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Long-term tolerability, safety and efficacy of adjunctive perampanel in the open-label, dose-ascending Study 231 and extension Study 233 in Japanese patients with epilepsy

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ABSTRACT

Purpose: To evaluate long-term tolerability, safety and efficacy of adjunctive perampanel in a Phase II, multicentre, open-label, dose-ascending Study 231 (NCT00849212) and its extension (Study 233; NCT00903786) in Japanese patients with refractory partial-onset seizures (POS), with/without secondarily generalised seizures.
Methods: In Study 231, patients received adjunctive perampanel ≤12 mg/day during a 10-week treatment period. Patients completing Study 231 could enter Study 233 (≤316-week treatment period). Assessments included monitoring of treatment-related treatment-emergent adverse events (TEAEs), median percent change in seizure frequency per 28 days, 50% responder and seizure-freedom rates. During Study 231, a pharmacokinetic analysis assessed the effects of enzyme-inducing antiepileptic drugs.
Results: Overall, 23/30 (76.7%) patients completed Study 231; 21/30 (70.0%) received perampanel ≥8 mg/day and 10/30 (33.3%) achieved a maximum tolerated dose of 12 mg/day. Median percent change in seizure frequency per 28 days was –35.0%. 50% responder rate was 37.0%; 4 (13.3%) patients achieved seizure freedom. Twenty-one patients entered Study 233. Mean duration of exposure was 195 weeks; 9 (42.9%) patients received perampanel for ≤208 weeks. Seizure control was sustained for 316 weeks in 3/21 (14.3%) patients; 2 achieved seizure freedom. Treatment-related TEAEs were tolerable; the most common was dizziness (Study 231, 53.3%; Study 233, 14.3%). Mean perampanel plasma concentrations were lower with concomitant carbamazepine vs non-inducers (152.7 ng/mL vs 389.4 ng/mL across perampanel groups); small patient numbers for non-inducers (n = 2) should be considered when interpreting these data.
Conclusion: Adjunctive perampanel demonstrated a favourable safety profile and long-term tolerability in Japanese patients with refractory POS for ≤316 weeks.

Abbreviations: AE, adverse event; AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBZ, carbamazepine; CYP, cytochrome P450; EIAED, enzyme-inducing antiepileptic drug; LOCF, last observation carried forward; OC, observed case; PB, phenobarbital; PGTC, primary generalised tonic-clonic; PHT, phenytoin; PK, pharmacokinetics; POS, partial-onset seizure; SD, standard deviation; SG, secondarily generalised; TEAE, treatment-emergent adverse event

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1. Introduction

Epilepsy is a common neurological disease that affects approximately 50 million people worldwide [1]. It is defined as a disorder of the brain and characterised by an enduring predisposition to generate epileptic seizures [2,3]. Multiple antiepileptic drugs (AEDs) have been developed to try to control seizures in patients with epilepsy; however, 20–30% of patients are still refractory to currently available drug treatments, thus, the development of novel AEDs is required [4–6].

Perampanel is a selective, non-competitive, orally active antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which plays crucial roles in mediating fast excitatory synaptic transmission, and generating and spreading epileptic activity [7–9]. Perampanel is approved for the adjunctive treatment of partial-onset seizures (POS), with or without secondarily generalised (SG) seizures, and for primary generalised tonic-clonic (PGTC) seizures in patients with epilepsy aged ≥12 years in Japan, as well as in multiple other countries around the world (POS indication, > 50 countries; PGTC seizures indication, > 40 countries) [9–12]. Perampanel is also approved for monotherapy use for POS in the United States in patients with epilepsy aged ≥12 years [9].

The clinical programme for the development of perampanel included 4 Phase II studies that evaluated the tolerability and safety of adjunctive perampanel in non-Japanese patients with refractory POS: Studies 206 [13], 208 [13], 235 [14] and 203 (unpublished data on file, Eisai Europe Ltd., Hertfordshire, UK). Subsequently, 3 pivotal, randomised, double-blind, placebo-controlled, Phase III studies were conducted in a total of 1480 non-Japanese patients with refractory POS, with or without SG seizures, who were receiving 1–3 concomitant AEDs: Studies 304 [15], 305 [16] and 306 [17]. Patients who completed Studies 206 or 208 could enter the extension Study 207 [18], and patients who completed Studies 304, 305 or 306 could enter the extension Study 307 [19]. These extension studies supported the favourable safety, tolerability and efficacy profile of adjunctive perampanel for up to 4 years in patients with POS [18,19].

Here, we report the results of Study 231, an open-label, dose-ascending study, and its extension study (Study 233), which explored the long-term tolerability, safety and efficacy of adjunctive perampanel in Japanese patients with refractory POS, with or without SG seizures. Since enzyme-inducing AEDs (EIAEDs), such as carbamazepine (CBZ), oxcarbazepine and phenytoin (PHT), have previously been shown to cause a 3-, 2- and 2-fold increase in perampanel clearance, respectively [20,21], a sub-analysis of Study 231 only, also investigated drug–drug interactions between perampanel and concomitant EIAED use.

2. Methods

2.1. Standard protocol approvals, registration and patient consents

Study 231 (ClinicalTrials.gov identifier: NCT00849212) was conducted between March and November 2009, and Study 233 (ClinicalTrials.gov identifier: NCT00903786) was conducted between June 2009 and October 2016 at 9 sites in Japan. Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, and the standards specified in the articles of the Pharmaceutical Affairs Law and the Standards for the Conduct of Clinical Studies, as well as being consistent with Good Clinical Practice guidelines for studies conducted in Japan. The institutional review board approved the studies for each study centre, and all patients provided written informed consent.

2.2. Patients

Eligible patients for Study 231 were male or female, between ≥20 and < 65 years of age and diagnosed with POS, with or without SG seizures, according to the International League Against Epilepsy classification of epileptic seizures [22]. Patients had uncontrolled seizures for the previous 2 years, despite at least 12 weeks' treatment with more than 1 standard AED. If ≥1 benzodiazepine was used for the treatment of anxiety, sleep disorders, etc., this was counted as 1 concomitant AED. Patients received stable doses of 1–3 concomitant AEDs for at least the 8 weeks before enrolment in the observation period, only 1 of which was permitted to be an EIAED (such as CBZ, PHT, phenobarbital [PB] or primidone). Finally, patients had to have ≥3 POS during the previous 4 weeks prior to observation start and no 21-day, seizure-free period during the previous 8 weeks before treatment start based on medical records. Simple POS without motor signs or auras only were not counted.

Patients were excluded from Study 231 if they had status epilepticus within the previous 12 months, a history of Lennox-Gastaut syndrome or psychogenic seizures, presence of generalised seizures (e.g. absence, myoclonic) or had seizure clusters in the 8 weeks before enrolment in the observation period when individual seizures could not be counted. Patients were also excluded if they had undergone surgery for epilepsy within the previous 2 years, received barbiturates within the previous 8 weeks (other than for seizure control) or had severe liver or kidney disease. Patients who were pregnant, likely to get pregnant or were lactating were also excluded. Full inclusion and exclusion criteria for Study 231 are shown in Supplementary Table 1.

2.3. Study designs and objectives

Study 231 was a Phase II, multicentre, open-label, exploratory study. The primary objective was to assess the tolerability and safety of adjunctive perampanel and define the maximum tolerated dose in Japanese patients. The preliminary efficacy of adjunctive perampanel in Japanese patients was also evaluated in this study.

Study 231 comprised a 4-week observation period and 10-week treatment period, consisting of 6-week titration and 4-week maintenance periods. During the observation period, patients were assessed to ensure that they met the inclusion criteria. During the titration period, perampanel was administered orally at bedtime at an initial once-daily dose of 2 mg, with weekly up-titration in 2-mg increments to a maximum once-daily dose of 12 mg. If the investigator considered that up-titration was not appropriate based on tolerability, the dose was maintained at the same level or one 2-mg down-titration was permitted. During the maintenance period, patients continued to receive the same perampanel dose achieved at the end of titration.

Study 233 was an open-label extension study designed for patients who were continuing to receive perampanel at the end of the maintenance period of Study 231. Study 233 comprised a treatment period (≤316 weeks) and 4-week follow-up period. The primary objective was to evaluate the long-term safety, tolerability and efficacy of adjunctive perampanel. During the treatment period, patients continued to receive perampanel at the same dose they achieved at the end of Study 231.

2.4. Tolerability and safety assessments

Tolerability and safety were assessed for patients with evaluable safety data who received at least 1 dose of perampanel during the titration and maintenance periods of Study 231 or during the treatment period of Study 233. Patients reported signs and symptoms of treatment-emergent adverse events (TEAEs), which were checked by the investigator at each visit and recorded on a case report form. The investigator also judged the causal relationship for all TEAEs as unrelated or related to the study drug. Treatment-related TEAEs included any TEAEs that were deemed to be possibly related or probably related to the study drug by the investigator. Regular visits were held during both studies and included assessment of treatment-related TEAEs, clinical laboratory parameters, vital signs and 12-lead electrocardiogram.