2 STUDY SYNOPSIS

Name of Company: Eisai Co., 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:	

Study Title

An Open-label Extension Study to Evaluate the Safety and Tolerability of Perampanel (E2007) Administered as an Adjunctive Therapy in Epilepsy Subjects

Investigators/Sites

Hitoshi Sejima, MD, PhD, et al. Multicenter: 8 sites in Japan (refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None.

Study Period

12 May 2015 to 21 Sep 2016

This study was continued until perampanel was commercially available in Japan with respect to the indication or formulation of the designated study (Study E2007-G000-332 [hereafter referred to as Study 332]).

Phase of Development

Phase 3 (Note: As per regulatory requirements, at the time that perampanel's indication or formulation of the designated study [Study 332] was approved by the regulatory authority, the study became a post-marketing study in Japan)

Objective(s)

To evaluate the safety and tolerability of perampanel given as an adjunctive therapy in subjects with epilepsy subjects.

Methodology

This study consisted of 2 phases:

- Screening – The subject started the study once the Screening assessments were completed and the subject was qualified for participation.
- Treatment – Safety assessments were conducted by the investigator.

Only subjects who were participating in the designated perampanel study as below and who in the opinion of the investigator continued to benefit from treatment with perampanel were eligible for this study. Subjects entered this study on the same dose of perampanel that they were receiving at the end of their participation in the designated perampanel study as below.

Doses of perampanel and concomitant antiepileptic drugs (AEDs) were allowed to be adjusted based on clinical judgment. A minimum perampanel dose of 2 mg per day was required to continue in the study. The maximum daily dose of perampanel permitted was 12 mg per day.

Designated perampanel study: Study 332 (with at least 52 weeks of total exposure to perampanel)

The visit intervals in this study were every 26 weeks.

End of study visit was required to be conducted within 3 months from the launch of perampanel in Japan.

For the subjects who did not switch to commercially available perampanel within 3 months after the launch of perampanel in Japan, Discontinuation Visit was conducted.

Subjects who did not tolerate the minimum dose of 2 mg per day during the study were discontinued from the study.

The investigator was allowed to discontinue the subject from the study at any time for safety or administrative reasons. When the investigator discontinued the study, Discontinuation Visit was conducted.

A Follow-up visit was conducted 4 weeks after Discontinuation Visit in the discontinued subject. Follow-up visit was not required once the investigational drug was switched to commercial product.

Number of Subjects (Planned and Enrolled)

Planned: This study was open only to subjects who were participating in the designated perampanel study. Enrolled (ie, signed informed consent): 7 subjects. Treated: 7 subjects.

Diagnosis and Main Criteria for Inclusion

Indication: Epilepsy

Main Criteria for Inclusion: Subjects participating in the designated perampanel study as below and who in the opinion of the investigator continued to benefit from treatment with perampanel were eligible for this study.
Designated perampanel study: Study 332 (with at least 52 weeks of total exposure to perampanel)

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

Test treatment: Perampanel was available in 2 mg tablets.

Dose and mod of administration: Subjects started this study with the dose that they were receiving at the end of their participation in the previously participated designated perampanel study. Doses of perampanel were allowed to be adjusted based on clinical judgment. A minimum perampanel dose of 2 mg per day was required to continue in the study. The maximum daily dose of perampanel permitted was 12 mg per day.

Lot numbers: P34001ZZ

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

Not applicable.

Duration of Treatment

Treatment was continued as long as clinically appropriate according to the judgment of the

investigator. However, treatment of subjects was completed when perampanel became commercially available in Japan.

Assessments

Efficacy

Not applicable.

Safety

Safety was assessed by monitoring of adverse events (AEs), withdrawal from treatment, clinical laboratory tests (chemistry), vital signs and weight.

Other

Concomitant medication usage.

Statistical Methods

Analysis Sets

Safety Analysis Set included all subjects who signed informed consent, were eligible for this study, received at least 1 dose of study medication, and have at least 1 postdose safety assessment in this study.

Interim Analyses

Not applicable.

Efficacy Analyses

Not applicable.

Safety Analyses

All AEs, laboratory parameter, vital signs, and weight were presented in subject data listings.

The AE verbatim descriptions (investigator terms from the CRF) were classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were coded to the MedDRA (Version 19.0) lower level term (LLT) closest to the verbatim term. The number (percentage) of subjects with treatment-emergent AEs (TEAEs) was summarized by system organ class (SOC) and preferred term (PT). Summary statistics were presented for laboratory test values, vital signs, and weight.

Other Analyses

Concomitant AEDs were listed.

The number (percentage) of subjects who took concomitant AEDs at baseline (ie, at the beginning of the Screening Phase of this study was summarized by the AED type (ie, inducer AED, non-inducer AED) and World Health Organization Drug Dictionary (WHO DD) preferred term.

Sample Size Rationale

The study was open to all subjects participating in the designated perampanel study as below.
Designated perampanel study: Study 332

Results

Subject Disposition/Analysis Sets

A total of 7 subjects who had participated in the designated perampanel study (Study 332) provided informed consent and were enrolled in Study E2007-J000-341 (hereafter referred to as Study 341). All 7 subjects received at least 1 dose of perampanel and were included in the Safety Analysis Set.

Table 1 summarizes subject disposition and primary reason for discontinuation from study for enrolled subjects. Of the 7 subjects treated with perampanel, 1 subject discontinued from the study, and the remaining 6 subjects completed the study. The primary reason for discontinuation from study reported in the subject was subject choice.

Table 1 Subject Disposition and Primary Reason for Discontinuation From Study – Enrolled Subjects

	Perampanel
Enrolled, n	7
Not treated, n	0
Treated, n (%)	7 (100.0)
Completed, n (%)	6 (85.7)
Discontinued, n (%)	1 (14.3)
Primary reason for discontinuation[a, b], n (%)	
Adverse event	0
Lost to follow-up	0
Pregnancy	0
Subject choice	1 (14.3)
Inadequate therapeutic effect	0
Withdrawal of consent	0
Other	0

Enrolled subjects refer to subjects who signed informed consent forms.
Percentages are based on the number of subjects treated in Study 341.
CRF = case report form.
a: As reported on the Subject Disposition CRF.
b: Only one primary reason is recorded.
Source: Table 14.1.1

Demographic and Other Baseline Information

Demographic and Other Baseline Characteristics

The demographic characteristics and epilepsy-specific history at entry into the Study 332 are summarized for subjects in the Safety Analysis Set in Table 2 and Table 3, respectively. The mean ±SD age was 35.3±19.20 years. Of the 7 subjects, 4 subjects (57.1%) were male, and 3 subjects (42.9%) were female. The median time since onset of epilepsy was 6.6 years (range: 3 to 57 years). All 7 subjects were Japanese with tonic-clonic seizures.

Table 2 Demographic and Baseline Characteristics – Safety Analysis Set

Category	Perampanel (N=7)
Age (year)[a]	
n	7
Mean (SD)	35.3 (19.20)
Median	34.0
Min, Max	16, 73
Age group, n (%)	
<18	1 (14.3)
18 to <65	5 (71.4)
≥65	1 (14.3)
Sex, n (%)	
Male	4 (57.1)
Female	3 (42.9)
Race, n (%)	
Japanese	7 (100.0)
Weight (kg)[b]	
n	7
Mean (SD)	59.53 (12.075)
Median	57.50
Min, Max	40.5, 79.2
Height (cm)[b]	
n	7
Mean (SD)	158.43 (4.404)
Median	156.50
Min, Max	154.3, 165.9
BMI (kg/m^2)	
n	7
Mean (SD)	23.84 (5.585)
Median	21.91
Min, Max	16.5, 33.3

BMI = body mass index, Max = maximum, Min = minimum.
a: Age is calculated at date of informed consent.
b: For weight, height, and BMI, the baseline values were defined as the data measured in the baseline of Study 332.
Source: Table 14.1.2

Table 3 Epilepsy-Specific Past Medical History – Safety Analysis Set

Category	Perampanel (N=7)
Time since onset of epilepsy (year)	
n	7
Mean (SD)	16.9 (20.11)
Median	6.6
Min, Max	3, 57
Seizure type[a], n (%)	
Tonic-clonic	7 (100.0)
Myoclonic	5 (71.4)
Absence	5 (71.4)
Clonic	0
Tonic	0
Atonic	0

Epilepsy specific past medical history was defined as the data measured in the baseline of Study 332.
Max = maximum, Min = minimum.
a: Multiple seizure types were allowed to be recorded.
Source: Table 14.1.3

Concomitant Medication

The use of specific AEDs at baseline of Study 341 is summarized for the Safety Analysis Set in Table 4. All 7 subjects were taking non-inducer AEDs, while none was taking inducer AEDs. The most common AEDs taken were valproic acid (71.4%).

Table 4 Antiepileptic Drugs at Baseline – Safety Analysis Set

Type of AED AED	Perampanel (N=7)
Inducer AEDs[a], n (%)	0
Non-Inducer AEDs, n (%)	7 (100.0)
Clobazam	2 (28.6)
Clonazepam	2 (28.6)
Lamotrigine	3 (42.9)
Levetiracetam	3 (42.9)
Phenobarbital	1 (14.3)
Topiramate	1 (14.3)
Valproic acid	5 (71.4)
Zonisamide	1 (14.3)

Baseline is at the beginning of the Screening Phase of Study 341.
AED = antiepileptic drug.
a: Inducer AEDs include carbamazepine, oxcarbazepine, and phenytoin. All other AEDs are non-inducer AEDs.
Source: Table 14.1.4

Efficacy

Not applicable.

Safety

Extent of Exposure

The cumulative extent of exposure to perampanel is summarized for the Safety Analysis Set in Table 5. The mean ±SD cumulative duration of exposure to perampanel was 52.73±7.801 weeks for the Safety Analysis Set.

The mean ±SD average daily dose of perampanel during the study was 8.00±2.828 mg for the Safety Analysis Set (Table 14.3.1.1.2).

The mean ±SD modal dose of perampanel during the study was 8.0±2.83 mg for the Safety Analysis Set (Table 14.3.1.1.3). Note that each subject received the same doses during the study although doses of perampanel were allowed to be adjusted based on clinical judgment. The distribution of the dose received by subjects was 6 mg (4 subjects; 57.1%), 8 mg (1 subject; 14.3%), and 12 mg (2 subjects; 28.6%) (Listing 16.2.5.1).

Table 5 Cumulative Extent of Exposure to Study Drug – Safety Analysis Set

Extent of Exposure	Perampanel (N=7)
Any exposure, n (%)	7 (100.0)
>1 week	7 (100.0)
>13 weeks	7 (100.0)
>26 weeks	7 (100.0)
>39 weeks	7 (100.0)
>52 weeks	3 (42.9)
>65 weeks	0
Duration of exposure[a] (weeks)	
n	7
Mean (SD)	52.73 (7.801)
Median	51.29
Min, Max	43.0, 63.0

Max = maximum, Min = minimum.
a: Duration of exposure is calculated as (Last Dose Date – First Dose Date +1) / 7. This duration is based on Study 341.
Source: Table 14.3.1.1.1

Adverse Events

Overview of Adverse Events

Table 6 presents an overview of TEAEs for the Safety Analysis Set. TEAEs included those AEs for subjects that entered Study 341 that occurred from the first dose of study drug to the last visit of the study or on or after 30 days since the last dose of study drug, whichever comes later, or that were present at pretreatment (baseline of Study 341) but worsened in severity during the study.

Table 6 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Category	Perampanel (N=7) n (%)
TEAEs	6 (85.7)
Treatment-related TEAEs[a]	0
Severe TEAEs	0
Serious TEAEs	0
Deaths[b]	0
Other SAEs[c]	0
TEAEs leading to study drug dose adjustment	0
TEAEs leading to study / study drug withdrawal	0
TEAEs leading to study drug dose reduction	0
TEAEs leading to study drug dose interruption	0

Percentages are based on the total number of subjects.
For each row category, a subject with 2 or more adverse events in that category is counted only once.
SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Includes TEAEs considered by the investigator to be related to study drug or TEAEs with missing causality.
b: Includes all subjects with SAE resulting in death.
c: If a subject had both fatal and nonfatal SAEs, the subject is counted in the previous row and is also counted in this row.
Source: Table 14.3.1.2.1

Common Adverse Events

At least 1 TEAE occurred in 6 subjects (85.7%) in the Safety Analysis Set during the study. Table 7 presents all TEAEs reported during the study by MedDRA SOC and PT for the Safety Analysis Set. The most frequently reported TEAEs were nasopharyngitis (3 subjects; 42.9%). No treatment-related TEAEs were reported during the study (Table 6).

A subject listing of all AEs, treatment-emergent or otherwise, is provided in Listing 16.2.7.

Table 7 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Perampanel (N=7) n (%)
Subjects with any TEAE	6 (85.7)
Infections and infestations	3 (42.9)
Nasopharyngitis	3 (42.9)
Influenza	1 (14.3)
Injury, poisoning and procedural complications	3 (42.9)
Fall	1 (14.3)
Head injury	1 (14.3)
Humerus fracture	1 (14.3)
Metabolism and nutrition disorders	1 (14.3)
Diabetes mellitus	1 (14.3)
Hypercholesterolaemia	1 (14.3)
Hyperuricaemia	1 (14.3)

MedDRA Version 19.0
Percentages are based on the total number of subjects.
A subject with 2 or more adverse events in the same SOC (or with the same PT) is counted only once for that SOC (or PT).
MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.2.2

Analysis of Adverse Events

A summary of TEAEs by MedDRA SOC, PT, and maximum severity is provided in Table 14.3.1.2.4. All of the TEAEs were considered mild or moderate by the investigator. Only 1 moderate TEAE (fall) occurred in 1 subject during the study.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred, and no serious adverse events (SAEs) or TEAEs leading to discontinuation of study drug were reported during the study (Table 6).

Laboratory Results

Laboratory Parameters Over Time

There were no clinically important mean and median changes in clinical chemistry laboratory values over time for the Safety Analysis Set. Summary statistics for all clinical chemistry laboratory parameters during the study are provided in Table 14.3.4.1. Box plots of all clinical chemistry laboratory parameters are provided Figure 14.3.4.1.

Markedly Abnormal Laboratory Values

There were no markedly abnormal clinical chemistry laboratory values during the study

(Table 14.3.4.2). A markedly abnormal clinical chemistry laboratory value was defined as a laboratory result that worsened in severity to meet modified National Cancer Institute (NCI) toxicity criteria of Grade 2 or higher on treatment.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs and Weight

There were no clinically important mean and median changes in vital signs and weight over time for the Safety Analysis Set. Summary statistics for all vital signs and weight values during the study are provided in Table 14.3.5.1. Box plots of all vital signs and weight values are provided in Figure 14.3.5.1.

There were no clinically notable vital signs during the study (Table 14.3.5.2). Clinically notable reductions in body weight occurred in 1 subject (14.3%), while clinically notable elevations in body weight occurred in 3 subjects (42.9%) during the study (Table 14.3.5.2); however, there were no TEAEs of weight increased or weight decreased in the Safety Analysis Set. The criteria for clinically notable vital signs and weight are presented in Table 8.

Table 8 Criteria for Clinically Notable Vital Signs and Weight

Variable	Criterion Value	Change Relative to Baseline
Systolic Blood Pressure	>180 mmHg	Increase of ≥20 mmHg
	<90 mmHg	Decrease of ≥20 mmHg
Diastolic Blood Pressure	>105 mmHg	Increase of ≥15 mmHg
	<50 mmHg	Decrease of ≥15 mmHg
Pulse Rate	>120 bpm	Increase of ≥15 bpm
	<50 bpm	Decrease of ≥15 bpm
Weight	–	Increase of >7% from baseline
		Decrease of >7% from baseline

Clinically notable means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline of Study 341.
bpm = beat per minute.

Conclusions

Adjunctive treatment with perampanel daily doses up to 12 mg was safe and well tolerated among subjects with epilepsy. The exposure to perampanel in this study did not reveal unknown or unexpected safety risks.

Date of Report

21 Feb 2017