Clinical Study Report

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An Open-label, Observational, Prospective, Multicenter Study to Evaluate the Long-term Efficacy and Safety of Perampanel as Monotherapy in Subjects Age 4 Years and Older with Focal Onset Seizures

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1 Study Outline

Study title	An Open-label, Observational, Prospective, Multicenter Study to Evaluate the Long-term Efficacy and Safety of Perampanel as Monotherapy in Subjects Age 4 Years and Older with Focal Onset Seizures
Public Title (Acronym)	PORTABLE Study

Overview	**Purpose of the study** Perampanel (PER) is an antiepileptic drug with a novel mechanism of action that was discovered in Japan, and suppresses excessive neuronal excitation by selectively and non-competitively antagonizing AMPA(α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid)-type glutamate receptors on the postsynaptic membrane[1]. It was launched in Japan in 2016, and has been approved as monotherapy and combination therapy for partial seizures including secondary generalized seizures in epilepsy patients aged 4 years or older, and as combination therapy for tonic-clonic seizures in epilepsy patients aged 12 years or older who are not sufficiently responsive to other antiepileptic drugs[2]. On the other hand, the only clinical trial involving first-line monotherapy using PER from the start of epilepsy treatment was a phase Ⅲ study conducted jointly by Japan and Korea[3]. To contribute to the establishment of clinical evidence, we conducted this study because it is considered necessary to accumulate data on long-term seizure suppression effects and safety, as well as changes in QOL related to emotional, social, and employment/school attendance. **Objective** To evaluate the efficacy and safety of PER used in anti-seizure medications (ASM) – treatment naïve patients with epilepsy **Endpoints** <Seizure record> ・ Occurrence or freedom of seizure <QOL> ・ EuroQOL 5 Dimensions 5-Level (EQ-5D-5L) (including visual analog scale [VAS]) ・ PedsQL-Generic Core Scale: Physical, emotional, social, and employment/school functioning dimensions <Adherence> ・ Compliance rate

<Sleep assessment (to be performed using a wearable device* only in participants who have provided consent and available)>

・ Total sleep time, sleep efficiency, sleep onset latency, awakening, and sleep stage, etc.

*Patch electroencephalograph (EEG) sensor S1 (PGV K.K.)

<Safety>

・ Adverse events

Primary endpoint:

Seizure freedom rate at Month 24 (Months 18–24)

Secondary endpoints:

1. Seizure freedom rates at Month 6 (Months 3–6), Month 12 (Months 6–12), Month 18 (Months 12–18), and Month 30 (Months 24–30)
2. Seizure freedom rate at Month 12 (Months 0–12) and Month 24 (Months 0–24)
3. PER-retention rate (at Month 6, Month 12, Month 18, Month 24, and Month 30)
4. Changes in EQ-5D-5L and PedsQL-Generic Core Scale from baseline to each evaluation time point
5. Adverse events

Exploratory objectives:

1. Changes in sleep-related parameters from baseline based on data obtained in sleep assessment tests
2. PER compliance rate during the observation period
3. Factors related to efficacy (seizure freedom at Month 3, Month 12, and Month 24, etc.)

Study design

Open-label, single-arm, multicenter, and exploratory, observational study

Study population

Inclusion criteria:

1) Patients aged 4 years or older who can provide informed consent (or their legal representative if the patient is a minor)
2) Patients who have received a diagnosis of epilepsy with focal onset seizure as defined in the International League Against Epilepsy Classification (2017)
3) Newly diagnosed treatment-naive or recurrent patients. For patients with recurrence, those who have recurrence at least 2 years after the end of the last ASM treatment
4) Patients who start a monotherapy with PER

Exclusion criteria:

1) Patients who have used an ASM (including a rescue drug) for longer than 2 weeks in total within 2 years
2) Patients previously treated with PER
3) Patients with a history of hypersensitivity to any component of PER (tablet, fine granules) (including excipients)
4) Patients with severe hepatic impairment (Child-Pugh Class C)
5) Patients who have participated in other studies and used an investigational drug or investigational device within 4 weeks of the first dose of PER
6) Patients who are judged by the investigator/sub-investigator to be ineligible

Name of study drug

Perampanel (trade name: Fycompa®)

Method of administration

The drug should be administered at the physician's discretion based on the dosage and administration in

	the package insert. **Concomitant medications/therapies** No restrictions on concomitant medications/therapies, including add-on ASM **Method of the study** Upon electronic or written informed consent, the participant will receive the research tablet. Each participant will complete the seizure record, QOL questionnaires, and adherence using the research tablet. (off-site assessment) The investigator/sub-investigator will check concomitant medications and adverse events with participants at their visit for routine medical care. (on-site assessment) A wearable device (patch EEG sensor S1) will be provided to participants aged 20 years or older at the time of informed consent who have a tendency to insomnia and give consent for sleep assessment, and they will undergo the sleep assessment test at home. The first sleep assessment test will be performed before the first dose of PER. Furthermore, only the participants who have remained on the monotherapy with PER for at least 3 months and used the same dose within 4 mg to 8 mg for at least 4 weeks should undergo the second sleep assessment test between Month 3 and Month 12. (off-site assessment) **Target sample size** 60 patients **Study site or institution** Japan (about 10-15s with epilepsy specialists institutions) **Study period (planned)** Total study period: April 2021 to June 2025 (from the date of approval by the ethical review board to the fixation of the clinical study report) Enrollment period: May 2021 to June 2022 (1 year and 2 months) Observation period: May 2021 to December 2024 (treatment period for each participant: up to 30 months) **Study Organization** Representative study institution: International University of Health and Welfare, Narita Hospital Principal investigator: Naoki Akamatsu, Professor, Department of Neurology, International University of Health and Welfare, School of Medicine, **Consultation Center** The consultation desk for participants, etc. will be provided in the written information and informed consent form of each study institution.

2 Study Findings

Completion date	6-Nov-2024
Result actual enrolment	61 subjects
Baseline Characteristics	**■Demographic characteristics** Of the 61 patients background, 36 (59.0%) were male; the mean age was 38.0 years (4 to 89 years); the disease duration was less than 10 years in 53 (86.9%); developmental disorders were present in 8 (13.1%); the mean seizure frequency was 0.7 (2.9) times/month; the temporal lobe was 26 (42.6%); and the frontal lobe was 16 (26.2%); seizure type were focal impaired awareness seizures (FIAS) 27 (44.3%) , focal to bilateral tonic-clonic seizures (FBTCS) 22(36.1%), and focal motor seizures (FMS) 21(34.4%) in that order; lack of sleep 13 (21.3%) was the most common seizure trigger. [Subgroup analysis of demographic characteristics] By age category (< 18 years/18 to < 65 years/≥ 65 years): The disease duration tended to be longer in the group aged 18 to < 65 years (mean 5.9 years, median 1.5 years (0 to 40 years)) than in the group aged < 18 years (mean 1.4 years, median 0.5 years (0 to 5 years)); and in the group aged ≥ 65 years (mean 2.4 years, median 0.7 years (0 to 10 years)). In the group aged < 18 years, the incidence of complicated developmental disorder was 40.0%, which was higher than in the group aged 18 to < 65 years (5.6%) and in the group aged ≥ 65 years (0.0%). In the group aged < 18 years, the average seizure frequency was 0.6 times/month, which was lower than in the group aged 18 to < 65 years (3.6 times/month) and in the group aged ≥ 65 years (3.8 times/month). The frontal lobe was the most common (46.7%) in the group aged <18 years, but the temporal lobe was the most common in the group aged 18 to < 65 years and the group aged ≥ 65 years (44.4% and 80.0%, respectively). In the seizure type, FIAS were the most common (50.0%) in the group aged 18 to < 65 years and the group aged ≥ 65 years, respectively. In the group aged < 18 years, FBTCS (46.7%), and FMS (40.0%) were the most common. In the seizure trigger, lack of sleep was the most common (40.0%) in the group aged < 18 years, compared with the group aged 18 to < 65 years (16.7%) and the group aged ≥ 65 years (10.0%). Prescription history during the study period (PER monotherapy/ASM combination): The disease duration was similar in the monotherapy group (mean 4.4 years, median 0.7 years (0 to 40 years)), and in the ASM combination group (mean 3.8 years, median 2.0 years (0 to 23 years)). However, the incidence of concomitant developmental disorders was higher in the ASM combination group (17.6%) than in the monotherapy group (11.4%). The mean seizure frequency was also higher in the ASM combination group (5.0 times/month) than in the monotherapy group (2.1 times/month). The frontal and temporal lobes accounted for 31.8% of the seizures in the monotherapy group, while the temporal lobes accounted for 70.6% of the seizures in the ASM combination group. FBTCS accounted for 43.2% of the seizures in the monotherapy group, followed by FMS (40.9%) and FIAS (34.1%). FIAS accounted for 70.6% of the seizures in the ASM combination group. Sleep deprivation was the most common trigger for seizures in the monotherapy group (27.3%) than in the ASM combination group (5.9%). Focal onset seizure type (absence/presence of FBTCS): 77.3% of the subjects with FBTCS were males, and the proportion of males was higher than that of the subjects without FBTCS. The mean duration of disease in the group without FBTCS was 5.9 years, and the median was 1.8 years (0 to 40 years), which was longer than that in the group with FBTCS (1.2 years, and the median was 0.3 years (0 to 7 years)). The prevalence of developmental disorders in the group with FBTCS and the group without FBTCS was 13.6% and 12.8%, respectively. The mean frequency of seizures was 4.2 times/month in the group without

FBTCS, which was higher than 0.6 times/month in the group with FBTCS. Seizure localization in the group without FBTCS was 51.3% in the temporal lobe and 30.8% in the frontal lobe. In the group with FBTCS, the focal area was 27.3% in the temporal lobe and 18.2% in the frontal lobe, respectively. In the group without FBTCS, FIAS were 53.8% and FMS were 51.3%, respectively. In the group with FBTCS, FIAS were 27.3%. Regarding triggers of seizures, lack of sleep was 31.8% in the group with FBTCS, which was higher than 15.4% in the group without FBTCS.

Dose (modal dose: < 4 mg/≥ 4 mg):

Disease duration was similar in the group with < 4 mg and ≥ 4 mg, with the mean of 4.1 years, the median of 1.3 years (0 to 23 years), and the mean of 4.3 years, the median of 0.8 years (0 to 40 years), respectively. Complications of developmental disorders were 9.4% in the group with < 4 mg and 17.2% in the group with ≥ 4 mg. The frequency of seizures was 3.6 times/month in the group with < 4 mg and 2.1 times/month in the group with ≥ 4 mg. Seizure localization was the temporal lobe in 50.0% of the group with <4 mg, and the temporal lobe and the frontal lobe in 34.5% of the group with ≥ 4 mg. FIAS were the most common in 53.1% of the group with < 4 mg, while FMS were the most common in 48.3% of the group with ≥ 4 mg. Regarding triggers of seizures, the proportion of sleep deprivation was 18.8% in the < 4 mg group and 24.1% in the ≥ 4 mg group.

Dose (initial dose: < 2 mg/2 mg/≥ 2 mg):

The mean duration of disease was 2.4 years and the median 0.9 years (0 to 10 years) in the < 2 mg group, and the mean 5.0 years and the median 1.1 years (0 to 40 years) in the 2 mg group. The mean frequency of seizures was 3.1 times/month in the 2 mg group and 2.5 times/month in the < 2 mg group. Seizure localization was the temporal lobe in 50.0% and the frontal lobe in 31.3% in the < 2 mg group, but 38.6% in the temporal lobe and 25.0% in the frontal lobe in the 2 mg group. FIAS were the most common in both the < 2 mg group and the 2 mg group, and the corresponding percentages were 56.3% and 40.9%, respectively. The trigger of seizures was lack of sleep in 18.8% and 20.5% in the < 2 mg and 2 mg groups, which were similar in both groups.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1):

The mean duration of disease was 5.6 years, the median 2.2 years (0 to 37 years) in the frontal lobe group, the mean 4.3 years, the median 1.3 years (0 to 40 years) in the temporal lobe group, the mean 0.8 years, the median 0.5 years (0 to 2 years) in the other regions group, and the mean 4.0 years, the median 1.1 years (0 to 23 years) in the unknown region group. The incidence of developmental disorders was 25.0% in the group with the frontal lobe as the seizure localization and 20.0% in the group with unknown seizure localization. The frequency of seizures in the group with other seizure localization was the highest at an average of 6.1 times/month, followed by 3.3 times/month in the group with the temporal lobe as the seizure localization and 3.1 times/month in the group with unknown seizure localization. The most common seizure type in each group was FMS (81.3%) in the group with the frontal lobe as the seizure localization, FIAS (65.4%) in the group with the temporal lobe as the seizure localization, FBTCS and FIAS (both 66.7%) in the group with other seizure localization, and FBTCS(60.0%) in the group with unknown seizure localization. Lack of sleep was the trigger of seizures in 31.3% of the group with the frontal lobe as the seizure localization, 33.3% in the group with other seizure localization, and 20.0% in the group with unknown seizure localization while it was 11.5% in the group with the temporal lobe as the seizure localization.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed, unknown)) (2):

In the other group including the group with unknown seizure localization the mean duration of disease was 3.1 years, the median 0.6 years (0 to 23 years), developmental disorder was combined in 14.3%, seizure frequency was 3.9 times/month on average, FBTCS was 61.9%, and lack of sleep

was the trigger of seizures in 23.8%.

■Administration of PER/ASM

The initial dose was less than 2 mg in 16 patients (26.2%) and 2 mg in 44 patients (72.1%). The median of modal dose was 3.0 mg and the mean of modal dose was 3.2 mg. Anti-seizure medication were added in 17 patients (27.9%), of which 1 drug was added in 12 patients (19.7%) and 2 or more drugs were added in 5 patients (8.2%). The most frequently used ASM was lacosamide in 14 patients (23.0%), followed by levetiracetam in 5 patients (8.2%).

[Subgroup analysis of PER/ASM administration]

By age group (< 18 years/18 to < 65 years/≥ 65 years):

In the group aged < 18 years, the initial dose was < 2 mg in 6 patients (40.0%) and 2 mg in 9 patients (60.0%), the modal dose was 4.0 mg in the median and 3.5 mg in the mean, and less than 4mg was in 7 of 15 patients (46.6%). ASM was added in 4 patients (26.7%). All patients received 1 additional drug, lacosamide in 2 patients (13.3%), and levetiracetam in 1 patient (6.7%). In the group aged 18 to < 65 years, the initial dose was < 2 mg in 4 patients (11.1%) and 2 mg in 32 patients (88.9%). The modal dose was 3.5 mg in the median and 3.2 mg in the mean, and the dose was < 4 mg in 18 of 36 patients (50.0%). ASM was added in 10 patients (27.8%), with 1 additional drug and 2 or more additional drugs in 5 patients (13.9%) each. Lacosamide in 10 patients (27.8%) and levetiracetam in 4 patients (11.1%). In the group aged ≥ 65 years, the initial dose was < 2 mg in 6 patients (60.0%) and 2 mg in 3 patients (30.0%). The modal dose was 2.0 mg in the median and 2.9 mg in the mean, and the dose was < 4 mg in 7 of 10 patients (70.0%). ASM was added in 3 of 10 patients (30.0%), all with 1 additional drug, and lacosamide in 2 patients (20.0%).

Prescription history during the study period (PER monotherapy/ASM combination):

In the monotherapy group, the initial dose was < 2 mg in 9 patients (20.5%) and 2 mg in 34 patients (77.3%). The modal dose was 3.5 mg in the median and 3.2 mg in the mean, and the dose was < 4 mg in 22 of 44 patients (50.0%). In the ASM combination group, the initial dose was < 2 mg in 7 patients (41.2%) and 2 mg in 10 patients (58.8%). The modal dose was 2.0 mg in the median, 3.1 mg in the mean, and < 4 mg in 10 of 17 patients (58.8%). In addition, 1 ASM was added in 12 patients (70.6%), and 2 or more were added in 5 patients (29.4%).

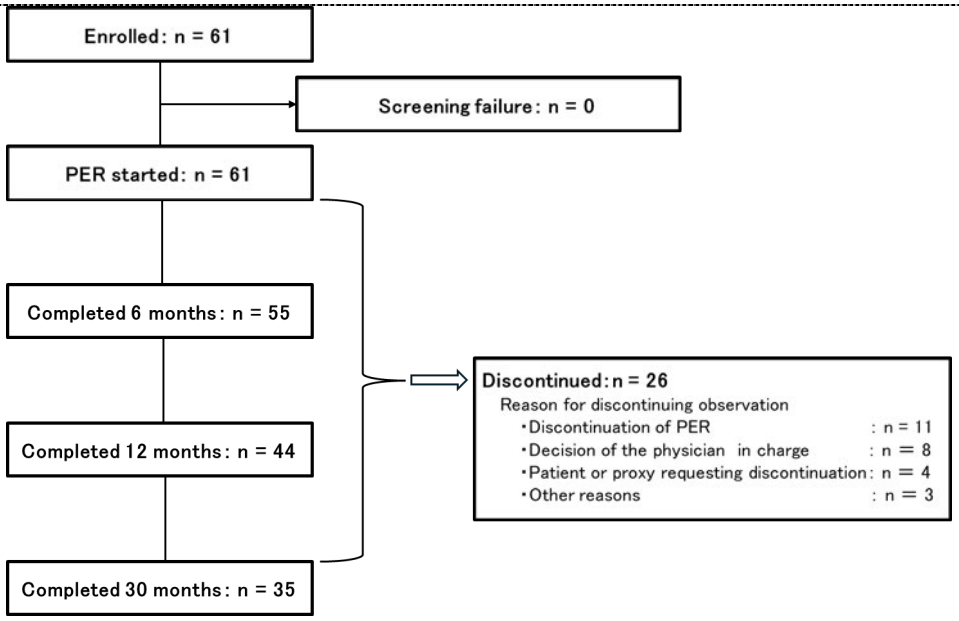
Focal onset seizure type (absence/presence of FBTCS):

In the population without FBTCS, the initial dose was < 2 mg in 12 patients (30.8%) and 2 mg in 27 patients (69.2%). The modal dose was 3.0 mg in the median, 3.2 mg in the mean, and < 4 mg in 20 of 39 patients (51.3%). In 14 patients (35.9%), 1 ASM was added in 9 patients (23.1%), 2 or more were added in 5 patients (12.8%). Lacosamide was added in 13 patients (33.3%), and levetiracetam was added in 4 patients (10.3%). In the population with FBTCS, the initial dose was < 2 mg in 4 patients (18.2%), 2 mg in 17 patients (77.3%). The modal dose was 2.5 mg in the median, 3.1 mg in the mean, and < 4 mg in 12 of 22 patients (54.5%). In 3 patients (13.6%), 1 ASM was added in all patients. Lacosamide was added in 1 patient (4.5%), and levetiracetam was added in 1 patient (4.5%).

Dose (modal dose: < 4 mg/≥ 4 mg):

In the population with < 4 mg, the initial dose was < 2 mg in 10 patients (31.3%), 2 mg in 22 patients (68.8%), and the modal dose was 2.0 mg in the median, 2.0 mg in the mean. ASM was added in 10 patients (31.3%), 1 ASM was added in 7 patients (21.9%), and 2 or more drugs were added in 3 patients (9.4%). Lacosamide was added in 8 patients (25.0%), and levetiracetam was added in 3 patients (9.4%). In the ≥ 4 mg group, the initial dose was < 2 mg in 6 patients (20.7%) and < 2 mg in 22 patients (75.9%), and the modal dose was 4.0 mg in the median and 4.5 mg in the mean. ASM was added in 7 patients (24.1%), 1 ASM was added in 5 patients (17.2%), 2 or more drugs were

	added in 2 patients (6.9%), lacosamide in 6 patients (20.6%), and levetiracetam in 2 patients (6.9%). Dose (initial dose: < 2 mg/2 mg/≥ 2 mg): In the < 2 mg group, the modal dose was 2.0 mg (median) and 3.1 mg (mean), and the modal dose was < 4 mg in 10 of 16 patients (62.5%). ASM was added in 7 patients (43.8%), 1 ASM was added in 5 patients (31.3%), 2 more drugs were added in 2 patients (12.5%), lacosamide in 5 patients (31.3%), and levetiracetam in 3 patients (18.8%). In the 2 mg group, the modal dose was 3.5 mg (median) and 3.2 mg (mean), and the modal dose was < 4 mg in 22 of 44 patients (50.0%). ASM was added in 10 patients (22.7%), 1 ASM was added in 7 patients (15.9%), 2 more drugs were added in 3 patients (6.8%), lacosamide in 9 patients (20.5%), and levetiracetam in 2 patients (4.5%). Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1): In the frontal lobe group, the initial dose was < 2 mg in 5 patients (31.3%), 2 mg in 11 patients (68.8%), and the modal dose was 4.0 mg in the median and 3.7 mg in the mean, and the dose was < 4 mg in 6 of 16 patients (37.5%). ASM was added in 2 patients (12.5%), 1 additional drug and ≥ 2 additional drugs in 1 patient (6.3%), lacosamide in 2 patients (12.6%), and levetiracetam in 2 patients (12.6%). In the patients with the temporal lobe as the seizure localization, the initial dose was < 2 mg in 8 patients (30.8%), 2 mg in 17 patients (65.4%), and the modal dose was 2.0 mg in the median and 2.9 mg in the mean. The dose < 4 mg was 16 (61.5%) of 26 patients. ASM was added in 12 patients (46.2%), 1 ASM was added in 7 patients (26.9%), 2 or more drugs were added in 5 patients (19.2%), lacosamide in 11 patients (42.3%), and levetiracetam in 4 patients (15.3%). In the patients with other seizure localization, the initial dose was < 2 mg in 2 patients (33.3%), 2 mg in 4 patients (66.7%), and the modal dose was 4.0 mg in the median and 4.0 mg in the mean. The dose < 4 mg was 2 (33.3%) of 6 patients. 1 ASM was added in 2 patients (33.3%), lacosamide in 1 patient (16.7%), and levetiracetam in the other patient (16.7%). In the patients with unknown seizure localization, the initial dose was < 2 mg in 2 patients (13.3%), 2 mg in 13 patients (86.7%), and the modal dose was 2.0 mg in the median and 2.8 mg in the mean. The dose < 4 mg was 10 (66.7%) of 15 patients. ASM was added in 3 patients (20.0%), and 1 ASM was added to all of them. Lacosamide was added in 2 patients (13.3%). Seizure localization (frontal/temporal/other (parietal/occipital/multilobed/unknown)) (2): In the patients with unknown seizure localization, the initial dose was < 2 mg in 4 patients (19.0%), 2 mg in 17 patients (81.0%), and the modal dose was 2.0 mg in the median and 3.1 mg in the mean. The dose < 4 mg was 12 (57.1%) of 21 patients. ASM was added in 5 patients (23.8%), and lacosamide was added in 3 patients (14.3%), and levetiracetam in 1 patient (4.8%).
Information on progress according to clinical study design	Between June 2021 and June 2022, 61 patients were enrolled. Of 55 patients who completed 6 months, 44 patients who completed 12 months, and 35 patients who completed 30 months, 26 patients discontinued observation. The reasons for discontinuing observation were discontinuation of PER in 11 patients, decision of the physician in charge in 8 patients (3 patients continued PER), patient or proxy requesting discontinuation in 4 patients (2 patients continued PER), and other reasons in 3 patients (1 patient continued PER). Sleep evaluation data were obtained in 2 patients.
Participant flow	



Summary of the occurrence of diseases

■Incidence of side effects in the entire population

Side effects were observed in 20 patients (32.8%). The major side effects were somnolence in 9 patients (14.8%), dizziness in 7 patients (11.5%), and mental disorders such as affect lability in 5 patients (8.2%).

Serious side effects were reported in 2 patients. A teenage patient died from a fall about 8 months after PER monotherapy. There were no other side effects, including aura symptoms, and the cause of the fall was unknown. Although an accident may have occurred, it was considered difficult to completely rule out a causal relationship because of the events during PER administration. The other case was a spinal compression fracture in the 70s that occurred approximately 24 months after PER monotherapy. The direct cause of the fracture was considered to be a fall from the bed, but since the fracture occurred during the night while the patient was sleeping, it was considered difficult to deny a causal relationship because the falling from the bed could have been caused by epilepsy.

■Somnolence, dizziness/vertigo, and psychiatric disorders (Time of onset and duration)

In somnolence, the mean number of days from the start of PER administration to the onset of the event was 32.4 days, with the median of 20.0 days. The mean duration from the onset of the event to remission/recovery was 286.7 days, with the median of 197.0 days. In dizziness/vertigo, the mean number of days from the start of PER administration to the onset of the event was 117.1 days, with the median of 91.5 days. The mean duration from the onset of the event to remission/recovery was 107 days, with the median of 31.0 days. In patients with psychiatric disorders, the mean number of days from the start of PER administration to the onset of an event was 112.2 days, and the median was 56.0 days. The mean duration from the onset of an event to remission or recovery was 209.6 days, and the median was 101.0 days.

■Subpopulation analysis of side effects

By age group (< 18 years/18 to < 65 years/≥ 65 years):

In the group aged < 18 years, side effects were observed in 5 patients (33.3%): somnolence in 2 patients (13.3%), dizziness in 2 patients (13.3%), and psychiatric disorders in 2 patients (13.3%). In the group aged 18 to < 65 years, side effects were observed in 12 patients (33.3%): somnolence in 7 patients (19.4%), dizziness in 4 patients (11.1%), and psychiatric l disorders in 1 patient (2.8%). In the group aged ≥ 65 years, side effects were observed in 3 patients (30.0%): dizziness in 1

	patient (10.0%), and psychiatric disorders in 2 patients (20.0%). Prescription history during the study period (PER monotherapy/ASM combination): In the group using PER alone, side effects were observed in 12 patients (27.3%): somnolence in 6 patients (13.6%), dizziness in 3 patients (6.8%), and psychiatric disorders in 2 patients (4.5%). In the group using ASM, side effects were observed in 8 patients (47.1%): somnolence in 3 patients (17.6%), dizziness in 4 patients (23.5%), and psychiatric disorders in 3 patients (17.6%). Focal onset seizure type (absence/presence of FBTCS): In the group without FBTCS, side effects were observed in 11 patients (28.2%): somnolence in 5 patients (12.8%), dizziness in 5 patients (12.8%), and psychiatric disorders in 2 patients (5.1%). In the group with FBTCS, side effects were observed in 9 patients (40.9%): somnolence in 4 patients (18.2%), dizziness in 2 patients (9.1%), and psychiatric disorders in 3 patients (13.6%). Dose (modal dose: < 4 mg/≥ 4 mg): In the group with < 4 mg, side effects were observed in 9 patients (28.1%): somnolence in 4 patients (12.5%), dizziness in 4 patients (12.5%), and psychiatric disorders in 2 patients (6.3%). In the group with ≥ 4 mg, side effects were observed in 11 patients (37.9%): somnolence in 5 patients (17.2%), dizziness in 3 patients (10.3%), and psychiatric disorders in 3 patients (10.3%). Dose (initial dose: < 2 mg/2 mg/≥ 2 mg): In the group with < 2 mg, side effects were observed in 3 patients (18.8%): somnolence in 1 patient (6.3%), dizziness in 1 patient (6.3%), and psychiatric disorders in 2 patients (12.5%). In the group with 2 mg, side effects were observed in 16 patients (36.4%): somnolence in 8 patients (18.2%), dizziness in 6 patients (13.6%), and psychiatric disorders in 3 patients (6.8%). Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1): In the group with the frontal lobe as the seizure localization, side effects were observed in 4 patients (25.0%), including somnolence in 1 patient (6.3%) and psychiatric disorders in 2 patients (12.5%). In the group with the temporal lobe as the seizure localization, side effects were observed in 11 patients (42.3%), including somnolence in 6 patients (23.1%), dizziness in 2 patients (7.7%), and psychiatric disorders in 3 patients (11.5%). In the group with other seizure localization, side effects were observed in 2 patients (33.3%), including somnolence in 1 patient (16.7%) and dizziness in 2 patients (33.3%). In the group with unknown seizure localization, side effects were observed in 4 patients (26.7%), including somnolence in 1 patient (6.7%), dizziness in 3 patients (20.0%), and psychiatric l disorders in 1 patient (6.7%). Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed, unknown)) (2): In the group with other seizure localization, side effects were observed in 6 patients (28.6%), including somnolence in 2 patients (9.5%), dizziness in 5 patients (23.8%), and psychiatric disorders in 1 patient (4.8%).
Data analysis and results of the primary and secondary endpoints [*] [*]	**[Primary endpoint]** **Seizure freedom rate at 24 months (18-24 months)** The denominator was the total number of patients who started treatment, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 49.2% (30/61). On the other hand, the denominator was the number of patients evaluated during the period, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 83.3% (30/36). **[Secondary endpoints]** **Seizure freedom rate at 6 months (3-6 months), 12 months (6-12 months), 18 months (12-18 months), and 30 months (24-30 months)**

The denominator was the total number of patients who started treatment, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 59.0%, 45.9%, 47.5%, and 44.3%, respectively. On the other hand, the denominator was the number of patients evaluated during each period, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 70.6%, 66.7%, 80.6%, and 79.4%, respectively.

Seizure freedom rate at 12 months (0–12 months) and 24 months (0–24 months)

The denominator was the total number of patients who started treatment, and the numerator was the number of patients who were able to continue treatment without seizures during the evaluation period was 36.1% and 26.2%, respectively.

Seizure freedom rate (Kaplan–Meier method)

The cumulative seizure freedom rate at 6, 12, 18, 24, and 30 months was 54.9%, 45.6%, 41.4%, 41.4%, and 36.0%, respectively. The median time to first seizure event was 6.5 months.

Treatment retention rate

The overall PER treatment retention rate at 6, 12, 18, 24, and 30 months was 85.0%, 76.3%, 67.2%, 67.2%, and 63.5%, respectively. The PER monotherapy retention rate was 73.5%, 61.2%, 55.6%, 55.6%, and 53.7%, respectively.

QOL

QOL was assessed using EQ-5D-5L and PedsQL at baseline and 1, 3, 6, 12, 18, 24, and 30 months. There were no significant changes in EQ-5D-5L compared to baseline throughout the observation period. PedsQL scores by parents showed a temporary decline at 1 month of treatment, but increased by 6 months and were maintained from 12 months to 30 months.

[Exploratory evaluation]

Sleep evaluation

Only 2 patients could be evaluated for sleep, but sleep parameters such as sleep latency, early awakening, and number of awakenings improved in one patient. In the other patient, there was improvement in sleep parameters such as sleep duration and sleep onset latency, although the results were obtained only at one time point each during the screening and treatment phases.

Adherence

The percentage of patients whose medication compliance rate was 80% or more was 86.2%, 89.3%, and 88.2% at 1, 3, and 6 months, respectively, and was less than 90%, but was 93.5% to 100% from 12 months to 30 months, indicating good medication compliance throughout the study period.

Efficacy Factors

Factors related to efficacy (Seizure freedom rate at 3, 12, and 24 months) were analyzed by logistic regression analysis, using subject background factors as explanatory variables. Efficacy factors included the presence/absence of FAS (odds ratio, 0.18) and FIAS (odds ratio, 0.15) at 3 months, the presence/absence of FIAS (odds ratio, 0.11) and seizure freedom at 3 months (odds ratio, 7.33) at 12 months, and the presence/absence of seizure freedom at 3 months (odds ratio, 6.90) at 24 months. As a result of variable selection (stepwise method) using variables that were significant in univariate analysis, at 3 months, both the presence/absence of FAS (odds ratio, 0.04) and FIAS (odds ratio, 0.04) were selected as model variables, and at 12 months, the presence/absence of

seizure freedom at 3 months (odds ratio, 4.36) and the presence/absence of FIAS (odds ratio, 0.17) were selected as model variables; at 24 months, the presence/absence of seizure freedom at 3 months (odds ratio, 6.90) was selected as model variable.

Subpopulation analysis

■Seizure freedom rate (1-1: Proportion using the total number of patients who started treatment as the denominator and the number of patients who were able to continue treatment without seizures during the evaluation period as the numerator; 1-2: Proportion using the number of patients evaluated during each period as the denominator and the number of patients who were able to continue treatment without seizures during the evaluation period as the numerator)

By age group (< 18/18 to < 65/≥ 65):

In the group aged < 18 years, both seizure freedom rate 1-1 (73.3% to 46.7%) and seizure freedom rate 1-2 (84.6% to 87.5%) tended to be higher than in other age groups (1-1: 52.8% to 44.4% in the group aged 18 to < 65 years, 60.0% to 40.0% in the group aged ≥ 65 years, 1-2: 65.5% to 84.2% in the group aged 18 to < 65 years, 66.7% to 57.1% in the group aged ≥ 65 years, respectively).

Prescription history during the study period (PER monotherapy/ASM combination):

The seizure freedom rate 1-1 was higher in the group treated with PER alone than in the group treated with ASM (75.0% to 50.0%, 17.6% to 29.4%, respectively). On the other hand, there was a large difference in seizure freedom rate 1-2 between the group treated with PER alone (86.6%, 81.3%) and the group treated with ASM (23.1%, 20.0%) at 6 and 12 months, but the seizure freedom rate from after 18 months was similar in both groups (82.8% to 78.6%, 71.4% to 83.3%).

Focal onset seizure type (absence/presence of FBTCS):

Seizure freedom rate 1-1 and seizure freedom rate 1-2 tended to be higher in the group with FBTCS (1-1: 77.3% to 63.6%, 1-2: 94.4% to 87.5%) than in the group without FBTCS (1-1: 48.7% to 33.3%, 1-2: 57.6% to 72.2%).

Dosage (modal dose: < 4 mg/≥ 4 mg):

Seizure freedom rate 1-1 decreased in the group with the modal dose ≥ 4 mg (65.5%, 37.9%, 41.4%, 48.3%, 34.5% at 6, 12, 18, 24, 30 months), on the other hand those rate in the group with the modal dose < 4mg remained in the 50% throughout the period (53.1%, 53.1%, 53.1%, 50.0%, 53.1%). Seizure freedom rate 1-2 in the group with the modal dose < 4mg (63.0% to 89.5%) was higher than that in the group with the modal dose ≥ 4 mg (79.2% to 66.7%).

Dosage (initial dose: < 2 mg/2 mg/≥ 2 mg):

Seizure freedom rate 1-1 tended to be higher in the group with the initial dose < 2 mg (56.3% to 50.0%) than in the group with the initial dose 2 mg (59.1% to 43.2%). On the other hand, in the seizure freedom rate of 1-2, the seizure freedom rate of the group receiving the initial dose of 2 mg (74.3% to 90.5%) tended to be higher than that of the group receiving the initial dose of < 2 mg (60.0% to 66.7%).

Seizure localization (frontal lobe/temporal lobe /other (parietal lobe, occipital lobe, multilobed)/unknown) (1):

The seizure freedom rate of 1-1 (87.5% to 56.3%) and 1-2 (93.3% to 81.8%) in the group with the frontal lobe as the seizure localization tended to be higher than that of the group with the temporal lobe as the seizure localization (46.2% to 26.9%, 57.1% to 58.3%, respectively). The seizure freedom rate of the group with the other localization including multilobed (1-1: 50.0% to 33.3%, 1-2: 60.0% to 66.7%) was also similar to that of the group with the temporal lobe as the seizure localization. The seizure freedom rate of the group with the unknown localization (1-1: 46.7% to 60.0%, 1-2: 63.6% to 100.0%) was similar to that of the group with the temporal lobe and other seizure localization at 6 months of PER treatment, but was similar to that of the group with the frontal lobe as the seizure localization from after 12 months.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed, unknown)) (2):

When the group with the unknown localization was included in the group with the other localization, the seizure freedom rate was higher in the order of the group with the frontal lobe (1-1: 87.5% to 56.3%, 1-2: 93.3% to 81.8%), the group with the other localization (1-1: 47.6% to 52.4%, 1-2: 62.5% to 91.7%), and the group with the temporal lobe (1-1: 46.2% to 26.9%, , 1-2: 57.1% to 58.3%).

■Seizure freedom rate (2): The total number of patients for whom treatment was initiated as the denominator, and the number of patients who were able to continue treatment without seizures in the duration from the start of treatment to each assessment time point as the numerator

By age category (< 18 years/18 to < 65 years/≥ 65 years):

The seizure freedom rate at 12 months was 53.3% in the group aged < 18 years, 40.0% in the group aged ≥ 65 years, and 27.8% in the group aged 18 to < 65 years. The seizure freedom rate was highest in the group receiving the seizure site of < 18 years. At 24 months, the seizure freedom rate in the group aged ≥ 65 years (40.0%) was higher than in the group aged < 18 years (33.3%) and the group aged 18 to < 65 years (19.4%).

Prescription history during the study period (PER monotherapy/ASM combination):

Seizure freedom rates in the PER monotherapy group were 47.7% at 12 months and 36.4% at 24 months, whereas that was 5.9% at 12 months and none of the patients remained seizure-free at 24 months in the ASM group.

Focal onset seizure type (absence/presence of FBTCS):

Seizure freedom rates in the group with FBTCS were 54.5% at 12 months and 45.5% at 24 months, which tended to be higher than those in the group without FBTCS (25.6%, 15.4%).

Dose (modal dose: < 4 mg/≥ 4 mg):

Seizure freedom rates in the group with the modal dose of < 4 mg were 40.6% at 12 months and 28.1% at 24 months, which tended to be higher than those in the group with the modal dose of ≥ 4 mg (31.0%, 24.1%).

Dose (initial dose: < 2 mg/2 mg/≥ 2 mg):

Seizure freedom rates in the group with the initial dose of < 2 mg and 2 mg were 31.3% and 36.4%, respectively, at 12 months, and 25.0% and 25.0%, respectively, at 24 months.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1):

Seizure freedom rates in the group with a seizure localization in the frontal lobe were 50.0% at 12 months and 37.5% at 24 months, which tended to be higher than those in the group with a seizure localization in the temporal lobe (30.8%, 23.1%). Seizure freedom rates in the group with a seizure localization unknown were 40.0% and 26.7%, respectively, which were next higher than those in the group with a seizure site in the frontal lobe. In the group with other seizure localization, there were no patients whose seizures were suppressed until 12 or 24 months.

Seizure localization (frontal/temporal/other (parietal/occipital/multilobed/unknown)) (2):

In the group with other seizure sites including the group with unknown seizure localization, the seizure freedom rate was 28.6% at 12 months and 19.0% at 24 months, which was similar to the seizure freedom rate in the group with temporal lobe seizure localization.

■Seizure freedom rate (3): Kaplan-Meier analysis using the first seizure as an event.

By age group (< 18 years/18 to < 65 years/≥ 65 years):

The seizure freedom rate in the group aged < 18 years was 66.7% at 6 months, 60.0% at 12 months, 52.5% at 18 months, 52.5% at 24 months, and 52.5% at 30 months, which was the highest compared

to the group aged 18 to < 65 years (54.0%, 40.5%, 36.5%, 36.5% and 36.5%, respectively) and the group aged ≥ 65 years (40.0%, 40.0%, 40.0%, 40.0% and 20.0%, respectively).

Prescription history during the study period (PER monotherapy/ASM combination):

The seizure freedom rate in the group using PER alone was 69.8% at 6 months, 62.0% at 12 months, 56.1% at 18 months, 56.1% at 24 months, and 48.9% at 30 months. In the group using ASM, the seizure freedom rate was 17.6% at 6 months, 5.9% at 12 months, and no patients maintained seizure freedom after 18 months.

Focal onset seizure type (absence/presence of FBTCS):

The seizure freedom rate in the group with FBTCS was 81.3% at 6 months, 66.1% at 12 months, 60.1% at 18 months, 60.1% at 24 months, and 54.1% at 30 months, which was higher than that in the group without FBTCS (39.7%, 34.0%, 30.6%, 30.6% and 24.5% respectively).

Dosage (modal dose: < 4 mg/≥ 4 mg):

The seizure freedom rate in the group with the modal dose of < 4 mg was 52.0% at 6 months, 48.5% at 12 months, 48.5% at 18 months, 48.5% at 24 months, and 43.1% at 30 months, which was higher than that in the group with the modal dose of ≥ 4 mg (58.6%, 42.6%, 33.2%, 33.2% and 28.4%, respectively).

Dosage (initial dose: < 2 mg/2 mg/≥ 2 mg):

The seizure freedom rate in the group with the initial dose of 2 mg was 58.2% at 6 months, 47.6% at 12 months, 44.4% at 18 months, 44.4% at 24 months, and 44.4% at 30 months, which was higher than that in the group with the initial dose of < 2 mg (43.8%, 37.5%, 30.0%, 30.0% and 20.0% respectively). Although there was only 1 patient in the group with an initial dose of ≥ 2 mg, seizure freedom was maintained from 6 to 24 months.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1):

The seizure freedom rate by seizure site was higher in the group with the frontal lobe as the seizure localization (at 6 months: 68.8%; at 12 months: 62.5%; at 18 months: 54.7%; at 24 months: 54.7%; at 30 months: 54.7%), in the group with unknown seizure localization (63.2%, 54.2%, 43.3%, 43.3% and 43.3% respectively), and in the group with the temporal lobe as the seizure localization (42.0%, 33.6%, 33.6%, 33.6% and 22.4% respectively). In the group with other seizure localization, seizure freedom was not maintained after 6 months (33.3%).

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed, unknown) (2):

Seizure freedom rates with seizure localization in other regions including cases with unknown seizure localization was 54.0%, 42.0%, 33.6%, 33.6% and 33.6% respectively.

■EQ-5D-5L

By age category (< 18 years/≥ 18 years):

The utility value of EQ-5D-5L was 0.8978 in the median at baseline in the group aged ≥ 18 years, lower than 1.0000 at baseline in the group aged < 18 years, but maintained at 1.0000 from 1 month to 30 months in all groups.

■PedsQL

By age category (1) (< 18 years/≥ 18 years):

The total PedsQL score was 86.41 at baseline in the group aged < 18 years, lower than 92.39 at baseline in the group aged ≥ 18 years, but remained similar from 1 month to 30 months.

By age category (2) (Young Children (5 to 7 years)/Children (8 to 12 years)/Teens (13 to 17 years)/Young Adults (18 to 25 years)/Adults (≥ 26 years):

The total PedsQL score from baseline to 30 months in the Children group was 70.65 to 76.63,

which was lower throughout the evaluation period than in the Teens (91.30 to 100.00), Young Adults (94.57 to 97.83), and Adults (88.04 to 98.34) groups. There were no cases in the Young Children group.

By age category(3) (Parents of Young Children (5 to 7 years)/Children (8 to 12 years)/Teens (13 to 17 years):

The total PedsQL score from baseline to the 30 months in the Parents of Teens group (88.04 to 98.37) was higher than that in the Parents of Children group (75.00 to 88.04) throughout the study period.

■Sleep-related data

Subgroup analysis was not performed due to the number of cases being two.

■Treatment retention rate

By age group (< 18 years/18 to < 65 years/≥ 65 years):

The treatment retention rate in the group aged < 18 years was 86.7% at 6 months, 80.0% at 12 months, 66.7% at 18 months, 66.7% at 24 months, and 59.3% at 30 months, which was similar to that in the group aged 18 to < 65 years (83.0%, 73.9%, 64.2%, 64.2% and 61.0% respectively). The treatment retention rate in the group aged ≥ 65 years was the highest at 90.0%, 80.0%, 80.0%, 80.0%, and 80.0%, respectively.

During the study period (PER monotherapy/ASM combination):

The treatment retention rate in the group using PER monotherapy was 88.5% at 6 months, 83.4% at 12 months, 78.2% at 18 months, 78.2% at 24 months, and 75.5% at 30 months, which was higher than that in the group using ASM (76.5%, 58.8%, 41.2%, 41.2% and 35.3% respectively).

Focal onset seizure type (absence/presence of FBTCS):

The treatment retention rate at 6 months was 86.9% in the group without FBTCS, which was higher than that in the group with FBTCS, which was 81.8%. The treatment retention rate after 12 months in the group with FBTCS was 81.8% at 12 months, 77.0% at 18 months, 77.0% at 24 months, and 77.0% at 30 months, which was higher than that in the group without FBTCS (72.7%, 61.1%, 61.1% and 55.0%, respectively).

Dose (modal dose: < 4 mg/≥ 4 mg):

The treatment retention rate in the group with the modal dose of < 4 mg was 84.4% at 6 months, 77.9% at 12 months, 67.7% at 18 months, 67.7% at 24 months, and 67.7% at 30 months, which was similar to the treatment retention rate in the group with the modal dose of ≥ 4 mg (85.7%, 74.3%, 66.5%, 66.5% and 58.7%, respectively).

Dose (initial dose: < 2 mg/2 mg/≥ 2 mg):

The treatment retention rate in the group with the initial dose of < 2 mg was 93.8% at 6 months, 87.5% at 12 months, 87.5% at 18 months, 87.5% at 24 months, and 80.8% at 30 months, which was higher than the seizure retention rate in the group with the initial dose of 2 mg (81.5%, 71.4%, 58.6%, 58.6% and 56.0% respectively). Only 1 patient in the group with the initial dose of ≥ 2 mg continued treatment until 30 months.

Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed)/unknown) (1):

The treatment retention rate in the group with the seizure localization in the frontal lobe was 93.8% at 6 months, 87.1% at 12 months, 80.4% at 18 months, 80.4% at 24 months, and 73.7% at 30 months, which was higher than that in the group with the seizure localization in the temporal lobe (84.0%, 71.1%, 62.2%, 62.2% and 57.4%, respectively), other seizure localizations (83.3%, 83.3%, 62.5%, 62.5% and 62.5% respectively), and unknown seizure localizations (73.3%, 66.7%, 60.0%, 60.0% and 60.0%, respectively).

	Seizure localization (frontal lobe/temporal lobe/other (parietal lobe, occipital lobe, multilobed, unknown)) (2): The treatment retention rate in the group with the seizure localization in other regions, including cases with unknown seizure localization was 76.2% at 6 months, 71.4% at 12 months, 61.2% at 18 months, 61.2% at 24 months, and 61.2% at 30 months, which was similar to that in the group with the seizure localization in the temporal lobe (84.0%, 71.1%, 62.2%, 62.2% and 57.4% respectively).
Discussion	**1. Summary of Monotherapy Use** As a first-line monotherapy for PER in this study, the primary endpoints, seizure freedom rate at 24 months were 49.2% (seizure freedom rate 1-1) and 83.3% (seizure freedom rate 1-2). The secondary endpoints of seizure freedom rate at 6, 12, 18, 30 months were 59.0%, 45.9%, 47.5%, 44.3% (seizure freedom rate 1-1) and 70.6%, 66.7%, 80.6%, 79.4% (seizure freedom rate 1-2), showing efficacy and persistence of efficacy. As evidence of first-line monotherapy for PER, in a phase Ⅲ study conducted jointly with Japan and Korea [3], the seizure freedom rate was 63.0% for 4 mg monotherapy and 74.0% for 4 or 8 mg monotherapy in 89 patients. In overseas clinical studies, the seizure freedom rate was 69.8% at 6 months and 65.1% at 12 months in a report by Ma et al.[5], in Chinese patients, 63% and 52%, respectively, in a report by Xu et al.[6], in Chinese patients, 80% and 76%, respectively, in a report by Chinvarun et al.[7], in Thai patients, and 71.0% and 71.7%, respectively, in a report by Zhao et al.[8], in Chinese pediatric patients. As for the seizure freedom rate at 12 months in new epilepsy patients treated with other drugs, Baulac et al., in a phase Ⅲ double-blind study [9], reported zonisamide 67.6%, carbamazepine extended-release formulation 74.7%, and Li et al., in a clinical study [10], reported levetiracetam 65.7% and lamotrigine 60.2%, showing similar efficacy compared with these drugs. The retention rate of PER in this study was 85.2% at 6 months and 70.5% at 12 months. Similar results were obtained from Ma et al. (78.6% and 70.0%, respectively), Xu et al. (70% and 63%, respectively), and Chinvarun et al. (73% and 61%, respectively). In a phase Ⅲ study of first-line monotherapy conducted jointly with Japan and Korea [11], among patients who showed efficacy at 4 mg, 80.4% did not have seizures during the titration period, suggesting the possibility of efficacy at lower doses .In the present study, many patients continued treatment with 4 mg or less (90.1% of patients with the modal dose of 4 mg or less at 12 months). This may be due to the fact that seizure resolution was judged to be achieved at the lower dose, or that patients started treatment with less than 2 mg or were carefully titrated to manage adverse reactions. When the duration of dose increase from the initial dose to 4 mg was totaled, it took approximately 2 months overall, and patients aged 65 years or older were more carefully titrated over approximately 4 months. In the above-mentioned real-world clinical reports from China and Thailand, the dose of 4.0 mg was also used at the lower dose. In addition, 16 patients (26.2%) were concomitantly administered with other drugs, which suggests that rational multi-drug combination therapy is often considered without dose increase. Furthermore, there was no difference in seizure freedom and retention rates between the group with the modal dose of < 4 mg and the group with the modal dose of ≥ 4 mg, suggesting that some patients may be effective and tolerable even at the lower dose. Side effects occurred in 20 patients (32.8%). The major Side effects were somnolence (14.8%), dizziness (11.5%), affect lability (3.3%), affective disorder, anger, irritability, and fall (1.6% each). The side effects to the nervous system were similar in the < 4 mg and ≥ 4 mg groups (21.9% and 24.1%, respectively) at the modal dose, but at the initial dose < 2 mg group tended to have fewer than 2 mg group (12.5% and 27.3%, respectively). In the results of the phase Ⅲ study [3], in which the dose was fixed at 4 mg or 8 mg, dizziness occurred in 31.5%, and in the pooled analysis of the clinical studies[12], it was reported that side effects to the nervous system disorders tended to increase in a dose-dependent manner, and that they were more frequent at the start of treatment or in the

titration phase. Therefore, it is possible that the tendency of the low incidence of side effects to the nervous system disorders in this study was attributable to the low-dose regimen used in clinical studies.

In this study, not only tablets but also fine granules were used for low-dose use. Fine granules are useful not only for children and patients with impaired swallowing function who have difficulty taking tablets, but also for small doses and dose adjustment.

2. Monotherapy in children (< 18 years)

The median modal dose of PER in the pediatric population was 4.0 mg, with a mean of 3.5 mg. The results showed that PER was used at a low dose, similar to 4.4 mg in a post-marketing surveillance study of children in Japan [13] and 4.0 mg in clinical reports on monotherapy in China [5), 6), 8)]. In the pediatric population, seizure freedom and retention rates tended to be higher than those in other age groups. This was partly due to the low seizure frequency of 0.6 times/month at the start of treatment and the high rate of FBTCS [5), 6)] in which PER is expected to be effective, at 46.7%. In clinical reports on monotherapy in China [5)], the seizure resolution rate of FBTCS in patients under 18 years of age was similarly high, and in clinical reports on monotherapy in patients under 14 years of age and over 14 years of age [6)], the efficacy of PER in patients under 14 years of age and FBTCS was high. In the pediatric population, PER may be initiated at a low dose and titrated carefully. In the Asia Expert Opinion [14] on the use of PER in pediatric epilepsy, dose settings such as starting dose and titrating dose according to body weight and age were also proposed. In addition, PER has been reported to be effective in a wide range of seizure types [15]. In particular, in FBTCS, there is a report [16] suggesting that the inhibition mechanism associated with the increase of AMPA receptors is disrupted, leading to the transition from FBTCS. Thus, PER is expected to be effective in a wide range of seizure types.

The total number of side effects was 32.8% in the whole group and 33.3% in the group aged < 18 years, showing no change in trend. In the group aged < 18 years, there was a tendency to have coexisting developmental disorders as a background (40%), but the incidence of psychiatric side effects in these patients was not significantly different from that in the whole group (13.3% and 8.2%, respectively).

3. Monotherapy use in the elderly

In the elderly group aged ≥ 65 years, the median modal dose of PER was 2.0 mg and the mean was 2.7 mg. In the Japanese post-marketing surveillance [17] of concomitant use with other drugs, the average daily dose was 3.0 mg in the group aged ≥ 65 years, and the elderly tended to use less than 4 mg. In addition, the total number of side effects was 32.8% in the whole group and 30.0% in the group aged ≥ 65 years, showing a similar incidence. PER has little interaction with other drugs, is a small tablet administered once a day, and from the viewpoint of medication adherence, it is possible to continue treatment at a low dose and may be suitable for the elderly. In the Asia Expert Opinion on the use of PER in epilepsy in the elderly, it is proposed to start at 1 mg or 2 mg and then gradually increase by 1 mg over 3to4 weeks [18]. When PER is started at less than 2 mg, the titration may be carried out carefully, and it is considered to be a useful method of use in the elderly who are concerned about nervous system side effects.

4. Effect on QOL of patients and guardians

There was no overall deterioration in QOL except for a temporary decrease in PedsQL of guardians after 1 month. The previous report [19] showing improvement in QOL by PER treatment was the result of combination therapy in patients with a long history of epilepsy treatment. The result of not deteriorating QOL in this study was considered to be due to the background of patients

	with a high original QOL, as there were many first-episode patients with low seizure frequency at the start of treatment. Although PedsQL of guardians decreased after 1 month, it increased by 6 months. This may reflect side effects such as somnolence that appeared temporarily after PER treatment, anxiety and stigma of guardians regarding medication, and mental burden of considering illness related to work and school. **5. Effects on sleep** Although only 2 cases were reported regarding sleep, improvement trends such as increased sleep efficiency and decreased number of awakenings were observed. One case was male in his 30s with focal epilepsy (unknown seizure localization). The duration of the disease was 20 years. There was no developmental disorder, FAS, no trigger for seizures, and a family history of epilepsy. PER started at 2 mg/day, increased to 4 mg/day after 1 month, and decreased to 2 mg/day after 10 months. The average seizure frequency before the start of the study was 30 times/month. Focal consciousness retention seizure occurred 1 time after 1 week and 1 time after 3 months of PER administration, but no seizure occurred until 12 months later. There were no add-on ASM, and mild dizziness was observed as a side effect, but there was no significant change in QOL over the 30 months. The evaluation was performed at 3 months later of PER administration. The other case showed improvement in sleep parameters such as sleep time and sleep latency, although the results were obtained only at one time point during the screening and treatment phases. The case was female in her 40s with focal epilepsy (frontal lobe as the seizure localization). The duration of the disease was 7.3 years. There was no developmental disorder, FMS, no trigger for seizures, and a family history of epilepsy. The average seizure frequency before the start of the study was 0.3 times/month. PER was started at 2 mg/day and taken for 6 months. Thereafter, the case did not take medication for 4 months and PER was resumed at 1 mg/day at 10 months after the start of the study. The sleep evaluation was conducted at 13 months after study entry (2 months after resumption of PER). The case did not take medication again at 15 months after the study entry (4 months after resumption of PER). Finally, the study was discontinued at 26 months after the study entry. No seizure occurred. There were no add-on ASM, and no side effect was observed. QOL declined at the 6 months but recovered until the 12 months. Previous reports [19), 20), 21), 22)] also evaluated the effect of PER treatment on sleep using PSG and sleep scale, and showed a decrease in mid-awakening time, an increase in N3 sleep, and improvements in the Pittsburgh Sleep Quality Index. It has also been reported that PER monotherapy is suitable for elderly patients with epilepsy who also have sleep disorders because it is desirable that antiepileptic drugs do not adversely affect sleep [23)].
Brief summary	The efficacy and safety of PER monotherapy in untreated patients with epilepsy, including children and elderly patients, at 30 months of treatment were confirmed, suggesting that PER may be the first choice. Although it should be noted that the maintenance dose of PER monotherapy is 4 to 8 mg in the package insert, a lower dose may be sufficient in patients with untreated epilepsy in clinical practice. The efficacy and safety of PER monotherapy were similar to those reported in clinical trials and in clinical and other studies in other countries.