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Perampanel Study 207: long-term open-label evaluation in patients with epilepsy

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Objectives – Evaluate interim long-term tolerability, safety and efficacy of adjunctive perampanel, a novel α-amino-3-hydroxy-5-methyl-5-isoxazolepropionic acid (AMPA)-receptor antagonist, in patients with refractory partial-onset seizures. *Materials and methods* – Study 207, an open-label extension (OLE) study (ClinicalTrials.gov identifier: NCT00368472), enrolled patients (18–70 years) who completed one of two randomized, placebo-controlled, dose-escalation Phase II studies. The OLE Treatment Phase comprised a 12-week Titration Period (2 mg increments of perampanel every 2 weeks to 12 mg/day, maximum) and a Maintenance Period, during which patients continued treatment up to a planned maximum of 424 weeks (~8 years). Interim analysis data cut-off date was 1 December, 2010. *Results* – Of 180 patients completing the Phase II studies, 138 enrolled in study 207. At the time of interim analyses (approximately 4 years after study start), over a third (n = 53, 38.4%) remained on perampanel; 41.3% (n = 57) of patients had >3 years of exposure; and 13.0% (n = 18) had at least 4 years' exposure. Mean ± standard deviation (SD) duration of exposure was 116 ± 75 weeks and mean ± SD dose during the OLE Maintenance Period was 7.3 ± 3.3 mg. No new safety signals emerged with long-term treatment. Consistent with previous studies, the most common treatment-emergent adverse events were as follows: dizziness, headache and somnolence. Overall median (range) per cent change from baseline in seizure frequency per 28 days during open-label treatment was −31.5% (−99.2 to 512.2). *Conclusions* – Long-term – up to 4 years – adjunctive perampanel had a favourable tolerability profile in patients with refractory partial-onset seizures. Improvements in seizure control were maintained with long-term treatment.

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Introduction

Open-label extension (OLE) studies can provide essential information on the long-term safety and tolerability of a therapy, particularly in assessing treatment-emergent adverse events (TEAEs) that may not have manifested in the shorter, randomized study. Additional long-term efficacy information can also be quantified. These are especially important where a new therapeutic target or novel mechanism of action may be involved.

Perampanel is a selective, non-competitive antagonist of α-amino-3-hydroxy-5-methyl-5-isoxazolepropionic acid (AMPA) receptors, the principal receptor involved in glutamate-mediated fast excitatory post-synaptic neurotransmission. AMPA receptors play a critical role in the generation and spread of epileptic activity (1). Overstimulation of AMPA receptors contributes to the ionic imbalance and excitotoxicity induced by excessive glutamate neurotransmission (2, 3). Perampanel has been shown to inhibit AMPA-induced excitability in cultured rat cortical neurons and to reduce seizure activity in rodent epilepsy models (4).

While other antiepileptic drugs (AEDs) such as felbamate and topiramate have been postulated to act (in part) via non-selective inhibition

of post-synaptic glutamate receptors (5), perampanel is the only selective inhibitor at post-synaptic AMPA receptors to be reported in Phase III epilepsy trials (6–8).

A global clinical trial programme assessed the efficacy and safety of adjunctive perampanel in patients with refractory partial-onset seizures. In two placebo-controlled, dose-escalation Phase II studies, perampanel was well tolerated across a dose range of 2–12 mg/day and showed evidence of efficacy (9). Subsequently, three placebo-controlled Phase III studies assessed adjunctive perampanel in treatment-resistant patients. Once-daily perampanel (4–12 mg/day) significantly reduced seizure frequency and increased responder rates compared with placebo (6–8) with generally favourable tolerability and safety profiles.

Extension studies were performed as part of the perampanel clinical development programme in patients who completed the dose-escalation Phase II studies and in those who had completed the pivotal Phase III trials. Here, we report the findings of an interim analysis of the Phase II OLE study 207, performed approximately 4 years after the start of the study.

Methods

Patients

Patients who completed study 206 (ClinicalTrials.gov identifier: NCT00144690) or study 208 (NCT00416195) were eligible. These were randomized, double-blind, placebo-controlled, dose-escalation Phase II studies that recruited adults aged 18–70 years with a diagnosis of epilepsy with partial-onset seizures, with or without secondary generalization (9). Patients had uncontrolled partial-onset seizures despite taking stable doses of 1–3 approved AEDs. Patients in both studies were randomized to adjunctive therapy with oral perampanel or placebo. In study 206, perampanel (once or twice daily) was titrated over 8 weeks from 1 mg/day to a maximum of 4 mg/day. In study 208, once-daily perampanel was titrated over 12 weeks from 2 mg/day to a maximum of 12 mg/day (once daily in the evening). Patients completing study 206 or 208 were eligible for the OLE study if they provided written informed consent and met the inclusion/exclusion criteria (Table S1).

Study design and objectives

Open-label extension study 207 (NCT00368472) was performed in 48 centres in Australia, Europe and the USA. The study protocol and other relevant documentation were approved by participating centres' independent ethics committees or institutional review boards. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice.

Study 207 enrolled between October, 2006 and May, 2010. The data cut-off for this interim analysis was 1 December, 2010. The primary objective was to evaluate the long-term tolerability and safety of once-daily adjunctive perampanel (up to 12 mg/day). The secondary objective was to assess whether the efficacy of perampanel demonstrated in those Phase II studies was maintained with long-term use.

Patients entered OLE study 207 as soon as possible after the final visit of study 206 or study 208, on the same concomitant AED regimens they received during the double-blind studies. The OLE had two phases: an Open-label Treatment Phase and a 4-week Follow-up Phase. The OLE Treatment Phase comprised a 12-week Titration Period and a Maintenance Period of up to 424 weeks. Study 208 patients entered the OLE on the same perampanel dose they completed the Phase II study on. During Titration, doses were increased by 2 mg every 2 weeks to a maximum of 12 mg/day on the basis of individual tolerability and seizure control. Patients entering from study 206 had their dose titrated up to 2 mg during the Titration Period. The maximum dose of perampanel for patients entering the OLE from study 206 was initially set at 4 mg/day; however, the results of study 208 demonstrated that doses of perampanel higher than 4 mg/day were tolerable (9). Consequently, the study 206 protocol was amended to allow patients to titrate to doses of perampanel up to 12 mg/day at the discretion of the investigator. Patients who received placebo during studies 206 and 208 underwent titration to perampanel treatment by 2 mg every 2 weeks during the Titration Period to a maximum of 12 mg/day.

Adjustment of perampanel dose to an individual's optimum dose (based on tolerability and efficacy) was permitted. Patients unable to tolerate doses of at least 2 mg/day were discontinued. During the OLE, concomitant AEDs could be reduced in dose, discontinued or changed at the investigators' discretion.

Tolerability and safety assessments

Adverse events (AEs) were monitored throughout the OLE and double-blind studies. TEAEs were defined as AEs that either (i) began in the period

between the first day of perampanel administration and 30 days after the last dose or (ii) began before the first day of administration and increased in severity during perampanel treatment. The 'first day of perampanel administration' was the start of double-blind treatment (for patients randomized to perampanel in studies 206 and 208), or the start of the Transition Phase of study 206 (for patients receiving placebo in that study), or the start of the OLE Titration Period (for patients receiving placebo in study 208).

Other tolerability and safety assessments included clinical laboratory evaluations, vital sign monitoring, body weight measurements, 12-lead electrocardiogram (ECG) and physical and neurological examinations.

Efficacy assessments

Efficacy was assessed using seizure-count data from patient diaries. Efficacy endpoints included: (i) median percentage change in seizure frequency (all partial-onset seizure types) per 28 days relative to pre-perampanel baseline and (ii) responder rates (proportion of patients experiencing $\geq 50\%$ reduction in seizure frequency per 28 days relative to pre-perampanel baseline). The pre-perampanel baseline was defined as the Pre-randomization Phase of studies 206 and 208 (for patients randomized to perampanel) or all of the phases of studies 206 and 208 (for patients randomized to placebo).

Statistical analyses

The safety population included all patients who received at least one dose of open-label perampanel and underwent at least one safety assessment. Efficacy analyses were performed in the intent-to-treat population: all patients who received at least one dose of open-label perampanel and had valid seizure data from the OLE. Analyses of efficacy data were descriptive, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints.

Results

Patients

Of 180 patients who completed studies 206 and 208 (9), 138 patients were enrolled into study 207. Overall, 101 (73.2%) patients had participated in study 206 and 37 (26.8%) in study 208. Forty-three (31.2%) patients were randomized to placebo in the double-blind studies (study 206, $n = 35$; study 208, $n = 8$) and 95 (68.8%) had been randomized to perampanel (study 206, $n = 66$; study 208, $n = 29$). Approximately, 80.0% of patients entering the OLE had no prior exposure to perampanel or had been exposed to a maximum dose of 4 mg in the core Phase II studies. At the interim analysis cut-off date, ~4 years after study commencement, 53 (38.4%) patients remained on study (Table 1). Reasons for discontinuation are listed in Table 1. In this study, patients who discontinued because of a lack of efficacy were captured under 'withdrawn patient consent' or 'other'.

Baseline demographics, disease history and concomitant AED use are summarized in Table 2. No differences in demographics or disease history were observed between those who enrolled and those who chose not to participate (data not shown). Discontinuation rates were similar among patients previously randomized to placebo and those previously randomized to perampanel (60.5% vs 61.1%, respectively).

A large majority of patients were taking 2–3 AEDs at baseline ($n = 107$, 77.5%); the average number of AEDs per patient was 1.9 (Table 2). The four most commonly used AEDs were carbamazepine, lamotrigine, levetiracetam and valproic acid. The majority of patients in the OLE experienced complex partial and secondarily generalized seizures at baseline (Table 2).

Perampanel exposure

Table 3 summarizes the extent of exposure to perampanel in patients who underwent OLE. Overall, 119 (86.2%) patients received >6 months' treatment with perampanel; 96 (69.6%) received

Table 1 Patient disposition (safety/ITT population)

	All patients ($n = 138$)
Study completion, *n* (%)	
Completed	1 (0.7)[a]
Ongoing	53 (38.4)
Discontinued	84 (60.9)
Reason for discontinuation, *n* (%)	
Adverse event	18 (13.0)
Treatment non-compliance	3 (2.2)
Protocol violation	1 (0.7)
Investigator/sponsor request	1 (0.7)
Withdrawn patient consent	32 (23.2)
Diary non-compliance	1 (0.7)
Other	28 (20.3)
Pregnancy	1 (0.7)
Lost to follow-up	1 (0.7)
Investigator/patient request	1 (0.7)
Lack of efficacy	25 (18.1)

[a]This patient completed the study before the duration of the Maintenance Period was extended by protocol amendment from 220 weeks to 424 weeks.
ITT, intent-to-treat.

Table 2 Patient demographics and clinical characteristics (safety/ITT population). All data shown in the table were collected at the start of, or during, the baseline phases of the two preceding randomized, double-blind studies

Variable	All patients (n = 138)
Mean age (SD), years	40.7 (11.9)
Sex, *n* (%)	
Male	58 (42.0)
Race, *n* (%)	
Asian/Pacific	1 (0.7)
Black	5 (3.6)
White	128 (92.8)
Other	4 (2.9)
Mean height (SD), cm	168.7 (9.1)
Mean weight (SD), kg	75.1 (19.5)
Mean time since onset of epilepsy (SD), years	23.2 (13.4)
Seizure type at baseline, *n* (%)	
Simple partial	64 (46.4)
Complex partial	131 (94.9)
Secondarily generalized	88 (63.8)
Seizure frequency per 28 days at baseline, median (min, max)	9 (0, 223)
No. concomitant AEDs at baseline, *n* (%)	
1 AED	31 (22.5)
2 AEDs	94 (68.1)
3 AEDs	13 (9.4)
Most common concomitant AEDs at baseline, *n* (%)[a]	
Carbamazepine	48 (34.8)
Lamotrigine	47 (34.1)
Levetiracetam	34 (24.6)
Valproic acid	32 (23.2)
Topiramate	31 (22.5)
Oxcarbazepine	29 (21.0)

[a]Data shown for AEDs used in $\geq$10% of all patients.
AED, antiepileptic drug; ITT, intent-to-treat; SD, standard deviation.

Table 3 Extent of exposure to perampanel (safety/ITT population)

Variable	All patients (n = 138)
Duration of exposure, *n* (%)[a]	
>13 weeks	135 (97.8)
>26 weeks	119 (86.2)
>52 weeks	96 (69.6)
>104 weeks	70 (50.7)
>156 weeks	57 (41.3)
>182 weeks	41 (29.7)
Mean (SD) duration of exposure, weeks[a]	116.4 (74.9)
Mean (SD) daily dose of perampanel, mg	
Open-label Titration Period	4.5 (1.7)
Open-label Maintenance Period	7.3 (3.3)
Entire perampanel treatment period[b]	5.9 (2.8)
Final dose achieved[c], *n* (%)	
<4 mg	21 (15.2)
4 mg	43 (31.2)
6 mg	14 (10.1)
8 mg	13 (9.4)
10 mg	17 (12.3)
12 mg	30 (21.7)

[a]Includes the preceding double-blind studies (unless the gap between exposure to perampanel in the double-blind studies and the open-label extension was >14 days; in such instances, only the longer of the two exposure periods was counted).
[b]Includes the preceding double-blind studies (excluding the 2-week transition phase of study 206 when patients received perampanel 1 mg/day).
[c]The final dose during the open-label perampanel treatment period, except for patients who received perampanel during the double-blind Phase II studies. In these patients, if the first dose in the Open-label Treatment Phase was $\geq$15 days after the last dose of double-blind study, the final dose is based on the double-blind or open-label perampanel treatment, whichever is longer.
ITT, intent-to-treat; SD, standard deviation.

Table 4 TEAEs (safety population)

	n = 138
Any TEAE, *n* (%)	129 (93.5)
Any treatment-related TEAE, *n* (%)	99 (71.7)
Any severe TEAE, *n* (%)	30 (21.7)
Any serious TEAE, *n* (%)	21 (15.2)
Death	1 (0.7)
Life-threatening	1 (0.7)
Required or prolonged hospitalization	19 (13.8)
Any TEAE leading to discontinuation, *n* (%)	17 (12.3)
Any TEAE leading to dose interruption, *n* (%)	6 (4.3)
Any TEAE leading to dose reduction, *n* (%)	45 (32.6)
Any TEAE leading to dose increase, *n* (%)	5 (3.6)

TEAE, treatment-emergent adverse event.

>1 years' treatment; 70 (50.7%) >2 years' treatment; 57 (41.3%) >3 years; and 18 patients (13.0%) had >4 years' exposure. The overall mean ± standard deviation (SD) exposure to perampanel was >2 years (116.4 ± 74.9 weeks). Almost all patients (n = 123, 89.1%) achieved a maximum tolerated dose (MTD) within the effective dose range (4–12 mg/day); 46% of patients achieved an MTD of 8–12 mg/day. The mean ± SD perampanel dose during the OLE Maintenance Period was 7.3 ± 3.3 mg; the mean ± SD perampanel dose over the whole duration of perampanel treatment (Double-blind Phase and OLE) was 5.9 ± 2.8 mg.

Tolerability and safety

Considering the lengthy exposures during this trial, 129 (93.5%) patients experienced $\geq$1 TEAE (Table 4); most TEAEs were mild or moderate in severity. There were three TEAEs reported in more than 15% of patients over the four trial years: dizziness (41.3%), headache (21%) and somnolence (19.6%). Frequencies of these three TEAEs were highest in the first year, then more than halved in the second year, and halved again in the third year: dizziness (30.4%, 14.7%, 3.7%, 6.7%, for years 1, 2, 3, 4 of the study, respectively); headache (16.7%, 4.6%, 2.4%, 5.0%); somnolence (17.4%, 5.5%, 1.2%, 1.7%).

Treatment-emergent adverse events occurring in >5% of patients are summarized in Table 5. There were more patients with dizziness ($\leq$4 mg/day: 10/45 [22.2%]; >4 mg/day: 47/93 [50.5%]) and somnolence ($\leq$4 mg/day: 8/45 [17.8%]; >4 mg/day: 19/93 [20.4%]) at higher doses. Anxiety (n = 10, 7.2%) was the only psychiatry-related

Table 5 TEAEs occurring in ≥5% of patients (safety population)

	n (%)
Dizziness	57 (41.3)
Headache	29 (21.0)
Somnolence	27 (19.6)
Fatigue	19 (13.8)
Contusion (bruising)	16 (11.6)
Back pain	14 (10.1)
Nasopharyngitis	14 (10.1)
Upper respiratory tract infection	14 (10.1)
Convulsion	13 (9.4)
Fall	13 (9.4)
Nausea	13 (9.4)
Vertigo	12 (8.7)
Skin laceration	11 (8.0)
Urinary tract infection	11 (8.0)
Anxiety	10 (7.2)
Neck pain	10 (7.2)
Rash	10 (7.2)
Diarrhoea	9 (6.5)
Irritability	8 (5.8)
Musculoskeletal pain	8 (5.8)
Tremor	8 (5.8)
Blurred vision	8 (5.8)
Ataxia	7 (5.1)
Cough	7 (5.1)
Peripheral oedema	7 (5.1)
Pain in extremity	7 (5.1)

TEAE, treatment-emergent adverse event.

TEAE that occurred in >5% of patients; there was no dose effect and nine of the ten patients reported the severity as mild. There were 20 falls in 13 (9.4%) patients (≤4 mg/day: 3/45 [6.7%]; >4 mg/day 10/93 [10.8%]). There were no serious TEAEs or early terminations owing to falls.

No TEAEs related to suicidality were reported. One patient became pregnant despite exclusion criteria requiring use of adequate contraception. This patient had received approximately 6 months of perampanel therapy and was discontinued from treatment following confirmation of pregnancy; the patient delivered a healthy, full-term infant. There were no perampanel-related overdoses.

Treatment-emergent adverse events led to the withdrawal of 17 (12.3%) patients from open-label treatment. TEAEs that caused the withdrawal of >1 patient from the OLE were dizziness (n = 3, 2.2%), vertigo (n = 2, 1.4%), upper abdominal pain (n = 2), fatigue (n = 2), headache (n = 2) and status epilepticus (n = 2). In the first year, 10 patients withdrew: five with TEAEs related to vertigo, dizziness or balance; one patient each with muscle spasms, peripheral oedema, fatigue, convulsion and recurrent breast cancer (the last two events were also serious TEAEs). In years 2, 3 and 4, there were one (anxiety disorder), five (feeling drunk, schizophrenia, first degree atrioventricular block, status epilepticus) and one (dizziness and confusion) withdrawals because of TEAEs.

Serious TEAEs were experienced by 21 (15.2%) patients; these were considered possibly related to treatment in four patients (convulsion, schizophrenia, status epilepticus, grand mal convulsion) and probably related in one (epilepsy). Thirteen patients had serious AEs related to their epilepsy: five, two, four and two patients in years 1, 2, 3 and 4, respectively. There were two patients with pneumonias, three with cancers (recurrent breast cancer, breast carcinoma *in situ*, prostate neoplasm) and one each for schizophrenia, death and Guillain-Barré syndrome.

One patient, a 48-year-old female with morbid obesity, was found dead at home presumably following a cardiac arrest – the death was considered unrelated to perampanel treatment (12 mg/day); however, sudden unexpected death in epilepsy could not be ruled out.

No clinically important changes in mean laboratory values were observed and the incidence of markedly abnormal laboratory values was low. Four of 12 patients with markedly low neutrophil counts were receiving concomitant carbamazepine and/or valproic acid at baseline. Three (2.2%) patients had markedly low white blood cell values and were not receiving carbamazepine and/or valproic acid at baseline; no patients had abnormal platelet levels. Seven (5.1%) patients with hyponatraemia were all receiving concomitant carbamazepine or oxcarbazepine at baseline. One patient had an abnormally high alanine aminotransferase level (>5× upper limit of normal; 10–50 U/l) at Day 643 of treatment. Mean changes in vital signs were judged not to be clinically important.

The mean change in body weight at the end of treatment was 0.2 kg (range, −18.0 to 17.0 kg). The proportion of patients experiencing a shift from normal to abnormal ECG results between baseline and the end of treatment (11.9%) was similar to the proportion of patients whose ECG results shifted from abnormal to normal (10.4%). Findings of physical and neurological examinations were unremarkable.

Efficacy

Across all patients, the median (range) per cent change in seizure frequency per 28 days during the entire duration of open-label treatment (including the Titration Period) relative to pre-perampanel baseline was −31.5% (−99.2 to 512.2; n = 138). Over the OLE Maintenance Period only, the median (range) change from baseline was −39.4% (−99.2 to 542.4; n = 120). The responder

rate for the entire Open-label Treatment Phase was 37.0% (n = 138), and for the Maintenance Period only was 45.8% (n = 120).

The OLE allowed uncontrolled treatment, with modifications of other therapies permitted. The reduction in seizure frequency observed during the core Phase II studies (9) was maintained during long-term treatment. For patients who received at least 1 (n = 89), 2 (n = 66), 3 (n = 52) and 4 (n = 18) years of open-label perampanel treatment, the median per cent change from pre-perampanel baseline in 28-day seizure frequency over 1, 2, 3 or 4 years was −43.7%, −52.0%, −49.7% and −48.4%, respectively (Fig. 1A). The responder rate for these patients, at the end of 1, 2, 3 or 4 years, was 43.8%, 51.5%, 49.0% and 50.0%, respectively (Fig. 1B).

Among the 131 patients with complex partial seizures, with or without secondary generalization, the median per cent change in seizure frequency per 28 days across the entire OLE Treatment Phase was −44.7% and the responder rate was 45.8%. By the interim cut-off date, four patients (2.9%) had experienced a 100% reduction in seizure frequency, and 15 patients (10.9%) had a $\geq$75% reduction in seizures.

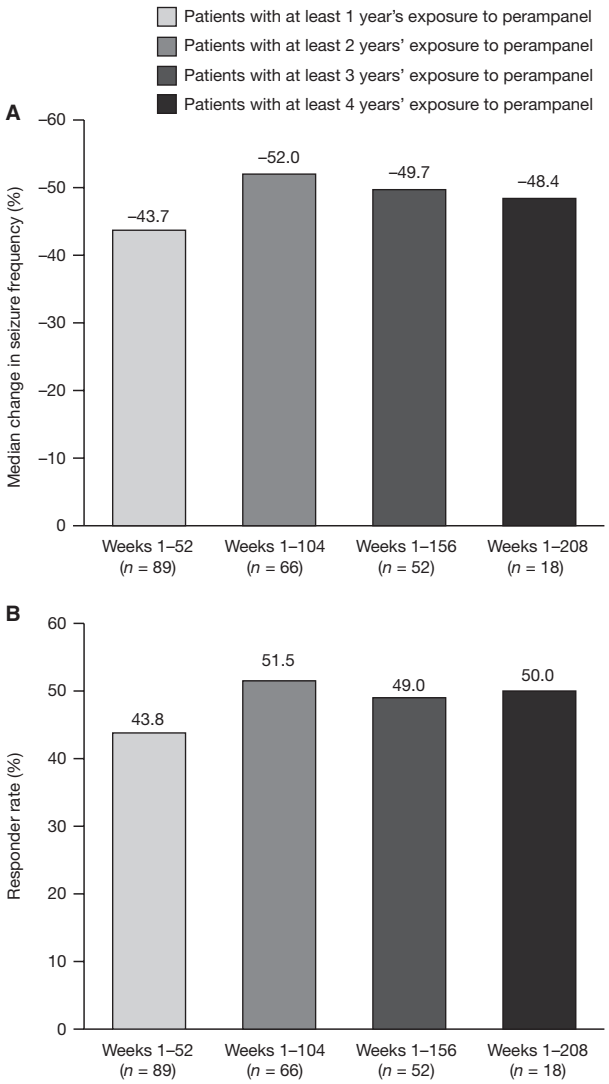

Figure 1. Efficacy analyses at the end of 1, 2, 3 and 4 years in patients with at least 1, 2, 3 and 4 years' open-label treatment with perampanel, respectively: (A) median per cent change in seizure frequency per 28 days relative to pre-perampanel baseline, and (B) responder rate.

Discussion

In this interim analysis of the ongoing Phase II OLE study 207, more than half the patients had >2 years' exposure to perampanel and >40% had >3 years' exposure. The average duration of exposure to perampanel was approximately 2.2 years (116 weeks). Long-term, once-daily adjunctive perampanel (2–12 mg/day) demonstrated acceptable tolerability in patients with partial-onset seizures. The patient retention rate at 4 years was approximately 38%, and importantly, no new safety signals emerged during long-term treatment with perampanel. The tolerability profile observed in the current study was consistent with that seen in shorter, randomized evaluations of perampanel (6–9). The previously demonstrated ability of perampanel to improve seizure control was also maintained, and no evidence of an exacerbation of seizures emerged following prolonged treatment.

Central nervous system-related effects are a common consequence of AED therapy and have been observed in long-term, open-label studies of other AEDs in patients with partial-onset seizures (10–13). When the long duration of this trial is taken into account (the majority of patients had >2 years' exposure to perampanel), the overall incidence of TEAEs seems low and is comparable to those previously reported in patients receiving AED treatment (14). The most common TEAEs reported were dizziness, somnolence and headache in the first year, consistent with the safety profile of perampanel in previous Phase II and III clinical trials (6–9). Moreover, the frequency of the three most common TEAEs diminished approximately 2-fold over each of the first 3 years. Dizziness and somnolence were considered to be adverse drug reactions (ADRs; causally related to perampanel treatment), however, while headache was a TEAE, it did not meet the criteria for an ADR. Most of the patients in this trial were on at least two AEDs (77.5%) at Baseline. AEDs that block sodium channels and that are known to be associated with dizziness were among the most commonly used concomitant AEDs. The

incidence of individual TEAEs related to psychiatric disorders was low, with only anxiety (mild) reported in >5% of patients (7.2%).

Although the validity of cross-study comparisons is limited, 1-year patient retention rates were comparable between the current OLE (70%) and reported long-term studies of other AEDs (59–77%) (10–13). Consistent with other studies in the perampanel development programme, no clinically notable effects on laboratory parameters, vital signs or 12-lead ECG were observed.

Assessment of the long-term anti-seizure effects of perampanel was a secondary objective, and improvements in seizure frequency and responder rates were maintained across the duration of the OLE. For example, in the 52 patients who were exposed to open-label perampanel treatment for at least 3 years, the 28-day seizure frequency was reduced by a median value of 49.7% compared with baseline, and the responder rate was 49%.

This interim analysis of OLE study 207 provides unusually long-term data in a Phase II study population. The data show that long-term adjunctive therapy with perampanel is safe, with acceptable tolerability. Improvements in seizure control were also maintained over the 4-year study period.

A significant proportion of patients with partial-onset seizures continue to experience seizures that are not controlled by currently available therapies. This trial reports the first long-term and successful treatment of refractory epilepsy patients with a selective, non-competitive AMPA inhibitor, further supporting the efficacy of perampanel observed in previous short-term studies. These trials establish the potential role of AMPA-receptor antagonists in contemporary epilepsy treatment.

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Conflicts of interest

This study was funded by Eisai Inc.

Ivan Rektor is currently an investigator for Eisai. Gregory L. Krauss is currently an investigator for Eisai, UCB Pharma, Neuronex, Sunovian and NIH/NIA. He is a consultant for Eisai as a member of the Epilepsy Study Consortium. Michal Bar is currently an investigator for Eisai. Victor Biton is currently an investigator for Eisai, Janssen, King, Medivation, Pfizer, Sepracor/Sunovion, UCB/Schwarz, Xenoport, Lundbeck, Schering-Plough/Merck, Upsher-Smith, SK Life Sciences and Wyeth. Jack A. Klapper is currently an investigator for Eisai. Nerija Vaiciene-Magistris is currently an investigator for Eisai. Robert Kuba is an investigator for Eisai and UCB Pharma and a consultant for UCB Pharma. David Squillacote is an employee of Eisai Inc. Michelle Gee is an employee of Eisai Ltd. Dinesh Kumar is an employee of Eisai Inc.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Main inclusion and exclusion criteria. Note: main criteria for the OLE study are shown; patients had to meet additional criteria to be recruited to the preceding double-blind studies (studies 206 and 208).

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