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Eisai Co., Ltd.

EISAI PRESENTS RESULTS FROM PHASE III TRIAL OF ANTIEPILEPTIC DRUG PERAMPANEL AS ADJUNCTIVE THERAPY FOR REFRACTORY PARTIAL-ONSET SEIZURES CONDUCTED IN ASIA INCLUDING JAPAN

ORAL PRESENTATION GIVEN AT 49TH CONGRESS OF THE JAPAN EPILEPSY SOCIETY

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that an oral presentation highlighting results from a Phase III clinical study (Study 335) of its in-house developed antiepileptic drug (AED) perampanel hydrate (global product name: Fycompa®) in patients with refractory partial-onset seizures conducted in Asia, including Japan, was given at the 49th Congress of the Japan Epilepsy Society held from October 30 to 31 in Nagasaki, Japan. In the study, perampanel demonstrated a significantly higher reduction in seizure frequency compared to placebo.

In Japan, new drug applications were submitted in July 2015 seeking the approval of perampanel as an adjunctive therapy for partial-onset and generalized tonic-clonic seizures based on the results of Study 335 and other studies.

Study 335 was a Phase III clinical study conducted in Asia, including Japan, to evaluate the efficacy and safety of adjunctive perampanel therapy in 710 patients aged 12 years and older with refractory partial-onset seizures. In this study, eligible patients receiving one to a maximum of three AEDs were randomized to receive perampanel (4 mg, 8 mg or 12 mg) or placebo.
In the study's primary endpoint of percent change in seizure frequency (per 28 days in the randomization phase relative to the pre-randomization phase), the percent change in the placebo group was -10.8% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was -17.3%, -29.0% and -38.0%, respectively. The difference between perampanel and placebo was statistically significant for the perampanel 8 and 12 mg groups ($p=0.0003$ for 8 mg, $p<0.0001$ for 12 mg).
Furthermore, in the study's secondary endpoint of percent change in seizure frequency of secondarily generalized seizures, the percent change in the placebo group was -12.1% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was -17.9%, -45.0% and -52.5%, respectively, demonstrating that perampanel, depending on dosage, reduces seizure frequency in secondarily generalized seizures as well, especially the 12 mg group which showed over a 50% reduction in seizure frequency.
The most common adverse events (>10% in the perampanel groups) observed in the study were dizziness, somnolence and nasopharyngitis.

Meanwhile, the results of an Asia-Pacific (Japan, China, South Korea, India, Australia) regional sub-group analysis of Study 332,[1] a global study of primary generalized tonic-clonic (PGTC) seizures in patients with generalized epilepsy, were also presented at this same congress meeting. Study 332 was a Phase III clinical study to evaluate the efficacy and safety of adjunctive perampanel as treatment for with PGTC seizures in 164 patients aged 12 years or older. A statistically significant improvement in the primary endpoint of change in PGTC seizure frequency, as well as the secondary endpoint of responder rate (percentage of patients who experience a 50% or greater reduction in PGTC seizure frequency per 28

days in the Maintenance period relative to baseline) was observed for perampanel compared to placebo. The results of the analysis showed that both change in PGTC seizure frequency and responder rate for Asia-Pacific region patients (42 patients) were similar to the total patient population results already presented, and there were no large regional differences in the incidence of adverse events.

Perampanel is a first-in-class AED discovered and developed by Eisai. With epileptic seizures being primarily mediated by the neurotransmitter glutamate, the agent is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors. Perampanel is approved in more than 45 countries including in Europe and North America, as well as countries in Asia such as Malaysia, Thailand, the Philippines and South Korea, as an adjunctive treatment for partial-onset seizures (with or without secondary generalized seizures) in patients with epilepsy aged 12 years and older, and has been launched in 25 countries around the world under the Fycompa brand name. Furthermore, perampanel was approved for an indication expansion regarding the adjunctive therapy of PGTC seizures in patients from 12 years of age with generalized epilepsy in the U.S. and Europe in June 2015.

Eisai considers epilepsy a therapeutic area of focus and by providing multiple treatment options in addition to perampanel as part of an extensive epilepsy product portfolio, Eisai seeks to make continued contributions to address the diverse needs of, as well as increasing the benefits provided to, patients with epilepsy and their families.

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[Notes to editors]

1. About perampanel hydrate (generic name, “perampanel”, global product name: Fycompa)

Perampanel is a first-in-class antiepileptic drug (AED) discovered and developed by Eisai. With epileptic seizures being primarily mediated by the neurotransmitter glutamate, the agent is a highly selective, noncompetitive AMPA receptor antagonist that reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors.

The agent is currently approved in more than 45 countries and territories, including Europe and the United States, as an adjunctive treatment (available as a once-daily oral dose) of partial-onset seizures (with or without secondarily generalized seizures) in adult and adolescent patients from 12 years of age with epilepsy, and has been launched in over 25 countries.

In June 2015, perampanel was approved in the United States and Europe for an additional indication of the adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures in adult and adolescent patients from 12 years of age with generalized epilepsy.

In July 2015, Eisai submitted a regulatory application for perampanel in Japan covering both PGTC seizures and partial-onset seizures based primarily on Study 332 and Study 335.

Meanwhile, Eisai has submitted applications for the approval of an additional oral suspension formulation of perampanel in Europe and the United States in June 2015, and is conducting Phase II studies in Europe and the United States for partial-onset epilepsy in pediatric patients.

2. About Study 335

Study title:	A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Perampanel Administered as an Adjunctive Therapy in Subjects with Refractory Partial-onset Seizures
Study population:	710 patients aged 12 years and older with partial-onset seizures receiving one to a maximum of three anti-epileptic drugs
Treatment administered:	Perampanel oral tablets, 4 mg/day, 8 mg/day or 12 mg/day, or placebo, once daily.
Duration of treatment:	Prerandomization Phase: 6 weeks; Randomization Phase: 19 weeks (Titration Period, 6 weeks; Maintenance Period, 13 weeks) Extension Phase: over 10 weeks
Study locations:	Japan, China, South Korea, Australia, Thailand, Malaysia, Taiwan
Primary endpoint:	Percent change in seizure frequency (per 28 days in the randomization phase relative to the pre-randomization phase)
Results:	-The percent change in seizure frequency in the placebo group was -10.8% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was -17.3%, -29.0% and -38.0 %, respectively. The difference between perampanel and placebo was statistically significant for the perampanel 8 and 12 mg groups (p=0.0003 for 8 mg, p<0.0001 for 12 mg). -As the study's secondary endpoint, the responder rate (percentage of patients who had at least a 50% reduction in seizure frequency in the Maintenance Period of the Randomization phase relative to the Prerandomization Phase) in the placebo group was 19.4% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was 23.0%, 36.0% and 43.3%, respectively, and the difference between perampanel and placebo was statistically significant in the perampanel 8 mg and 12 mg groups (p=0.0005 for 8 mg, p<0.0001 for 12 mg). -As another of the study's secondary endpoints, the percent change in seizure frequency of secondarily generalized seizures in the placebo group was -12.1% while in the perampanel (4 mg, 8 mg, 12 mg) groups it was -17.9%, -45.0% and -52.5%, respectively.
Adverse events:	The most common adverse events (>10% in the perampanel arms) were dizziness, somnolence and nasopharyngitis.

3. About Study 332[1]

Study title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Adjunctive Perampanel in PGTC Seizures
Study population:	164 patients aged 12 years and older with PGTC seizures receiving one to a maximum of three anti-epileptic drugs
Treatment administered:	(Placebo-controlled) Perampanel oral tablets, once daily, up to 8 mg/day (Titration Period), randomized dose 8 mg/day (Maintenance Period).
Duration of treatment:	Prerandomization Phase (Screening and Baseline Periods): up to 12 weeks Randomization Phase (treatment): 17 weeks (Titration Period, 4 weeks; Maintenance Period, 13 weeks) Extension Phase: over 38 weeks
Study locations:	U.S., Europe, Japan, Asia

Primary endpoint:	Percent change in PGTC seizure frequency (percent change from baseline in PGTC seizure frequency per 28 days during treatment)
Results:	-The percent change in PGTC seizure frequency observed for the perampanel group was -76.5%, which was statistically significant when compared to -38.4% for the placebo group ($p<0.0001$). -The responder rate (percentage of patients who experience a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance period relative to baseline) for the perampanel group was 64.2%, which was a statistically significant improvement over the responder rate for the placebo group of 39.5% ($p=0.0019$). -For patients who had been unable to adequately control PGTC seizures with existing AEDs, 30.9% of patients treated with perampanel were free of PGTC seizures (12.3% for placebo) during the 13 week Maintenance period.
Adverse events:	The most common adverse events (>10% in the perampanel group and greater than placebo) for perampanel and placebo were, respectively, dizziness, fatigue, headache, somnolence and irritability.
Sub-group analysis results:	-In the Asia-Pacific sub-group (42 patients), the percent change in PGTC seizure frequency was -66.8% for the perampanel group and -38.4% for the placebo group, while the responder rate was 59.5% for the perampanel group and 40.5% for the placebo group, which was consistent with the overall results. No large regional differences in the incidence of adverse events were observed.

4. About Primary Generalized Tonic-Clonic (PGTC) Seizures

Epilepsy affects nearly 1 million people in Japan, 2.9 million people in the United States, 6 million people in Europe, and more than 60 million people worldwide. As approximately 30% of patients with epilepsy are unable to sufficiently control their seizures with currently available AEDs,[2] this is a disease with significant unmet medical needs.

Epilepsy is broadly categorized by seizure type, with partial-onset seizures accounting for approximately 60% of epilepsy cases and generalized seizures accounting for approximately 40%. In a partial-onset seizure, an abnormal electrical disturbance occurs in a limited area of the brain, and sometimes may subsequently spread throughout the brain, becoming a generalized seizure (known as a secondarily generalized seizure). In a generalized seizure, abnormal electrical disturbances occur throughout the brain, and can be followed by a loss of consciousness or physical symptoms manifested throughout the whole body.

PGTC seizures are one of the most common and most severe forms of generalized seizures, accounting for approximately 60% of generalized epilepsy and approximately 20% of all epilepsy cases.[3]

[1] French JA, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. *Neurology* 2015; 85, 950–957

[2] "The Epilepsies and Seizures: Hope Through Research. What are the epilepsies?" National Institute of Neurological Disorders and Stroke, accessed June 19, 2015, http://www.ninds.nih.gov/disorders/epilepsy/detail_epilepsy.htm#230253109

[3] Hauser WA, et al. *Epilepsia*, 34(3):453-468,1993