2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Perampanel oral tablet	Referring to Module 5 of the Dossier	
Name of Active Ingredient: E2007/Fycompa®	Volume: Page:	

Study Title

A Prospective, Non-Interventional, Observational, Multicenter Study to Investigate Dosage, Effectiveness, and Safety of Perampanel when Used as First Adjunctive Therapy in the Routine Clinical Care of Subjects ≥12 Years with Partial Onset Seizures With or Without Secondary Generalization or with Primary Generalized Tonic–Clonic Seizures Associated with Idiopathic Generalized Epilepsy

Investigator/Sites

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Multicenter: 38 investigational sites in Spain (8 sites), Germany (2 sites), France (8 sites), Portugal (3 sites), Italy (9 sites), Denmark (2 sites), and Russia (6 sites).

Publication (Reference)

Not applicable.

Study Period

20 Jul 2020 to 12 Jan 2023

Phase of Development

Phase 4

Objectives

Primary Objective

The primary objective of the study was to assess the retention rate of perampanel as a reliable proxy for overall effectiveness and tolerability in subjects aged ≥12 years who were prescribed perampanel (for partial onset seizures [POS] with or without secondary generalization [SG] or for primary generalized tonic-clonic seizures [PGTCS] associated with idiopathic generalized epilepsy [IGE], within its European Union [EU] license) as part of routine care and as the first adjunctive to antiepileptic drug (AED) monotherapy.

Secondary Objectives

1. To assess effectiveness of perampanel in reducing seizure frequency, overall and by seizure type, in the overall population and in relevant subpopulations
2. To measure retention time on perampanel
3. To evaluate the tolerability and safety of perampanel
4. To evaluate the dosing of perampanel (titration patterns and maintenance doses)

Exploratory Objectives

1. To explore the factors that influence retention on perampanel and time to drop-out
2. To explore the factors that influence seizure freedom
3. To evaluate the impact of adjunctive perampanel on quality of life (QOL), subjective daytime sleepiness, and cognitive function
4. To assess the use of concomitant AEDs over time

5. To explore the frequency of psychiatric adverse events (AEs) in subjects with and without prior occurrence of psychiatric AEs with prior AED monotherapy
Methodology This was a non-interventional, observational, prospective, multicenter study in subjects with a diagnosis of epilepsy (POS with or without SG or PGTCS associated with IGE), for whom the treating physician had made the decision to initiate perampanel as the first adjunctive to baseline AED monotherapy. The study sites (epilepsy and neurology centers) were pre-selected to ensure compatibility of their usual medical records with study endpoints. The study aimed to use a 12-month enrollment and a 12-month treatment period (and an interim analysis 6 months after enrollment had completed). Subjects were seen at baseline and then according to usual clinical practice, but a visit was included at approximately 6 months (±4 weeks) and approximately 12 months (±8 weeks). Data from visits at other times were recorded and analyzed (if feasible). The assessments of final visit were collected (if available) at the time of withdrawal or perampanel discontinuation if the subject withdrew from the study or discontinued perampanel. The time from first subject recruited to last subject out was planned to be 24 months. The end of the study was the date of the last study visit for the last subject.
Number of Subjects (Planned and Enrolled) Planned enrollment was approximately 300 subjects (including at least 50 subjects with PGTCS associated with IGE, and at least 50 subjects aged ≥12 to <18 years, and approximately 50 subjects aged ≥65 years). The number of subjects enrolled was 191, which was less than planned due to the impact of the coronavirus disease 2019 (COVID-19) pandemic upon subject recruitment.
Diagnosis and Main Criteria for Inclusion Subjects were eligible for participation in the study if they were at least 12 years of age at screening and had a diagnosis of epilepsy and a history of POS with or without SG or PGTCS associated with IGE (according to the International League Against Epilepsy [ILAE] Classification of Epileptic Seizures, 1981 and ILAE Classification of Epileptic Syndromes, 1989) who had previously been treated with 1 or 2 AEDs as monotherapy. Subjects with previous or current use of perampanel at the time of screening were excluded.
Test Treatment, Dose, Mode of Administration, and Batch Number(s) Perampanel was administered and dosed according to the judgment of the treating physician throughout this study. Perampanel was administered orally daily at bedtime. The investigator selected the appropriate dose and formulation for each subject. Commercially available perampanel was used. No investigational drug was administered as part of this study.
Reference Therapy, Dose, Mode of Administration, and Batch Number(s) Not applicable.
Duration of Treatment Subjects were observed for up to 12 months after initiation of perampanel treatment.
Assessments All data were obtained by personnel at the study site, by reviewing and entering information from subject medical records, from records of healthcare providers' interviews with subjects and/or caregivers at clinic visits, and from seizure diaries (where available) into a case report form (CRF). **Efficacy** Retention on perampanel was determined by treatment status (ongoing on perampanel or not), at each visit. Reasons for discontinuation were recorded. Number and type of seizures were collected from seizure diary data or if not available medical records and records of healthcare providers' interviews with subjects/caregivers at clinic visits. This information was used to calculate the seizure outcomes (responder rate, seizure frequency change, seizure freedom, and seizure worsening). Seizure frequency (for POS with or without SG, secondarily generalized tonic-clonic seizures

[SGTCS], and PGTCS) or days with seizures (for absence and myoclonic seizures) data was collected retrospectively during the 1 month up to the day before baseline (day of first dose of perampanel) to ensure adequate data to calculate baseline seizure frequency, for the 3-month period up to the day before the 6-month visit, and for the 6-month period up to the day before the 12-month visit. The decision to capture and analyze myoclonic and absence seizures based on counting days/week with seizures was made due to the high frequency and repetitiveness of the latter 2 seizure types, which complicate reliable quantification.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Pharmacogenomics

Not applicable.

Safety

Exposure to perampanel was assessed by recording perampanel dose at each visit and the titration schedule used to achieve maintenance dose (ie, frequency of perampanel dose increase).

Safety assessments consisted of monitoring and recording of all AEs and serious adverse events (SAEs), including any cognitive or psychiatric AEs. Information on AEs were collected by open/general questions to subjects at each visit including AEs documented in subject seizure diary data if these diaries were routinely used as part of usual clinical practice. Whether subjects had experienced psychiatric treatment-emergent adverse events (TEAEs) on previous AED monotherapies was recorded where available from medical records. Any spontaneously reported AEs between visits were also captured. Terms were collected verbatim and categorized using Medical Dictionary for Regulatory Activities (MedDRA) into preferred term (PT) and system organ class (SOC).

If available, baseline height and weight were collected from subject charts. At subsequent visits, weight was recorded for subjects 18 years or older if available; for adolescents (aged ≥12 to <18 years at baseline), height and weight were recorded if available.

Other

QOL was assessed using the Quality of Life in Epilepsy Inventory 10 (QOLIE-10) in subjects aged 18 years or older. The Quality of Life in Epilepsy Inventory for Adolescents 48 (QOLIE-AD-48) was used to assess QOL in subjects aged ≥12 to <18 years. Subjects completed the questionnaire at each visit if the QOLIE-10 or QOLIE-AD-48 was routinely used as part of clinical practice at that site. Subjects answered questions about aspects of health and daily activities that could be affected by epilepsy and its treatment, referring to the previous 4 weeks.

Daytime sleepiness was assessed subjectively using the Epworth Sleepiness Scale (ESS) in subjects aged 18 years or older. The Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) was completed in subjects aged ≥12 to <18 years. The test was administered at each visit if the test was routinely used as part of clinical practice at the site. In the ESS or ESS-CHAD, subjects rated the likelihood of their falling asleep, on a scale of increasing probability from 0 to 3, for 8 different situations that most people engage in during their daily lives. Questions referred to the subject's "usual way of life in recent times." Possible score ranged from 0 to 24: scores of ≤10 were considered normal and scores >10 were indicative of excessive daytime sleepiness (mild, 10-12; moderate 13-15; severe ≥16).

Cognitive function was assessed objectively using the neuropsychological screening tool EpiTrack® in subjects aged 18 years or older or EpiTrack Junior in subjects aged ≥12 to <18 years at sites that routinely used this tool as part of usual clinical practice. EpiTrack or EpiTrack Junior are short tests of neurocognitive function that subjects completed with paper and pencil. The test output is an age-corrected total score shown to be sensitive to AED effects.

Concomitant AED exposure was assessed by recording the name, dose, frequency of administration, and route of administration of concomitant AED used at each visit.

Statistical Methods

Data were summarized by the sponsor after study data were collected and data validation was completed.

Descriptive statistics were used to calculate number and percentage for categorical variables, and mean, standard deviation, median, interquartile range, minimum, and maximum, for continuous variables.

Study Endpoints

Primary Endpoint

The primary endpoint was the retention rate (the proportion of subjects remaining on perampanel) at 12 months in the Safety Analysis Set (SAS).

Secondary Endpoints

The following secondary endpoints were analyzed:

1. The retention rate at 6 months in the SAS.
2. The pragmatic seizure-free rate at 6 and 12 months (the number of subjects free of all seizures at 6 months [and for the previous 3 months], and free of all seizures at 12 months [and for the previous 6 months] expressed as a proportion of the Full Analysis Set [FAS]). There was no imputation for missing data. Subjects with completely missing data or not ongoing on perampanel at 6 or 12 months were assumed not to be seizure free.
3. The completer seizure-free rate at 6 and 12 months (the number of subjects free of all seizures at 6 months [and for the previous 3 months] and at 12 months [and for the previous 6 months] expressed as a proportion of the subjects taking perampanel at that time point).
4. Seizure frequency change (median percentage change relative to baseline) at 6 months (averaged over the previous 3 months) and at 12 months (averaged over the previous 6 months) in the FAS.
5. 50% responder rate at 6 and 12 months (proportion of subjects with ≥50% reduction in seizure frequency [averaged over the 3 months before the 6-month visit, and over the 6 months before the 12-month visit], relative to baseline) in the FAS.
6. Seizure worsening at 6 and 12 months (proportion of subjects with ≥10% increase in seizure frequency [averaged over the 3 months before the 6-month visit, and over the 6 months before the 12-month visit], relative to baseline) in the FAS.
7. Perampanel last dose at 6 and 12 months.
8. Proportion of subjects with perampanel dose increase every week, every 2 weeks, every 3 weeks, every 4 weeks, and >4 weeks during perampanel titration (if data was available).
9. Duration of treatment on perampanel.
10. Incidence of TEAEs at 0 to 6 and 0 to 12 months, in the SAS, including the overall rate of TEAEs (proportion of subjects with ≥1 TEAE), the rate of individual TEAEs (Medical Dictionary of Regulatory Activities version 25.1[MedDRAv25.1] PT), the World Health Organisation Drug (WHODrug Mar22B3G) and TEAEs by SOC.
11. Incidence of serious TEAEs; mild/moderate/severe TEAEs, and TEAEs leading to discontinuation.

Exploratory Endpoints

The following were exploratory endpoints:

1. QOLIE-10 and QOLIE-AD-48 total score and change from baseline at 6 and 12 months.
2. ESS and ESS-CHAD score and change from baseline at 6 and 12 months.
3. Age-corrected EpiTrack and EpiTrack Junior total score and change from baseline at 6 and 12 months.
4. Proportion of subjects with change in baseline AED (removal [conversion to perampanel monotherapy], reduction in dose, increase in dose, switch to different AED, addition of new concomitant AED).

Analysis Sets

The SAS included subjects who received at least 1 dose of perampanel and had at least 1 post dose safety measurement.

The FAS included subjects who received at least 1 dose of perampanel and had at least 1 post dose efficacy measurement (seizure outcomes).

Efficacy Analyses

The SAS was used to analyze retention data.

The primary efficacy analysis was the retention rate, defined as the number of subjects remaining on perampanel at 12 months, as a proportion of the SAS. This was summarized as the number and percentage of subjects (95% CI).

Retention rate was reported for the overall population and for key subpopulations as follows:

- By age (subjects aged ≥12 to <18 years; subjects aged ≥18 to <65 years; subjects aged ≥65 years at baseline)
- By seizure type (partial onset; primary generalized)
- By most common syndromes (including IGE)
- By concomitant AED
- By mechanism of action (MOA) of concomitant AED
- By inducer status (subjects with/without concomitant enzyme-inducing AED [EIAED])
- By seizure etiology
- By number of prior AED monotherapies.

Secondary Efficacy Analyses

The SAS was used to analyze retention data and the FAS was used to analyze seizure data.

Secondary efficacy analyses were as follows:

1. The retention rate, defined as the number of subjects remaining on perampanel at 6 months, as a proportion of the SAS, was summarized as the number and percentage of subjects (95% CI).
2. The pragmatic seizure-free rate, completer seizure-free rate, and responder rate, as well as the subjects with seizure worsening and with no change in seizure frequency, was summarized as the number and percentage of subjects (95% CI). For myoclonic and absence seizures, change in seizure activity was reported as the percentage change in number of days per week with seizures at 6 and 12 months as compared with baseline.
3. Percentage change in seizure-frequency was reported as mean, standard deviation, median (95% CI), minimum, and maximum.
4. Seizure-related outcomes were reported for POS with and without SG, SGTCS, PGTCS, myoclonic seizures, and absence seizures.
5. Retention rate and all seizure-related outcomes were reported for the overall population and for key subpopulations as follows:

- By age (subjects aged ≥12 to <18 years; subjects aged ≥18 to <65 years; subjects aged ≥65 years at baseline)
- By seizure type (partial onset; primary generalized)
- By most common syndromes (including IGE)
- By concomitant AED
- By MOA of concomitant AED
- By inducer status (subjects with/without concomitant EIAED)
- By seizure etiology
- By number of prior AED monotherapies

6. Retention over time was presented as a Kaplan–Meier plot (with 95% CIs) for the overall population and subpopulations (age [≥12 to <18 years; ≥18 to <65 years; ≥65 years]; seizure type [partial onset; primary generalized]; syndrome; concomitant AED; MOA of concomitant AED; EIAED status; seizure etiology; and number of prior AED monotherapies).

If feasible, logistic regression was used to identify:

- Predictors of retention at 12 months

- Predictors of seizure freedom at 12 months

If possible, Cox proportional hazards model was used to identify predictors of time to dropout.

Pharmacokinetic Analyses

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses

Perampanel dosing and exposure data was reported for the SAS.

Perampanel mean dose, modal dose, median dose, maximum dose, and last dose were summarized over the treatment period; perampanel last dose at 6 months and last dose at 12 months (or end of treatment); and duration of perampanel treatment was summarized as mean, standard deviation, median, 95% CI, minimum, and maximum. The titration patterns of perampanel were analyzed as the proportion of subjects with perampanel dose increase every week, every 2 weeks, every 3 weeks, every 4 weeks, and >4 weeks (number, percentage).

Perampanel dosing and exposure data was reported for the overall population and by seizure type, syndrome, age group, concomitant AED, and EIAED status.

The incidence of TEAEs was reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject was counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs was also summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs was also summarized by relationship to study drug (Yes [related] and No [not related]).

TEAEs were reported overall, and by perampanel maximum dose, seizure type, seizure etiology, syndrome, age group (≥12 to <18 years; ≥18 to <65 years; ≥65 years), concomitant AED, concomitant AED MOA, number of previous AEDs, and EIAED status.

The rate of TEAEs of special interest, including psychiatric TEAEs (those in the Psychiatric Disorders SOC), and cognitive TEAEs (using the 'dementia' standard medical query), was reported. Psychiatric TEAEs were summarized separately for subjects with and without prior psychiatric TEAEs on previous AED monotherapy. Psychiatric TEAEs were also summarized separately for subjects with and without a history of psychiatric events. The rate of individual TEAEs, mild/moderate/severe TEAEs, serious TEAEs, and TEAEs leading to discontinuation was reported for the overall population, and for key subpopulations.

Other Analyses

QOL was reported as the change in QOLIE-10 score from baseline to 6 and 12 months (mean, standard deviation, median, 95% CI, minimum, and maximum) in subjects aged 18 years or older. The QOLIE-AD-48 was used to assess QOL in subjects aged ≥12 to <18 years.

Change in daytime sleepiness was summarized as the change in ESS score from baseline to 6 and 12 months (mean, standard deviation, median, 95% CI, minimum, and maximum) for subjects aged 18 years or older. The ESS-CHAD was used to assess sleepiness in subjects aged ≥12 to <18 years. The proportion of subjects with excessive daytime sleepiness (score >10) at baseline, 6, and 12 months was summarized as number of subjects and percentage (95% CI). In addition, the proportion of subjects with a change in score from normal (≤10) to excessive sleepiness (>10) from baseline to 12 months and the proportion of subjects with a change in score from excessive sleepiness (>10) to normal (≤10) from baseline to 12 months were summarized as number of subjects and percentage (95% CI). Shift tables were also produced.

Cognitive function was summarized as change in EpiTrack age-adjusted total score from baseline to 6 and 12 months (mean, standard deviation, median, 95% CI, minimum, and maximum) in subjects aged 18 years or older. In this age group, the proportion of subjects with mild impairment (scores 29-31) and significant impairment (≤28) at baseline, 6, and 12 months was summarized as number of subjects and percentage (95% CI). The proportion of subjects with clinically important improvement (gain >3 points) from baseline to 12 months and the proportion of subjects with clinically important deterioration (loss >2 points) from baseline to 12 months in age-corrected EpiTrack total score were summarized as number of subjects and percentage

(95% CI). EpiTrack Junior was used to assess cognitive function in subjects aged ≥12 to <18 years. In adolescents, the proportion of subjects with mild impairment (scores 29-30) and significant impairment (≤28) at baseline, 6, and 12 months was summarized as number of subjects and percentage (95% CI). The proportion of subjects with clinically important improvement (gain >2 points) from baseline to 12 months and the proportion of subjects with clinically important deterioration (loss >1 point) from baseline to 12 months in age-corrected EpiTrack Junior total score were summarized as number of subjects and percentage (95% CI).

Changes in concomitant AEDs at 12 months relative to baseline were summarized: subjects with increase in dose of concomitant AED; with decrease in dose of concomitant AED; with addition of another concomitant AED; with change in the baseline concomitant AED; and with removal of baseline concomitant AED (ie, conversion to perampanel monotherapy).

Note: QOL and changes in concomitant AEDs at 12 months relative to baseline were analyzed as exploratory efficacy endpoints and ESS and EpiTrack were analyzed as exploratory safety endpoints.

Interim Analyses

An interim analysis was conducted when all subjects had entered the study and had 6-month data (ie, at approximately 18 months after study initiation). The 6-month results for retention rate, completer seizure-free rate, pragmatic seizure-free rate, and perampanel last dose were reported for POS with and without SG and for PGTCS. The purpose of this interim analysis was to obtain valuable information about perampanel outcomes and dosing, for early communication to epileptologists and general neurologists.

Sample Size Rationale

This study aimed to collect data from approximately 300 subjects. No formal sample size calculation was made, but this sample size was considered appropriate for a non-interventional, open-label study. The overall sample size was within the range of those from other Eisai observational studies of similar design (E2007-M065-412 [FAME study], N=105; E2007-G000-410, N=300; E2093-E044-404 [EPOS study], N=800). A retention rate of approximately 80% was anticipated. The size of specific subgroups allowed reporting of outcomes across these subgroups and the identification of potential predictors of retention and effectiveness.

The study aimed to include a minimum number of subjects in specific high-interest groups by selecting study sites with experience in these subject populations:

- Subjects with POS with and without SG: Approximately 200 subjects
- Subjects with PGTCS in IGE: Minimum of 50 subjects
- Subjects aged ≥12 to <18 years: Approximately 50 subjects (either seizure type)
- Subjects aged ≥65 years: Approximately 50 subjects (either seizure type)

Results

Subject Disposition/Analysis Sets

The number of enrolled subjects was 191. Of these subjects, 184 were treated with perampanel (22 subjects in the age group 12 to <18 years, 138 subjects in the age group 18 to <65 years, and 24 subjects in the age group ≥65 years. Of the 184 (100%) treated subjects, 135 (73.4%) subjects completed the study and 49 (26.6%) subjects discontinued from the study. The most common primary reason for discontinuation was AEs (22 [12.0%] subjects).

The number of subjects included in the SAS was 182, and 174 subjects were included in the FAS.

Demographic and Other Baseline Characteristics

Overall, the number (percentage) of subjects who were female was 94 (51.6%), and 88 (48.4%) subjects were male. Most subjects were white (163 [98.8%]). The median age was 36 (range: 12 to 84) years.

Overall, the median time since epilepsy diagnosis to the date of informed consent/assent was 3.0 years (range: 0 to 52 years). Most subjects had partial seizures (144 [79.1%]); of these subjects, most had partial seizures with SG seizures (98 [53.8%] subjects). Forty-three (23.6%) subjects had generalized seizures; of these subjects, most had tonic-clonic seizures (39 [21.4%]). Most subjects had no epileptic syndromes (155 [85.2%] subjects). The etiology of the disease for most subjects (89 [48.9%]) was unknown, followed by

structural brain anomalies or malformations (28 [15.4%]). Most subjects had no psychiatric disorder (144 [79.1%]).

The majority of subjects started 1 AED (113 [62.1%]) or 2 or more AEDs (68 [37.4%]) as monotherapy before baseline. Most baseline AEDs were the non-inducer type (148 [81.3%] subjects). Overall, levetiracetam was the most common non inducer AED at baseline (78 [42.9%] subjects).

Efficacy

Primary Endpoint

The overall retention rate on perampanel at 12 months was 0.742 (95% CI: 0.678 to 0.805). The retention rate on perampanel at 12 months by seizure type was 0.745 (95% CI: 0.671 to 0.818) in subjects with POS and 0.75 (95% CI: 0.609 to 0.891) in subjects with PGTCS. Kaplan-Meier analysis of the median time to discontinuation of perampanel was not estimable.

Secondary Endpoints

The overall retention rate at 6 months was 0.83 (95% CI: 0.775 to 0.884). The retention rate on perampanel at 6 months by seizure type was 0.825 (95% CI: 0.761 to 0.888) in subjects with POS and 0.861 (95% CI: 0.748 to 0.974) in subjects with PGTCS.

The overall pragmatic seizure-free rate was 0.379 (95% CI: 0.307 to 0.451) at 6 months and 0.362 (95% CI: 0.291 to 0.433) at 12 months. The pragmatic seizure-free rate at 6 months by seizure type was 0.348 (95% CI: 0.267 to 0.43) in subjects with POS, and 0.545 (95% CI: 0.376 to 0.715) in subjects with PGTCS. The pragmatic seizure-free rate at 12 months by seizure type was 0.341 (95% CI: 0.26 to 0.422) in subjects with POS, and 0.455 (95% CI: 0.285 to 0.624) in subjects with PGTCS.

The overall completer seizure-free rate was 0.440 (95% CI: 0.361 to 0.519) at 6 months and 0.467 (95% CI: 0.383 to 0.551) at 12 months. The completer seizure-free rate at 6 months by seizure type was 0.407 (95% CI: 0.316 to 0.498) in subjects with POS, and 0.600 (95% CI: 0.425 to 0.775) in subjects with PGTCS. The completer seizure-free rate at 12 months by seizure type was 0.441 (95% CI: 0.345 to 0.538) in subjects with POS, and 0.556 (95% CI: 0.368 to 0.743) in subjects with PGTCS.

The overall 50% responder rate was 0.603 (95% CI: 0.548 to 0.694) at 6 months and 0.644 (95% CI: 0.591 to 0.734) at 12 months.

The overall seizure worsening rate was 0.098 (95% CI: 0.054 to 0.142) at 6 months relative to baseline and 0.086 (95% CI: 0.045 to 0.128) at 12 months relative to baseline.

The overall median percentage change in seizure frequency per 28 days was -73.33% (95% CI: -92.86 to -51.28) at 6 months relative to baseline and -78.63% (95% CI: -100.00 to -66.34) at 12 months relative to baseline.

In the logistic regression analyses to identify predictors of retention at 12 months, no variables had a statistically significant effect on retention in the univariate analysis. In the multivariate analysis, age at diagnosis was found to influence retention with a younger age at diagnosis resulting in better retention (this variable was borderline statistically significant in the univariate analysis). In the logistic regression analyses to identify predictors of seizure freedom at 12 months, in the univariate analysis, the number of prior AEDs was found to influence seizure freedom with subjects taking 1 prior AED more likely to be seizure free than those taking 2 or more prior AEDs. In the multivariate analysis, none of the factors were found to influence seizure freedom.

Exploratory Endpoints Related to Efficacy

The mean (SD) change in QOLIE-10 total score at 6 months relative to baseline in the adult subgroup (≥18 years) was -0.02 (0.531; 95% CI: -0.68 to 0.64) in the observed cases (OC) and in the last observation carried forward (LOCF) analyses. The mean (SD) change in QOLIE-10 total score at 12 months relative to baseline in the adult subgroup was -0.82 (0.942; 95% CI: -1.99 to 0.35) in the OC analysis, and -0.54 (0.894; 95% CI: -1.29 to 0.21) in the LOCF analysis. Only a small number of subjects were included in this analysis due to the majority of subjects having missing data. No data was reported for QOLIE-AD-48 total score in the adolescent subgroup (12 to <18 years).

Most subjects (153 [86.9%] subjects) taking 1 AED at baseline were taking 1 AED at the end of the study. A shift from 1 AED at baseline to 0 AEDs at the end of study was reported in 14 (8.0%) subjects, and a shift from 1 AED at baseline to 2 AEDs at the end of the study was reported in 7 (4.0%) subjects.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Not applicable.

Safety

The mean (SD) modal dose was 5.0 (1.96) mg/day, with most subjects (98 [53.8%]) taking ≤4 mg/day, and 75 (41.2%) subjects receiving an up-titration of perampanel in line with the summary of product characteristics (SmPC).

The number of subjects exposed to perampanel was 182, with 136 (74.7%) subjects treated for a minimum of 39 weeks, and 97 (53.3%) subjects treated for a minimum of 52 weeks.

Overall, 96 (52.7%) subjects experienced at least 1 TEAE. The most common TEAEs (≥5%) were dizziness (19 [10.4%] subjects), irritability (16 [8.8%] subjects), somnolence (15 [8.2%] subjects), nasopharyngitis (13 [7.1%] subjects), and vertigo (11 [6.0%] subjects).

Overall, 11 (6.0%) subjects experienced at least 1 treatment-emergent SAE. The most common treatment-emergent SAEs were malignant neoplasm progression (2 [1.1%] subjects), seizure (2 [1.1%] subjects), and respiratory failure (2 [1.1%] subjects). Four (2.2%) subjects experienced at least 1 TEAE with an outcome of death during the study. All deaths occurred within 28 days after last dose, all were treatment emergent and none of the deaths were considered as related to study drug.

Overall, 36 (19.8%) subjects had TEAEs leading to study drug dose adjustment. The most common dose adjustment due to a TEAE was study drug withdrawal (22 [12.1%] subjects), followed by dose reduction (14 [7.7%] subjects).

Overall, 22 (12.1%) subjects experienced TEAEs leading to discontinuation of study drug. The most common TEAEs leading to discontinuation of study drug were irritability, aggression, dizziness, somnolence, seizure, and vertigo.

No changes of clinical importance in vital signs assessments (weight and mean body mass index [BMI]) over time were observed.

<u>Exploratory Endpoints Related to Safety</u>

In the adult subgroup (≥18 years), the mean (SD) changes of ESS scores were -0.6 (3.72, 95% CI: -2.5 to 1.4) in the OC and LOCF analyses at 6 months relative to baseline and -0.1 (2.87; 95% CI: -1.7 to 1.4) in the OC analysis and 0.3 (3.48; 95% CI: -1.3 to 1.9) in the LOCF analysis at 12 months relative to baseline. Shifts from normal daytime sleepiness at baseline to excessive sleepiness 12 months postbaseline in the adult subgroup were reported for 1 subject in OC analysis and for 2 subjects in LOCF analysis.

For the adolescent subgroup (≥12 to <18 years), no subjects had postbaseline data for ESS-CHAD scores.

In the adult subgroup (≥18 years), the mean (SD) change in EpiTrack age-corrected total score was -1.6 (5.50; 95% CI: -6.7 to 3.5) in the OC and LOCF analyses at 6 months relative to baseline and 0.8 (2.87; 95% CI: -3.8 to 5.3) in the OC analysis and -0.6 (4.72; 95% CI: -4.9 to 3.8) in the LOCF analysis at 12 months relative to baseline. In the adolescent subgroup (≥12 to <18 years), the mean (SD) change in EpiTrack Junior age-corrected total score was -0.8 (3.86; 95% CI: -6.9 to 5.4) in the OC and LOCF analyses at 6 months relative to baseline, and -1.3 (2.08; 95% CI: -6.5 to 3.8) in the OC analysis and -1.8 (1.89; 95% CI: -4.8 to 1.3) in the LOCF analysis at 12 months relative to baseline.

Conclusions

This study was a Phase 4 prospective, non-interventional, observational, multicenter study to investigate dosage, effectiveness, and safety of perampanel when used as first adjunctive therapy in the routine clinical care of subjects ≥12 years with a diagnosis of epilepsy (POS with or without SG or PGTCS associated with IGE).

Analyses of retention rate-related efficacy endpoints (analyzed in the SAS) showed the retention rates on perampanel at both 12 months (primary efficacy endpoint) and at 6 months (secondary efficacy endpoint). Similar retention rates were noted for subjects with POS and PGTCS at 12 months and at 6 months.

Analyses of seizure-related efficacy endpoints (analyzed in the FAS) indicated that perampanel reduced the occurrence of seizures. Similar results were noted for pragmatic seizure-free rate, completer seizure-free rate, and 50% responder rate both at 6 months and at 12 months.

Four (2.2%) subjects experienced at least 1 TEAE with an outcome of death during the study, none of which were considered as related to study drug. Among the reported treatment-emergent SAEs during the study, only one treatment-emergent SAE (mania) was considered related to study drug, which resolved without sequelae and the subject continued on treatment. No safety concerns relating to either suicidality or falls were reported. Overall, adjunctive AED monotherapy with perampanel appears effective in controlling seizures in adults and adolescents with POS with or without SG or for PGTCS associated with IGE. Perampanel is a first add-on, was generally safe and well tolerated especially when used early on. No new unexpected safety findings were observed.
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