

This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

SPONSOR is committed to disclosing publicly all medical research results that are significant to patients, health care providers or payers—whether favourable or unfavourable to the SPONSOR product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.

Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy.

Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Further redactions may be made to protect Eisai's commercially confidential information and intellectual property rights.

Anonymized patient data may be made available subject to an approved research proposal, please refer to Eisai Co., Ltd. corporate website for details on Clinical Trial Data Sharing

2 STUDY SYNOPSIS

Name of Company: Eisai Inc. and Eisai Ltd.	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: Perampanel	Volume: Page:	

<p>Study Title</p> <p>A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures</p>
<p>Investigators/Sites</p> <p>██████████ MD, ██████████ (Principal Investigator). Multicenter, 78 sites in 16 countries (Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania, Poland, Serbia, South Korea, United States; see Appendix 16.1.4 for list of investigators and sites).</p>
<p>Publication (Reference)</p> <p>None</p>
<p>Study Period</p> <p>13 Jul 2011 to 27 May 2014</p>
<p>Phase of Development</p> <p>Phase 3</p>
<p>Objectives</p> <p><u>Primary Objective:</u></p> <ul style="list-style-type: none"> To demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo, on primary generalized tonic-clonic (PGTC) seizures <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures To evaluate the efficacy of adjunctive perampanel therapy, compared to placebo, on other subtypes of primary generalized seizure (myoclonic, absence, and all seizures) <p><u>Exploratory Objectives:</u></p> <ul style="list-style-type: none"> To evaluate the pharmacokinetics (PK) of perampanel in subjects with inadequately controlled PGTC seizures To explore the efficacy of adjunctive perampanel therapy compared to placebo, on the physician-rated Clinical Global Impression of Change scale (CGI-C) and the time from the first dose date to the nth PGTC seizure event, where n = baseline seizure frequency per 28 days plus 1 To explore the relationship between plasma perampanel concentrations, efficacy, and safety using population pharmacokinetic/pharmacodynamic (PK/PD) modeling To evaluate the incremental difference in the percentage change from baseline in Overall Quality of Life

(QOL) in subjects who are “Responders” (ie, $\geq 50\%$ reduction in seizures) versus “Non-responders” [Note: Revised analysis reports descriptive statistics for each treatment arm, not Responders and Non-responders.]

- To evaluate the incremental difference in the rates of hospitalization and/or emergency room visits in subjects who are “Responders” (ie, $\geq 50\%$ reduction in seizures) versus “Non-responders” [Note: Revised analysis reports descriptive statistics for each treatment arm, not Responders and Non-responders.]

Methodology

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, adjunctive-therapy study with an open-label Extension Phase. Only the results of the Core Study are presented in this clinical study report (CSR).

The Core Study consisted of 2 phases: Prerandomization and Randomization. The Prerandomization Phase consisted of 2 periods: Screening (up to 4 weeks) and Baseline (4 or 8 weeks, depending on the accuracy of diary-documented seizures during Screening), during which subjects were assessed for eligibility to participate in the study. The Randomization Phase consisted of 3 periods: Titration (4 weeks), Maintenance (13 weeks), and Follow-up (4 weeks; only for those subjects not entering into the Extension Phase). At the start of the Randomization Phase, eligible subjects were randomized to the perampanel or placebo treatment groups in a 1:1 ratio.

During the 4-week Titration Period, subjects initially received perampanel 2 mg per day or matching placebo and were up-titrated weekly in 2-mg increments to a target dose of 8 mg per day or the highest tolerated dose. At the completion of the Titration Period, subjects entered the 13-week Maintenance Period on the last dose level achieved at the end of the Titration Period and continued taking this dose once daily for the duration of the Maintenance Period. Adjustment of the study drug dose level during the Maintenance Period was not recommended; however, according to the investigator’s clinical judgment, subjects with inadequate seizure control were allowed to have their dose increased by one 2-mg increment during the Maintenance Period and subjects who experienced intolerable adverse events (AEs) were allowed to have their dose decreased by one 2-mg increment.

Number of Subjects (Planned and Enrolled)

Planned: 164 subjects. Randomized: 164 subjects (82 perampanel, 82 placebo). Completed Core Study: 140 subjects (68 perampanel, 72 placebo).

Diagnosis and Main Criteria for Inclusion

Male and female subjects 12 years of age and older (18 years of age or older in Germany; less than 65 years of age in India) were eligible if they had a clinical diagnosis of PGTC seizures in the setting of idiopathic generalized epilepsy (with or without other subtypes of primary generalized seizures); had a routine electroencephalogram (EEG) within 5 years prior to or during the Baseline Period with features consistent with primary generalized epilepsy; had experienced ≥ 3 PGTC seizures during the 8-week period prior to randomization; and were taking fixed doses of 1 to 3 concomitant anti-epileptic drugs (AEDs) for a minimum of 30 days prior to Baseline (only 1 inducer AED was allowed; ie, carbamazepine, oxcarbazepine, or phenytoin). Before subjects could be randomized to study treatment, the Epilepsy Study Consortium confirmed the diagnosis (PGTC) and eligibility for inclusion into the study.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Perampanel was supplied as 2-mg oral tablets; batch numbers were: [REDACTED]

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Placebo oral tablets matching perampanel 2-mg oral tablets; batch numbers were: [REDACTED]

Duration of Treatment

The duration of treatment in the Core Study was 17 weeks (Randomization Phase: 4-week Titration Period and 13-week Maintenance Period).

Assessments**Efficacy**

Efficacy was assessed by seizure counts (via seizure diary) and the CGI-C.

Pharmacokinetics and Pharmacodynamics

Plasma concentrations of perampanel were determined in blood samples collected at designated timepoints. The data were subjected to population PK and PK/PD modeling for the relationship between exposure and the percent change from baseline in PGTC seizure frequency per 28 days and the occurrence and severity of the most frequently occurring AEs during the Maintenance Period; results are presented in a separate report.

Pharmacogenomics

Not applicable.

Safety

Safety was assessed by monitoring and recording all AEs, discontinuation from treatment, suicidal ideation and behavior (Columbia Suicide Severity Rating Scale [C-SSRS]), prior and concomitant medication usage, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, and changes in physical and neurological examinations. In addition, a Withdrawal Questionnaire was administered to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel.

Other

Other assessments included the Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P) and Healthcare Resource Utilization (HCRU).

Bioanalytical Methods

Plasma concentrations of perampanel were analyzed using a validated liquid chromatography with tandem mass spectrometry methodology.

Statistical Methods

The Full Analysis Set included all randomized subjects who received at least 1 dose of study drug and had any postbaseline seizure frequency data. The Safety Analysis Set included all randomized subjects who received at least 1 dose of study drug and had at least 1 postbaseline safety assessment. The Per Protocol (PP) Analysis Set, used only in the sensitivity analyses of the primary and key secondary endpoint, was a subset of subjects in the Full Analysis Set who did not have any major protocol deviations, were at least 80% compliant with the study medication during the Randomization Phase, and had diary compliance of at least 80% during the Prerandomization and Randomization Phases.

The primary efficacy endpoint was the percent change from baseline in PGTC seizure frequency per 28 days during treatment (Titration and Maintenance Periods combined), except for the purpose of European Union (EU) registration. The primary efficacy endpoint for the purpose of EU registration was the 50% responder rate (50% or greater reduction in PGTC seizure frequency during Maintenance Period relative to baseline). Percent change in seizure frequency was the key secondary efficacy endpoint for EU registration, and 50% responder rate was the key secondary efficacy endpoint for all other registrations. For the analysis of percent change in PGTC seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days across the Titration and Maintenance Periods combined were rank transformed separately. An analysis of covariance (ANCOVA) was conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline PGTC seizure frequency per 28 days as a covariate. The treatment difference was estimated using the Hodges-Lehmann estimator and associated 95% confidence interval (CI). Responder rates were analyzed using the Cochran–Mantel–Haenszel test stratified by pooled country.

The other secondary efficacy endpoints were the percent change in seizure frequency and 50% responder rate for all seizures and by primary generalized seizure subtype (absence and myoclonic). Exploratory and other efficacy endpoints were based both on variables related to seizure frequency, such as the proportion of categorized percent changes in seizure frequency over the Maintenance Period and the percentage of subjects who achieved seizure-free status (PGTC seizures and all seizures), and on more subjective measurements, such as the CGI-C.

Safety data, presented by treatment group, were summarized on an “as treated” basis using descriptive statistics

(n, mean, standard deviation [SD], median, minimum, and maximum for continuous variables; n [%] for categorical variables). Reported AEs were classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA, version 16.1), and summaries of AEs included treatment-emergent events (TEAEs), defined as those that emerged during treatment or worsened in severity during treatment. The following prespecified categories of TEAEs of special interest were summarized: suicidal ideation and behavior, abuse potential; alertness and cognition; hostility/aggression; psychosis and psychotic disorder; status epilepticus/convulsions; drug-related hepatic disorder abnormalities; cardiac and electrocardiogram (ECG) TEAEs; rash; fall; and accident/injury. Standardized MedDRA queries (SMQs) were used to identify relevant terms for most categories.

Results

Subject Disposition/Analysis Sets

Of the 307 subjects screened, 164 were randomly assigned to the placebo or perampanel treatment groups in a 1:1 ratio (82 placebo, 82 perampanel). All but 1 of the randomized subjects in the perampanel group received at least 1 dose of study drug. The percentage of randomized and treated subjects who completed the Core Study was similar for the placebo (n=72, 87.8%) and perampanel (n=68, 84.0%) groups. The most common reason for discontinuation was AEs: 9 (11.1%) subjects in the perampanel group were discontinued due to an AE compared with 5 (6.1%) subjects in the placebo group.

A total of 162 randomized and treated subjects (81 placebo, 81 perampanel) had postbaseline seizure frequency data and comprised the Full Analysis Set, the primary analysis set for efficacy. Each of the 163 randomized and treated subjects had at least 1 postbaseline safety assessment and was included in the Safety Analysis Set.

Demographic and Baseline Characteristics

The perampanel and placebo groups were comparable with respect to demographic and baseline disease characteristics. The 162 subjects who comprised the Full Analysis Set were racially diverse (53.7% White, 2.5% Black/African American, 22.2% Chinese, 19.8% Japanese and Other Asian, 1.9% Other races), and predominately between the ages of 18 and 64 years (85.8%), with 22 subjects (13.6%) <18 years of age (n=18, 11.1% <17 years of age). The majority of subjects were female (56.2%). The median time from diagnosis to randomization in the Safety Analysis Set was 14.54 years (range: 1.0 to 57.1). Overall, 33.7% of the subjects in the Safety Analysis Set were taking 1 AED, 46.0% were taking 2 AEDs, and 19.6% were taking 3 AEDs, and the frequency distribution was similar for the 2 treatment groups. A total of 27 subjects (16.6%) were taking an inducer AED (22.0% placebo, 11.1% perampanel).

Efficacy

The median percent change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to Prerandomization was greater with perampanel (-76.47%) than with placebo (-38.38%) (Full Analysis Set). The estimated median treatment difference from placebo of -30.81% was statistically significant ($P<0.0001$, based on rank ANCOVA), indicating a significant improvement in the reduction of PGTC seizure frequency for the perampanel group compared to placebo. The 50% PGTC responder rate during the Maintenance-LOCF (last observation carried forward) Period was significantly higher in the perampanel group (64.2%) than in the placebo group (39.5%) ($P=0.0019$). The findings of both primary efficacy analyses were supported by sensitivity analyses using different analysis populations and data from subsets based on demographic and baseline characteristics.

The efficacy of perampanel was additionally shown by the statistically significantly larger median percent change in the frequency of all seizures per 28 days during the Titration and Maintenance Periods observed for the perampanel group (-43.40%) compared with the placebo group (-22.87%); the estimated median treatment difference was -23.45% ($P=0.0018$). The 50% responder rate for all seizures during the Maintenance-LOCF Period was numerically, but not statistically, higher for perampanel (45.7%) compared with placebo (34.6%).

A minority of subjects in the Full Analysis Set experienced absence (37.0%) or myoclonic (29.0%) seizures during the Prerandomization Phase. The study was neither designed nor powered to detect a treatment difference from placebo in the frequency of these primary generalized seizure subtypes. Nevertheless, the median percent change in seizure frequency per 28 days during the Titration and Maintenance Periods (combined) for absence seizures was approximately 5-fold larger in the perampanel group compared with the

placebo group (-41.18% vs -7.58%), and the 50% responder rate for absence seizures during the Maintenance-LOCF Period was also higher for the perampanel group (48.1%) than for the placebo group (39.4%). There was a notable imbalance in the frequency of myoclonic seizures during the Prerandomization Phase, with the median baseline frequency approximately 4-fold lower in the placebo group compared with the perampanel group (3.50 vs 13.75, respectively). As a result, treatment differences in the frequency of this seizure subtype are difficult to interpret.

The median time to *n*th +1 PGTC seizure event was 43.0 days in the placebo group, but was not estimable for the perampanel group since fewer than 50% of subjects in this group had a PGTC seizure event. The *P* value for the difference from placebo ($P < 0.0001$), as assessed by a log-rank test, indicated that this difference was statistically significant. Nearly one-third of subjects in the perampanel group (30.9%) were free of all PGTC seizures during the Maintenance Period, and 23.5% were free of all seizures. These percentages were considerably higher than the percentages that were free of PGTC or all seizures for the placebo group (12.3% and 4.9%, respectively).

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Results from the population PK and PK/PD analyses are provided in a separate report (CPMS-E2007-008R-v1).

Safety

The median treatment duration was 17.0 weeks in the placebo and perampanel groups. The last daily dose of perampanel received was 8 mg for most subjects (84.0%), and no subject in the perampanel group received a last daily dose of 2 mg.

Treatment-emergent AEs occurred in 59 subjects (72.0%) in the placebo group and 67 subjects (82.7%) in the perampanel group. The most frequently ($\geq 10\%$) reported TEAEs in the perampanel group were dizziness (6.1% placebo, 32.1% perampanel), fatigue (6.1% and 14.8%, respectively), headache (9.8% and 12.3%, respectively), somnolence (3.7% and 11.1%, respectively), and irritability (2.4% and 11.1%, respectively); each of these except headache was reported at a ≥ 2 -fold higher rate than in the placebo group. No TEAE was reported by $\geq 10\%$ of subjects in the placebo group.

Across the Core Study, there was a single death in the perampanel group (accidental drowning, considered not related to study treatment). There was a likely case of sudden unexplained death in epilepsy (SUDEP) in the placebo group. Treatment-emergent serious adverse events (SAEs) occurred in a similar, small number of subjects in the perampanel ($n=6$, 7.4%) and placebo ($n=7$, 8.5%) groups, and all non-fatal SAEs resolved without sequelae in the perampanel group. The rates of TEAEs leading to discontinuation and the rates of TEAEs requiring study drug interruption or dose reduction were higher for perampanel than for placebo. The majority of SAEs and other significant events were transient and manageable (ie, the subjects recovered without sequelae).

During the 17 weeks of double-blind treatment in the Core Study, TEAEs that resulted in discontinuation of study drug occurred in 11.1% of subjects in the perampanel group and 6.1% of subjects in the placebo group. Dizziness and vomiting were the only individual TEAEs that led to the discontinuation of more than 1 subject in the perampanel group ($n=2$ each).

A total of 11.1% of subjects in the perampanel group and 7.3% of subjects in the placebo group had a TEAE resulting in dose adjustment or interruption. This higher rate in the perampanel group was primarily attributable to nervous system disorder TEAEs (mainly dizziness and somnolence) and irritability. For 6 of the 9 subjects in the perampanel group, the TEAE leading to dose adjustment or interruption occurred at a dose of 8 mg.

The following TEAEs of special interest were reported more frequently in the perampanel group than the placebo group: those related to alertness or cognition (14.6% placebo, 19.8% perampanel); TEAEs related to hostility/aggression (narrow + broad SMQ terms: 4.9% placebo, 18.5% perampanel [narrow SMQ terms only: 0% placebo, 2.5% perampanel]); TEAEs related to psychosis and psychotic disorders (narrow + broad SMQ terms 3.7% placebo, 7.4% perampanel [narrow SMQ terms only: 3.7% placebo, 3.7% perampanel]); and rash (1.2% placebo, 6.2% perampanel). The majority of these events were transient and manageable (ie, the subjects recovered without sequelae).

The incidence of TEAEs related to suicidal ideation or behavior was small and similar for the placebo ($n=3$,

3.7%) and perampanel (n=2, 2.5%) groups, and the overall occurrence of suicidality (suicidal ideation and behavior) reports, as assessed by the C-SSRS, was lower for the perampanel group (3.7%) than for the placebo group (6.1%). Similar, low rates of TEAEs were also noted in the following categories of special interest: status epilepticus and convulsions (4.9% placebo, 3.7% perampanel), cardiac and ECG TEAEs (2.4% placebo, 2.5% perampanel), drug-related hepatic disorder (1.2% placebo, 2.5% perampanel), and falls (1.2% placebo, 2.5% perampanel). There were no reports of abuse, misuse, or overdose with perampanel.

There were no clinically important mean changes in laboratory values during the study and no shifts of clinical concern, other than potentially for triglycerides. The percentage of subjects with at least 1 postbaseline triglyceride value above 50 or 100 mg/dL was higher in the perampanel group than in the placebo group among adult subjects (≥ 17 years); no such pattern was seen among the 18 adolescent subjects. The incidence of markedly abnormal laboratory values was low and generally comparable in the 2 treatment groups. One subject in the perampanel group had a treatment-emergent markedly abnormal elevation in triglycerides and the baseline value for this subject was above the normal range.

No subject in either treatment group had a markedly abnormal value for blood pressure or pulse rate, and there were no TEAEs of orthostatic hypotension during the Core Study.

There were small effects of perampanel, relative to placebo, on body weight. At the end of treatment in the Core Study, there was a mean increase in body weight in the perampanel group (+1.8 kg) compared with no change in the placebo group (0.1 kg). Overall, 11.1% of subjects in the perampanel group had a body weight gain of $\geq 7\%$ at the end of treatment compared with 3.7% of subjects in the placebo group. Weight increased was reported as a TEAE in 7.4% of perampanel-treated subjects (compared with 3.7% of placebo subjects), but no subject was discontinued for a TEAE of weight increased.

Among the subjects who completed the Withdrawal Questionnaire at the end of treatment (n=74 placebo; n=73 perampanel), most in both treatment groups ($>85\%$) rated each symptom “none” or “mild” at baseline and the end of treatment.

Other

The change in the Total QOLIE-31-P score (which is composed of the following domains: Energy, Mood, Daily Activities, Cognition, Medication Effects, Seizure Worry, Distress, and Overall QOL) at Week 17/End of Treatment was numerically higher for the perampanel group (median actual and percent changes of 3.3 and 4.79%) than for placebo subjects (median actual and percent changes of -1.2 and -1.36%). Of the individual subscale QOLIE-31-P scores, the change in Daily Activities and Distress scores at Week 17/End of Treatment were also numerically higher in the perampanel group for Daily Activities (median and actual percent changes: 5.0 and 26.58%, perampanel; 0.0 and 0.00%, placebo), Distress (3.6 and 5.88%, perampanel; 0.0 and 0.00%, placebo), and Cognition (4.2 and 32.79%, perampanel; 3.1 and 5.83%, placebo).

With regard to HCRU visits, the percentage of subjects requiring a visit to the emergency room during the Core Study was approximately 5-fold less for the perampanel group (2.5%) compared with the placebo group (12.2%). The percentage subjects requiring at least one unplanned provider visit or at least 1 hospitalization following an emergency room visit were similar between the perampanel and placebo groups.

Conclusions

Adjunctive treatment with perampanel daily doses 8 mg, achieved by weekly up-titration of 2 mg/day, was effective in improving seizure control in subjects 12 years and older with inadequately-controlled PGTC seizures. Perampanel administration at a dose of 8 mg/day for 17 weeks to this population was safe and well-tolerated, and the safety profile was similar to that in a population with refractory partial onset seizures. In conclusion, perampanel, given as adjunctive therapy, demonstrates a favorable risk/benefit ratio in an adolescent and adult population with inadequately-controlled PGTC seizures.

Date of Report

18 Jul 2014