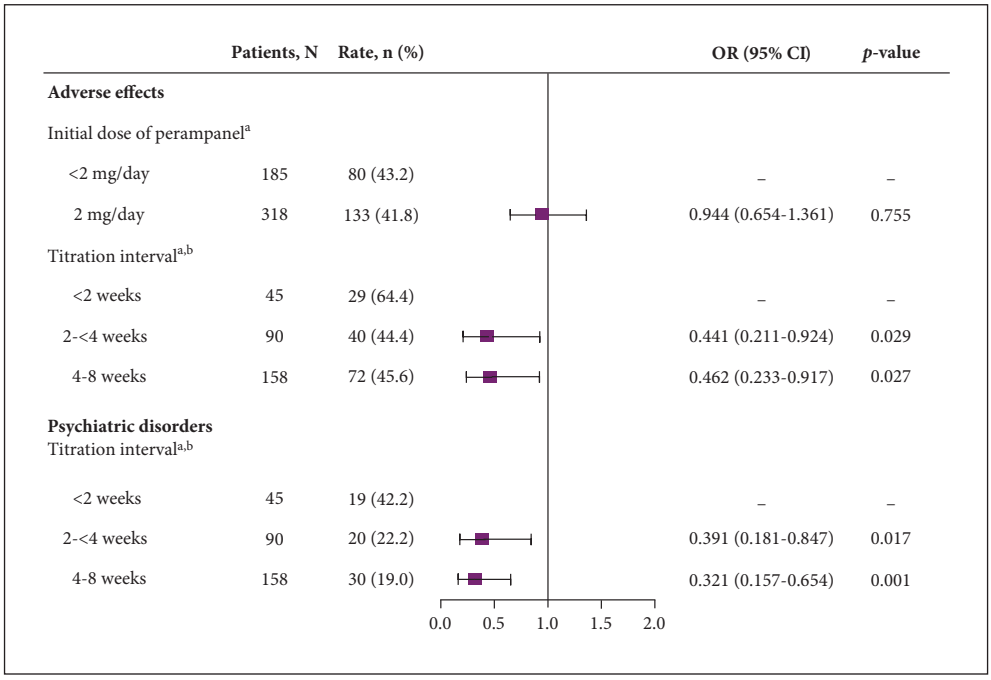
Efficacy

Figure 3 shows the 50% and 100% responder rates. The median (min, max) percent change in seizure frequency at the LOCF was −50.0 (−100.0, 200.0) for FAS with motor signs, −73.3 (−100.0, 0.0) for FAS without motor signs, −28.6 (−100.0, 2900.0) for FIAS, −62.6 (−100.0, 9900.0) for FBTCS, and −20.0 (−100.0, 1300.0) for GTCS. A multivariate analysis of background

▼ **Table 2.** Occurrence of adverse effects according to severity (safety analysis set).

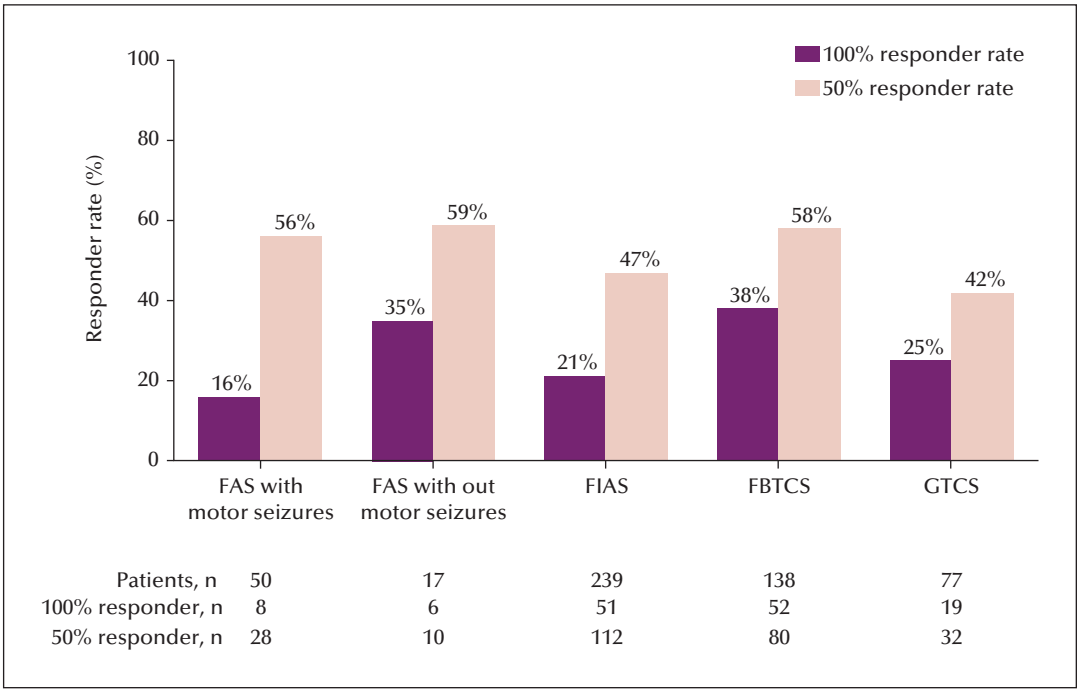
	All patients (*n*=505)	
	All grades	Severe
Number of patients who experienced adverse effects	213 (42.2)	9 (1.8)
Psychiatric disorders		
Irritability	43 (8.5)	0 (0.0)
Agitation	24 (4.8)	1 (0.2)
Aggression	12 (2.4)	0 (0.0)
Anger	8 (1.6)	0 (0.0)
Other	26 (5.1)	0 (0.0)
Nervous system disorders		
Somnolence	68 (13.5)	2 (0.4)
Dizziness	26 (5.1)	0 (0.0)
Seizure/epilepsy	16 (3.2)	1 (0.2)
Other	13 (2.6)	2 (0.4)

Data are n (%).
Adverse effects with frequency >1.0% are shown. For psychiatric disorders or nervous system disorders, adverse effects with frequency <1.0% are categorized as 'other'. If the same event occurred multiple times in the same patient, it was counted as one event. If both severe and non-severe events occurred in the same case, they were counted as one severe event.



■ **Figure 2.** Occurrence of adverse effects by initial dose and titration interval (safety analysis set).[a]Two patients who took an initial perampanel dose of 4 mg were excluded from the analysis.[b]Patients who had a titration interval ≥eight weeks were excluded from the analysis as the distribution of the titration interval was wide (8-102 weeks). CI: confidence interval; OR: odds ratio.

factors affecting the 50% responder rates in patient subgroups showed that developmental or cognitive impairment and the number of concomitant oral ASMs (≥two) were independent factors (OR=0.466, 95% CI: 0.259-0.836, *p*=0.010 and OR=0.357, 95% CI: 0.172-0.741, *p*=0.005, respectively).



■ **Figure 3.** Responder rates (efficacy analysis set). FAS: focal aware seizures; FBTCS: focal to bilateral tonic-clonic seizures; FIAS: focal impaired awareness seizures; GTCS: generalized tonic-clonic seizures.

Discussion

Information on the effectiveness of perampanel in Japanese adolescents with epilepsy in the real world has been awaited. The present study showed that perampanel was well tolerated in adolescent patients and was efficacious in reducing seizure frequency.

The mean daily dose of perampanel in the present study was similar to that of our previous study, which targeted patients aged ≥18 years (4.4 ± 2.3 mg/day vs. 3.7 ± 1.9 mg/day, respectively) [5]. However, the retention rate of perampanel in the present study was higher than that in our previous study (64.6% vs. 58.5%) at 52 weeks [5].

Regarding the safety profile of perampanel, the incidence of adverse effects observed in this study (42.2%) was similar to that reported in previous studies (33.6% in our previous study targeting patients aged ≥18 years [5] and 57.6% in a Phase III study of patients with refractory partial-onset seizures from the Asia-Pacific region [10]). The major adverse effects observed in this study are consistent with those reported in the Japanese package insert [4] and no new safety concerns arose. However, we found that incidences of aggression and irritability tended to be higher in the present study than in our previous study of perampanel in patients aged ≥18 years (aggression: 2.4% vs. 1.7%; irritability 8.5% vs. 4.0%) [5]. These higher incidences of aggression and irritability among adolescents are consistent with those previously reported [18, 19].

Regarding efficacy, the 50%/100% responder rates in the present study revealed a similar trend to those in our previous study in patients aged ≥18 years [5]. Overall, the results related to efficacy outcomes in the present study appear to be consistent with those of previous studies of perampanel [6, 10, 11, 20]; however, direct comparisons with other studies are difficult because of differences in study design, among other factors.

In the current study, a lower incidence of adverse effects was shown in patients with a longer titration interval (≥two weeks) versus those with a short titration interval (<two weeks). This outcome is in line with prior reports [21-24]. As the optimal dose of perampanel initiation and the pace of titration in clinical practice have not yet been clearly defined for Asian patient populations [25], our results may provide valuable additional information to this end. The tolerability profile of perampanel in Asian patients appears to be similar to that in non-Asian populations [6].

Limitations

First, this study was conducted as part of daily clinical practice, and participants were not required to complete a seizure diary. Second, in this study, we only evaluated the effects of perampanel in combination with other ASMs, not as monotherapy. Moreover, changes of concomitant ASMs to other ASMs were allowed during the observational period, potentially confounding our ability to assess the effects of perampanel. However, based on the fact that there were relatively few changes in concomitant oral ASMs, we consider that concomitant medications had a limited effect on the outcomes reported. Third, we did not compare perampanel with other drugs in this study, so we are unable to speculate on whether different outcomes would be obtained with other treatments.

Conclusions

In this large-scale, real-world, observational study, we investigated the safety and efficacy of combination therapy with perampanel in adolescent patients with drug-resistant, refractory epilepsy. We did not observe any unexpected safety issues, and our findings indicate that slow titration may reduce the incidence of adverse effects. These findings highlight the importance of perampanel as a clinical treatment option for adolescent patients with epilepsy. ■

Key points

- We assessed the safety and efficacy of perampanel for adolescent patients with epilepsy in real-world settings in Japan.
- This was a large-scale, prospective, observational post-marketing study with a 104-week observation period after the first treatment.
- Perampanel was well tolerated in adolescent patients and was efficacious in reducing seizure frequency.
- Our findings indicate that slow titration may reduce the incidence of adverse effects.

Supplementary material.
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures.
This study was funded by Eisai Co., Ltd. We thank Sally-Anne Mitchell, PhD, of Edanz (www.edanz.com), for providing medical writing support, which was funded by Eisai Co., Ltd, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). Yushi Inoue has received consultant fees from Eisai Co., Ltd, UCB Japan Co., Ltd, and GW pharmaceuticals. Kenta Sumitomo, Kazuhiro Matsutani, and Mika Ishii are employees of Eisai Co., Ltd.
Author contributions: All authors met the ICMJE's authorship criteria.
Data availability: Owing to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

References

1. Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, *et al*. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* 2011; 52: 1331-40.

2. Ceolin L, Bortolotto ZA, Bannister N, Collingridge GL, Lodge D, Volianskis A. A novel anti-epileptic agent, perampanel, selectively inhibits AMPA receptor-mediated synaptic transmission in the hippocampus. *Neurochem Int* 2012; 61: 517-22.

3. Satlin A, Kramer LD, Laurenza A. Development of perampanel in epilepsy. *Acta Neurol Scand Suppl* 2013; 197: 3-8.

4. Ficompa Tablets 2mg/Ficompa Tablets 4mg/Ficompa Fine Granules 1. https://www.info.pmda.go.jp/go/pack/1139014F1022_1_08/?view=frame&style=XML&lang=ja

5. Inoue Y, Sumitomo K, Matsutani K, Ishii M. Evaluation of the real-world effectiveness of perampanel in Japanese adults and older adults with epilepsy. *Epileptic Disord* 2022; 24(1): 123-32.

6. Tsai JJ, Ikeda A, Hong SB, Likasitwattanakul S, Dash A. Efficacy, safety and tolerability of perampanel in Asian and non-Asian patients with epilepsy. *Epilepsia* 2019; 60: 37-46.

7. Nishida T, Lee SK, Wu T, Tiamkao S, Dash A. Efficacy and safety of perampanel in generalized and focal to bilateral tonic-clonic seizures: a comparative study of Asian and non-Asian populations. *Epilepsia* 2019; 60: 47-59.

8. French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, *et al*. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. A randomized trial. *Neurology* 2015; 85: 950-7.

9. Lagae L, Villanueva V, Meador KJ, Bagul M, Laurenza A, Kumar D, *et al*. Adjunctive perampanel in adolescents with inadequately controlled partial-onset seizures: a randomized study evaluating behavior, efficacy and safety. *Epilepsia* 2016; 57: 1120-9.

10. Nishida T, Lee SK, Inoue Y, Saeki K, Ishikawa K, Kaneko S. Adjunctive perampanel in partial-onset seizures: Asia-Pacific, randomized phase III study. *Acta Neurol Scand* 2018; 137: 392-9.

11. Yamamoto T, Lim SC, Ninomiya H, Kubota Y, Shin WC, Kim DW, *et al*. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures with newly diagnosed epilepsy or recurrence of epilepsy after a period of remission: the open-label Study 342 (FREEDOM Study). *Epilepsia Open* 2020; 5: 274-84.

12. Renfroe JB, Mintz M, Davis R, Ferreira J, Dispoto S, Ferry J, *et al*. Adjunctive perampanel oral suspension in pediatric patients from ≥2 to <12 years of age with epilepsy: pharmacokinetics, safety, tolerability and efficacy. *J Child Neurol* 2019; 34: 284-94.

13. De Liso P, Vigevano F, Specchio N, De Palma L, Bonanni P, Osanni E, *et al*. Effectiveness and tolerability of perampanel in children and adolescents with refractory epilepsies – An Italian observational multicenter study. *Epilepsy Res* 2016; 127: 93-100.

14. Swiderska N, Tan HJ, Rajai A, Silwal A, Desurkar A, Martland T. Effectiveness and tolerability of Perampanel in children, adolescents and young adults with refractory epilepsy: a UK national multicentre study. *Seizure* 2017; 52: 63-70.

15. Lin KL, Lin JJ, Chou ML, Hung PC, Hsieh MY, Chou IJ, *et al*. Efficacy and tolerability of perampanel in children and adolescents with pharmacoresistant epilepsy: The first real-world evaluation in Asian pediatric neurology clinics. *Epilepsy Behav* 2018; 85: 188-94.

16. Sagar P, Wawryk O, Vogrin S, Whitham E, Kiley M, Frasca J, *et al*. Efficacy and tolerability of adjuvant perampanel: an Australian multicenter real-world observational study in refractory focal and generalized epilepsy syndromes. *Epilepsy Behav* 2021; 119: 107935.

17. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58: 522-30.

18. Kim HD, Chi CS, Desudchit T, Nikanorova M, Visudtibhan A, Nabangchang C, *et al*. Review of clinical studies of perampanel in adolescent patients. *Brain Behav* 2016; 6: e00505.

19. Rosenfeld W, Conry J, Lagae L, Rozentals G, Yang H, Fain R, *et al*. Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a combined extension study. *Eur J Paediatr Neurol* 2015; 19: 435-45.

20. Inoue Y, Kaneko S, Hsieh PF, Meshram C, Lee SA, Aziz ZA, *et al*. A *post hoc* analysis of the long-term safety and efficacy of perampanel in Asian patients with epilepsy. *Epilepsia* 2019; 60: 60-7.

21. Villanueva V, Garcés M, López-González FJ, Rodriguez-Osorio X, Toledo M, Salas-Puig J, *et al*. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: the FYDATA study. *Epilepsy Res* 2016; 126: 201-10.

22. 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.

23. Basheikh M, Sadler RM. Retention rate and efficacy of perampanel with a slow titration schedule in adults. *Can J Neurol Sci* 2020; 48: 1-7.

24. Shah E, Reuber M, Goulding P, Flynn C, Delanty N, Kemp S. Clinical experience with adjunctive perampanel in adult patients with uncontrolled epilepsy: a UK and Ireland multicentre study. *Seizure* 2016; 34: 1-5.

25. Chinvarun Y, Huang CW, Wu Y, Lee HF, Likasitwattanakul S, Ding J, *et al*. Optimal use of perampanel in Asian patients with epilepsy: expert opinion. *Ther Clin Risk Manag* 2021; 17: 739-46.

TEST YOURSELF

(1) What was identified as an important factor for the safety of perampanel use in this study?
A. Starting with lower dose
B. Slower titration
C. Both

(2) Which were the most commonly occurring adverse effects?
A. Fatigue, tremor, somnolence, and dizziness
B. Somnolence, irritability, dizziness, and agitation
C. Sedation, coordination disturbances, fatigue, irritability

(3) Which of the following was an independent factor associated with the occurrence of adverse effects in the patient sample?
A. Presence of psychiatric symptoms
B. Duration of disease ≥five years
C. Concomitant use of enzyme-inducing ASMs

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.