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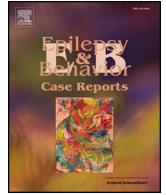
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Case Report

Evaluation of perampanel as monotherapy for focal seizures: Experience from open-label extension studies

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ABSTRACT

Perampanel, a selective, non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of focal seizures, with or without secondarily generalized seizures, and for primary generalized tonic-clonic seizures in patients with epilepsy aged ≥ 12 years. Perampanel was recently approved for monotherapy use for focal seizures in the U.S.A. Anti-seizure drug monotherapy may be preferable to polytherapy, which is generally associated with increased toxicity, non-compliance, and cost. Here, we report cases where patients had converted to perampanel monotherapy during open-label extension (OLEx) portions of 9 Phase II and III studies.

Of 2245 patients who enrolled in the OLEx studies, we identified 7 patients with drug-resistant focal seizures who discontinued all non-perampanel anti-seizure drugs and were maintained on perampanel monotherapy for ≥ 91 days until the end of data cut-off. Patients received perampanel monotherapy for up to 1099 days (157 weeks), most at a modal dose of 12 mg. Seizure data were available for 6 patients, of whom 5 had a $\geq 90\%$ reduction in overall seizure frequency between baseline and their last 13-week period of monotherapy (3 were seizure-free). Perampanel monotherapy was generally well tolerated and the safety profile during perampanel monotherapy was consistent with clinical and post-marketing experience in the adjunctive setting. This analysis included a small proportion of patients with highly drug-resistant focal seizures who converted to monotherapy during OLEx studies. While these limited data are encouraging in suggesting that perampanel might be useful as a monotherapy, further studies are required to explore outcomes in a less drug-resistant population, where a larger proportion of patients might benefit from monotherapy.

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Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; bid, twice daily; FDA, Food and Drug Administration; OLEx, open-label extension; qam, every morning; qd, once daily; qhs, every night at bedtime; qpm, every evening; SG, secondarily generalized; TEAE, treatment-emergent adverse event; tid, three times daily.

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1. Introduction

Perampanel, a selective, non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of focal seizures, with or without secondarily generalized (SG) seizures, and for primary generalized tonic-clonic seizures in patients with epilepsy aged ≥ 12 years [1,2]. Perampanel was recently approved for monotherapy use for focal seizures in the U.S.A.

It has been a regulatory standard for anti-seizure drugs to be initially evaluated for adjunctive use, given ethical concerns around the use of placebo-controlled trials for anti-seizure drug monotherapy [3].

However, since anti-seizure drug polytherapy is often associated with increased toxicity, non-adherence, and cost, monotherapy may be preferable in some clinical practice settings [4].

Despite challenges in trial design, many anti-seizure drugs have demonstrated efficacy as monotherapies [5]. In the U.S.A., several anti-seizure drugs have had their original indications expanded to include use in monotherapy settings, including lacosamide, lamotrigine extended release, and topiramate. Furthermore, the arguments of a white paper has recently advocated a unified indication for anti-seizure drugs, irrespective of concomitant anti-seizure drug use [3], and as a consequence, the Food and Drug Administration (FDA) has determined that it is acceptable to extrapolate data from adjunctive trials to the monotherapy setting.

Here, we report data from patients who converted to perampanel monotherapy during the open-label extension (OLEx) portions of Phase II and Phase III adjunctive studies. This analysis explores our understanding around the conversion to perampanel monotherapy for the treatment of focal seizures. In addition, and based on the FDA policy around extrapolation of adjunctive data to the monotherapy setting, these data formed part of the data that were submitted to the FDA, supporting the approval of perampanel monotherapy in the U.S.A. for the treatment of focal seizures (with or without SG seizures) in patients with epilepsy aged ≥ 12 years [2,6]. These data have also been submitted to the European Medicines Agency as part of the data in support of an amendment to the perampanel *Summary of Product Characteristics* to include monotherapy data in the *Clinical Section*.

2. Methods

The clinical development of perampanel as an adjunctive treatment included 9 Phase II and III studies in patients receiving 1–3 concomitant anti-seizure drugs. Eight were randomized, double-blind, placebo-controlled studies in patients with drug-resistant focal seizures, with or without SG seizures (Studies 206 [NCT00144690] and 208 [NCT00416195]: patients aged 18–70 years; Studies 304 [NCT00699972], 305 [NCT00699582], 306 [NCT00700310], and 335 [NCT01618695]: patients aged ≥ 12 years; and Study 235 [NCT01161524]: adolescent patients aged ≥ 12 to ≤ 17 years) [7–11], or primary generalized tonic-clonic seizures and idiopathic generalized epilepsy (Study 332 [NCT01393743]: patients aged ≥ 12 years) [12]. The remaining study was an open-label, dose-escalation Phase II study of adjunctive perampanel as an oral suspension in patients from the U.S.A. aged 2 to < 12 years with any seizure type (Study 232 [NCT01527006]).

All studies were performed in accordance with the Declaration of Helsinki, European Medicines Agency requirements, the U.S. Code of Federal Regulations, and the ICH-E6 Guideline for Good Clinical Practice. All participants gave written informed consent.

Patients who completed 1 of these studies could receive adjunctive perampanel (daily dose of up to 12 mg) in 1 of the following OLEx studies:

- Study 207 (patients enrolled from Studies 206 and 208; $n = 138$) [13]
- Study 307 (patients enrolled from Studies 304, 305, and 306; $n = 1218$) [14]
- Study 335 OLEx ($n = 596$)
- Study 235 OLEx ($n = 114$)
- Study 332 OLEx ($n = 138$)
- Study 232 OLEx ($n = 41$).

In all OLEx studies, concomitant anti-seizure drugs could be adjusted in dose or changed as clinically dictated (e.g., removed if seizures were well controlled with perampanel). Therefore, although perampanel

monotherapy was not an objective, it was a possibility if all non-perampanel anti-seizure drugs were discontinued.

This analysis included patients who discontinued all non-perampanel anti-seizure drugs during 1 of the OLEx studies, received perampanel as monotherapy for at least 91 days, and were able to continue monotherapy thereafter (until the relevant data cut-off date for each individual OLEx study). The time period of 91 days was selected with the aim of identifying cases where there was a clear decision to attempt conversion to monotherapy and to exclude cases where non-perampanel anti-seizure drugs were temporarily discontinued over a shorter period of time for any other reason (e.g., due to tolerability reasons or patient non-adherence). Throughout the studies, median percent change in seizure frequency per 28 days from pre-perampanel baseline was assessed and patients were monitored for treatment-emergent adverse events (TEAEs).

3. Results

3.1. Patients

Overall, 2245 patients with drug-resistant seizures, despite treatment with 1–3 concomitant anti-seizure drugs, were enrolled in the OLEx studies. Of these, 9 patients discontinued all concomitant anti-seizure drugs and took perampanel as monotherapy for at least 91 days.

Of these 9 patients, 7 continued to receive perampanel as monotherapy until data cut-off, and so met the criteria for inclusion in the present analysis. Six of these patients had received perampanel monotherapy in Study 307 (Patients 1–6), and 1 in the Study 235 OLEx (Patient 7). Five patients had received placebo in the double-blind treatment phase of the Core Study (Patients 1, 3, 4, 6, and 7) and 2 had received a non-effective dose of perampanel 2 mg (Patients 2 and 5), although all received an optimized perampanel dose in the OLEx studies. At baseline of the double-blind treatment phase, patients had been receiving 1 concomitant anti-seizure drug (Patients 3, 4, 5, and 7), 2 concomitant anti-seizure drugs (Patients 1 and 6), or 3 concomitant anti-seizure drugs (Patient 2).

The 7 patients comprised 1 female and 6 male patients, with an age range of 15–40 years. At baseline of the double-blind treatment phase, time since diagnosis of epilepsy ranged from 2.8 to 21.9 years, and seizure frequency per 28 days ranged from 0.5 to 93.8. Three patients had been experiencing focal seizures with motor signs (Patients 3, 4, and 5), 1 had been experiencing focal seizures without motor signs (Patient 1), 2 had been experiencing focal seizures with secondary generalization (Patients 4 and 6), and 5 had been experiencing focal impaired awareness seizures (complex partial seizures in the previous ILAE classification; Patients 1, 2, 5, 6, and 7).

The other 2 patients, who received perampanel monotherapy for 91 days, later reverted back to polytherapy (reasons for discontinuation of perampanel monotherapy unknown); these patients were not included in the analysis because they did not meet the pre-defined requirement for monotherapy to have continued until data cut-off. One of these patients was a 58-year-old female who received perampanel for 1126 days in Study 307, including 123 days as monotherapy (modal daily dose = 12 mg); during the only 13-week window where monotherapy was received throughout (Weeks 79–91 of perampanel treatment), this patient had a 68.4% reduction in seizure frequency compared with baseline. The other patient was a 6-year-old female who received perampanel for 287 days in the Study 232 OLEx, including 103 days as monotherapy (modal daily dose = 0.2 mg/kg); during the only 13-week window where monotherapy was received throughout (Weeks 27–39 of perampanel treatment), this patient had an 87.7% reduction in seizure frequency compared with baseline.

3.2. Perampanel treatment

Fig. 1 summarizes the time courses of treatment with perampanel and concomitant anti-seizure drugs in Patients 1–7. Patients received

Patient	Anti-seizure drug	Time window, weeks																		
		1-13	14-26	27-39	40-52	53-65	66-78	79-91	92-104	105-117	118-130	131-143	144-156	157-169	170-182	183-195	196-208			
1	Levetiracetam		1500 mg bid						1875 mg bid						500 mg qd ^a					
	Valproic acid	125 mg qam		250 mg qpm ^b																
	Perampanel	4-12 mg qd (modal dose: 12 mg)														10 mg qd				
2	Valproic acid	500 mg bid												X	X	X	X			
	Zonisamide	500 mg qd				200 mg bid		100 mg bid								X	X	X	X	
	Lamotrigine	250 mg qd				100 mg bid		50 mg bid								X	X	X	X	
	Perampanel	2-12 mg qd (modal dose: 2 mg)								12 mg qd						10 mg qd		X	X	X
3	Valproic acid	750 mg qd ^c												X	X	X	X			
	Perampanel	12 mg qd														X	X	X	X	
4	Oxcarbazepine	600 mg qd																X	X	
	Perampanel	6 mg qd												4 mg qd						X
5	Valproic acid	500 mg bid ^d														X	X			
	Perampanel	2-12 mg qd (modal dose: 2 mg)								12 mg qd										X
6	Carbamazepine	400 mg tid ^e												X	X	X				
	Topiramate	100 mg tid												X	X	X				
	Perampanel	12 mg qd														X	X	X		
7	Levetiracetam	1000 mg qd		500 mg qd								X	X	X	X	X	X	X	X	
	Perampanel	8 mg qd												X	X	X	X	X	X	

Fig. 1. Treatment time courses for the 7 patients who received perampanel monotherapy. Anti-seizure drug shown for each time window is the treatment given for the majority of that time window. ^aLevetiracetam 500 mg qd administered as rescue medication on 1 day only; ^bvalproic acid 250 mg qpm dose replaced with 125 mg qhs for last 2 weeks of treatment; ^cvalproic acid dose down-titrated to 500 mg qd for 6 weeks and then 250 mg qd for last 6 weeks of treatment; ^dvalproic acid dose down-titrated to 500 mg qd for 4 weeks and then 250 mg qd for last 4 weeks of treatment; ^ecarbamazepine dose down-titrated to 400 mg qd for last 6 weeks of treatment. X = time window occurs after the data cut-off for given patient. bid, twice daily; qam, every morning; qd, once daily; qhs, every night at bedtime; qpm, every evening; tid, three times daily.

perampanel monotherapy for up to 1099 days (157 weeks), most at a modal dose of 12 mg. The duration of treatment and modal doses for the individual patients were: Patient 1—594 days (excluding 1 day of rescue medication with levetiracetam 500 mg in Week 15), modal dose = 12 mg; Patient 2—345 days, modal dose = 12 mg; Patient 3—203 days, modal dose = 12 mg; Patient 4—1099 days, modal dose = 4 mg; Patient 5—273 days, modal dose = 12 mg; Patient 6—409 days, modal dose = 12 mg; and Patient 7—181 days, modal dose = 8 mg.

Concomitant anti-seizure drugs included an enzyme-inducing anti-seizure drug in 2 patients (Patient 4, oxcarbazepine; Patient 6, carbamazepine). Concomitant anti-seizure drugs were generally down-

titrated gradually (valproic acid in Patients 1, 3, and 5; zonisamide and lamotrigine in Patient 2; carbamazepine in Patient 6; levetiracetam in Patient 7), although they were discontinued abruptly in some cases (levetiracetam in Patient 1; valproic acid in Patient 2; oxcarbazepine in Patient 4; topiramate in Patient 6; see Fig. 1 for full details).

3.3. Changes in seizure frequency

Fig. 2 shows changes in seizure frequency for the 6 patients in Study 307. At their last 13-week time window, 5 of these patients had at least a 90% reduction in seizure frequency compared with baseline (Patients 2-5), with 3 of these achieving complete seizure

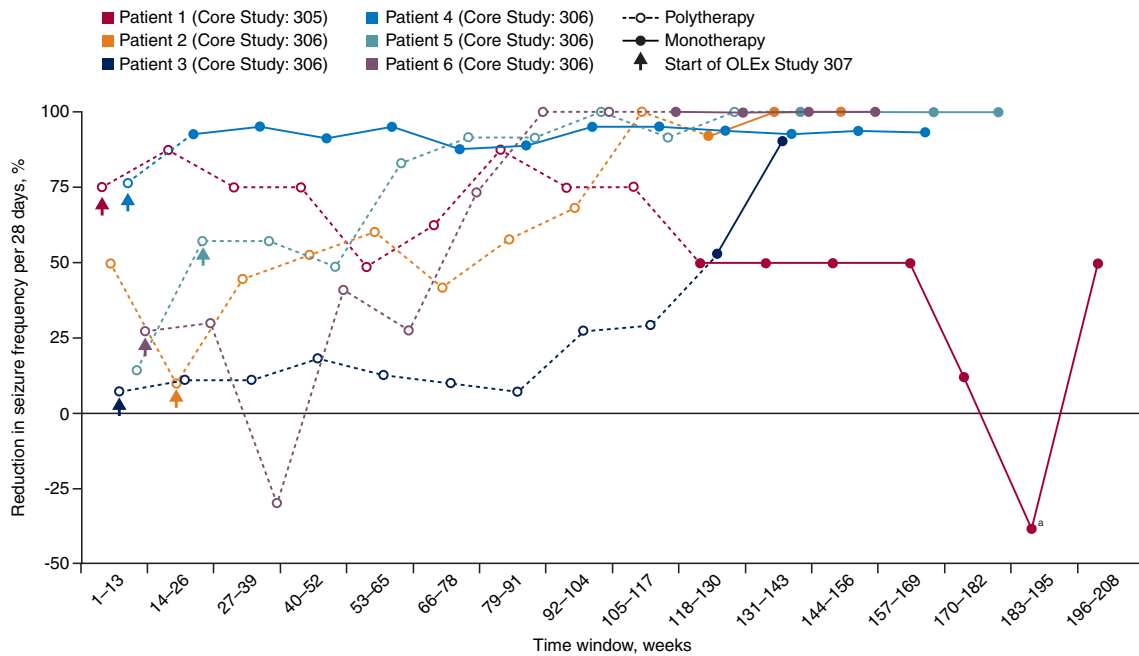


Fig. 2. Reductions in seizure frequency per 28 days during polytherapy and monotherapy for 6 patients in Study 307. Week 1 represents the start of perampanel treatment either during the double-blind phase of Studies 304, 305, and 306, or the OLEx Study 307. ^aLevetiracetam 500 mg once daily administered as rescue medication on 1 day during this monotherapy period. OLEx, open-label extension.

freedom (Patients 2, 5, and 6). The other patient had a 49.7% reduction in seizure frequency (Patient 1).

For patients with focal impaired awareness seizures or SG seizures at baseline, there were reductions of >90% in the frequency of these seizure types throughout perampanel monotherapy (focal impaired awareness seizures: Patients 1, 2, 5, and 6; SG seizures: Patients 4 and 6).

Full seizure data were unavailable for the patient in the Study 235 OLEx (Patient 7), although it was reported that this patient did not experience any seizures over the final 6 months of the study, after converting to monotherapy.

3.4. Tolerability

Five patients experienced TEAEs during perampanel monotherapy; no TEAEs occurred in more than 1 patient. There were no deaths and only 1 serious TEAE (Patient 4; colitis), which was not considered to be related to perampanel treatment.

The most common class of TEAEs observed was psychiatric disorders, which were experienced by 2 patients. The psychiatric disorders reported during the studies were irritability, mood swings, nervousness, and panic attack (all $n = 1$).

4. Discussion

Here, we report data from patients who converted to perampanel monotherapy during the OLEx portions of Phase II and Phase III studies of perampanel. These data may reflect certain clinical practices, as dosing was more flexible in the OLEx portion of these studies than in the double-blind treatment phases, with daily perampanel dose titrated to a maximum of 12 mg and adjustment of concomitant anti-seizure drugs permitted.

Of the 2245 patients with drug-resistant seizures, despite treatment with 1–3 concomitant anti-seizure drugs, who enrolled in the OLEx studies, 7 patients, all with focal seizures (with or without SG seizures), converted to perampanel monotherapy. In most cases, concomitant anti-seizure drugs were down-titrated gradually, however, they were also stopped abruptly in some cases. The duration of perampanel monotherapy treatment was relatively long at up to 1099 days (>3 years), and most patients received perampanel at a modal dose of 12 mg. The limited analysis suggested that the patients generally maintained a similar, or numerically better, level of seizure control during perampanel monotherapy than during prior adjunctive perampanel treatment. Furthermore, perampanel monotherapy appeared to be well tolerated, with no TEAE occurring in more than 1 patient and no drug-related serious TEAEs. The safety profile during perampanel monotherapy was consistent with clinical and post-marketing experience in the adjunctive setting, and no unique TEAEs were observed.

As the OLEx studies were not placebo controlled, a major limitation is that the seizure reductions could have been due to spontaneous improvements in the state of the disease rather than perampanel treatment. This has previously been suggested in a study of patients with drug-resistant epilepsy in which 27/225 (12%) patients became seizure-free for at least 12 months following anti-seizure drug treatment [15]. Of these patients, a new anti-seizure drug had been added within 3 months of remission in 13 cases, a dose had been changed but no anti-seizure drug added in 7 cases, and in 7 cases there was neither a new anti-seizure drug nor dose change during the previous 3 months, suggesting that the state of the disease in these patients improved without any intervention [15]. This is further supported by a matched, prospective study that reported seizure outcomes following anti-seizure drug switching in both seizure-free and non-seizure-free patients with focal epilepsy [16]. Among patients who had not been seizure-free during the previous 6 months, 10/27 (37.0%) patients who switched to a different anti-seizure drug became seizure-free at 6 months compared with 15/27 (55.6%) patients who remained on the same anti-seizure drug [16]. There was no evidence to suggest that changes in drug

therapy led to improvements in seizure control in the non-seizure-free patients, thereby suggesting that improvements in seizure control in some drug-resistant patients may be spontaneous rather than due to therapeutic alterations [16]. Similar results were also observed in an earlier mixed, prospective–retrospective study [17]. Indeed, such fluctuations between seizure freedom and seizure relapse have been observed during long-term follow-up in 1/6 adults with newly diagnosed epilepsy [18]. Nonetheless, the 7 patients who received perampanel monotherapy in the current studies were identified as having highly drug-resistant epilepsy, and it has previously been suggested that the likelihood of achieving seizure freedom decreases once a patient is identified as drug-resistant [15,18]. For example, in a previous study of 1098 untreated patients, 49.5% of patients taking their first anti-seizure drug regimen (all were taking monotherapy) were seizure-free at the time of their last follow-up visit (median follow-up of 7.5 years); however, of those patients taking a second anti-seizure drug regimen ($n = 398$), 36.7% became seizure-free (25.4% were taking monotherapy and 11.3% were taking combination therapy), and of those taking a third anti-seizure drug regimen ($n = 168$) only 24.4% became seizure-free (15.5% were taking monotherapy and 8.9% were taking combination therapy). The probability of seizure freedom continued to decrease with each successive drug regimen [18]. In addition, patients who took perampanel monotherapy for <91 days, or who attempted to withdraw concomitant anti-seizure drugs but failed to do so, were not included. Better-designed studies may be informative in specifically examining perampanel use in this setting, and helping to identify the patient populations most likely to benefit, before any firm conclusions are drawn.

This analysis included a small proportion of patients with highly drug-resistant focal seizures who converted to treatment with perampanel monotherapy during OLEx studies. While these limited data are encouraging in suggesting that perampanel might be useful as a monotherapy, further studies are required to explore outcomes in a less drug-resistant population, where a larger proportion of patients might benefit from monotherapy.

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Submitting author's declaration

I acknowledge that all co-authors have been substantially involved in the study and/or preparation of the manuscript; no undisclosed groups or persons have had a primary role in the study and/or in the manuscript preparation; and all co-authors have seen and approved the submitted version of the paper and accept responsibility for its content.

Disclosure of conflicts of interest

PK, and/or his institution, has received speaker or consultancy fees, and/or research grants, from Eisai, Novartis, and UCB Pharma.

SM has participated in advisory boards and performed consultation for Eisai, UCB Pharma, and Upsher-Smith, and has also been a speaker for GlaxoSmithKline.

AL is an employee of Eisai Inc.

AP is an employee of Eisai Ltd.

KC is a former employee of Eisai Ltd.

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