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Tolerability and safety of perampanel: two randomized dose-escalation studies

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Objectives – To evaluate, for the first time in patients with epilepsy, the tolerability and safety of escalating doses of oral perampanel, a novel, selective, non-competitive AMPA antagonist, as adjunctive therapy for refractory partial-onset seizures. *Materials and methods* – Two consecutive, randomized, double-blind, dose-escalation studies recruited adults (18–70 years) with uncontrolled partial-onset seizures receiving one to three concomitant antiepileptic drugs. In study 206, patients were treated for 12 weeks (8-week dose-titration, 4-week dose-maintenance) with placebo or perampanel (up to 4 mg/day, dosed once- or twice-daily). In study 208, patients received placebo or perampanel once-daily (up to 12 mg) for 16 weeks (12-week titration, 4-week maintenance). *Results* – Overall, 153 patients were randomized into study 206 (perampanel twice-daily, n = 51; perampanel once-daily, n = 51; placebo, n = 51). Study 208 included 48 patients (perampanel once-daily, n = 38; placebo, n = 10). The highest dose in study 206 – 4 mg/day – was well tolerated, with similar proportions of patients tolerating once-daily (82.4%) and twice-daily (82.4%) perampanel and placebo (82.4%) treatments. In study 208 most patients tolerated doses of ≥ 6 mg perampanel once-daily in a Kaplan–Meier analysis. In both studies, the most common adverse events were CNS-related; most were of mild/moderate severity. *Conclusions* – Perampanel was well tolerated across doses of 4–12 mg/day. The studies showed preliminary evidence of efficacy and identified doses to be evaluated in larger clinical studies.

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Introduction

Glutamate is the principal excitatory neurotransmitter in the brain, and the glutamatergic system has been implicated in the pathogenesis of numerous neurological disorders (1). In patients with epilepsy, for example, sustained increases in extracellular glutamate concentrations have been measured in the hippocampus prior to, and during, seizure activity (2). The post-synaptic effects of glutamate are largely mediated by three types of ionotropic receptor, each named after one of its selective agonists: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartic acid (NMDA) (3). Preclinical studies point to an important role for these receptors in the generation and propagation of epileptic seizures. Systemic or intracerebrovascular administration of AMPA elicits robust seizure activity in animal models (4), while expression of amygdala-kindled seizures in mice is critically dependent on AMPA receptor activation (5). Studies in rat neocortical neurons have also established that ionotropic glutamate receptors mediate the paroxysmal depolarization shift (PDS) (6, 7). The PDS is an overt post-synaptic depolarization that can be considered the intracellular correlate of the interictal spike, the simplest identifiable unit of epileptiform activity seen on electroencephalography in humans (8).

The continuing search for new antiepileptic drugs (AEDs) is driven by the need to help the 20–30% of patients for whom current treatments are ineffective and/or associated with intolerable

side effects (9). Perampanel (2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile) is a selective, non-competitive and orally active AMPA-receptor antagonist shown to be effective in various preclinical seizure models (10). Pretreatment with oral perampanel has been shown to increase seizure latency dose-dependently following intracerebroventricular infusion of AMPA to induce clonic seizures (11). In Phase I clinical studies in healthy subjects, perampanel was well tolerated and displayed favorable pharmacologic properties, including good oral bioavailability and a long half-life (approximately 70–100 h) (12).

Here, we present the results of two consecutive Phase IIa dose-escalation studies (study 206 and study 208), performed primarily to evaluate the tolerability and safety of oral perampanel, titrated across a dose range of 2–12 mg/day, as adjunctive therapy in patients with refractory partial-onset seizures. Study 206 explored the tolerability and safety of perampanel titrated up to 4 mg/day, given once-daily (QD) or twice-daily (BID), compared with placebo. Study 208 evaluated the tolerability and safety of gradual titration up to a maximum dose of 12 mg/day (QD dosing). These were Phase IIa dose-finding studies and permitted only a preliminary evaluation of efficacy – study 206 was well controlled, but evaluated low perampanel doses, while study 208 had a small control population and evaluated tolerability of higher doses. Data from these studies played a crucial role in guiding the design of the ongoing Phase III epilepsy trial program for perampanel.

Methods

Patients

Both studies enrolled adults aged 18–70 years with a body weight ≥40 kg and a diagnosis of epilepsy with partial-onset seizures with or without secondary generalization. Eligible patients had uncontrolled partial onset-seizures despite treatment with a minimum of three different AEDs for any duration within the past 2 years. At the time of study entry, patients had to be taking stable doses of one to two AEDs (study 206) or one to three AEDs (study 208) and, during the 2 months before randomization, had to experience a monthly average of ≥4 (study 206) or ≥3 (study 208) partial seizures with or without secondarily generalization, with no 21-day seizure-free period. In study 206, patients must have had three or more documented seizures during the 28-day baseline period prior to randomization in order to be randomized (for detailed inclusion/exclusion criteria, see Table S1).

Patients/legal guardians provided written informed consent. Study protocols were approved by participating centers' institutional review boards or independent ethics committees. The studies were performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice.

Study objectives and designs

Study 206 – Study 206 was a randomized, double-blind, placebo-controlled, dose-escalation, parallel-group Phase II study performed in 43 centers in Australia, Europe and the USA between March 2005 and February 2007 (study code: E2007-A001-206; ClinicalTrials.gov identifier: NCT00144690). The primary objective of the study was to determine whether doses of perampanel up to 4 mg/day were well-tolerated in this patient population and to define the maximum tolerated dose (MTD). Secondary objectives included assessment of perampanel safety and the preliminary evaluation of efficacy.

The study had four phases (Fig. 1A). At the end of the 4-week baseline period, eligible patients were randomized (1:1:1) to placebo, perampanel BID, or perampanel QD. Randomization was stratified according to whether patients used ≥1 concomitant CYP-inducing AED, or non-CYP-inducing AEDs only. Oral perampanel was started at a dose of 1 mg/day (0.5 mg BID/1 mg QD) at the beginning of the 8-week titration phase. Doses were then titrated in 1 mg/day increments every 2 weeks to a maximum of 4 mg/day (2 mg BID/4 mg QD). In the 4-week maintenance phase, patients continued on the final dose achieved during titration. All patients received perampanel 1 mg QD in the final 2-week transition phase.

Study 208 – Study 208 was a randomized, double-blind, placebo-controlled, dose-escalation, parallel-group Phase II study conducted at 17 centers in Australia and Europe between March 2007 and January 2008 (E2007-G000-208; NCT00416195). The primary objective was to determine the tolerability and safety of perampanel (up to 12 mg QD). A preliminary assessment of efficacy was also performed.

At the end of the 4-week baseline period, eligible patients were randomized (3:1) to placebo or perampanel QD (starting dose, 2 mg QD) with randomization stratified by CYP-inducing AED use (Fig. 1B). In the 12-week titration phase, perampanel was titrated by 2 mg/day increments every 2 weeks to a maximum of 12 mg QD.

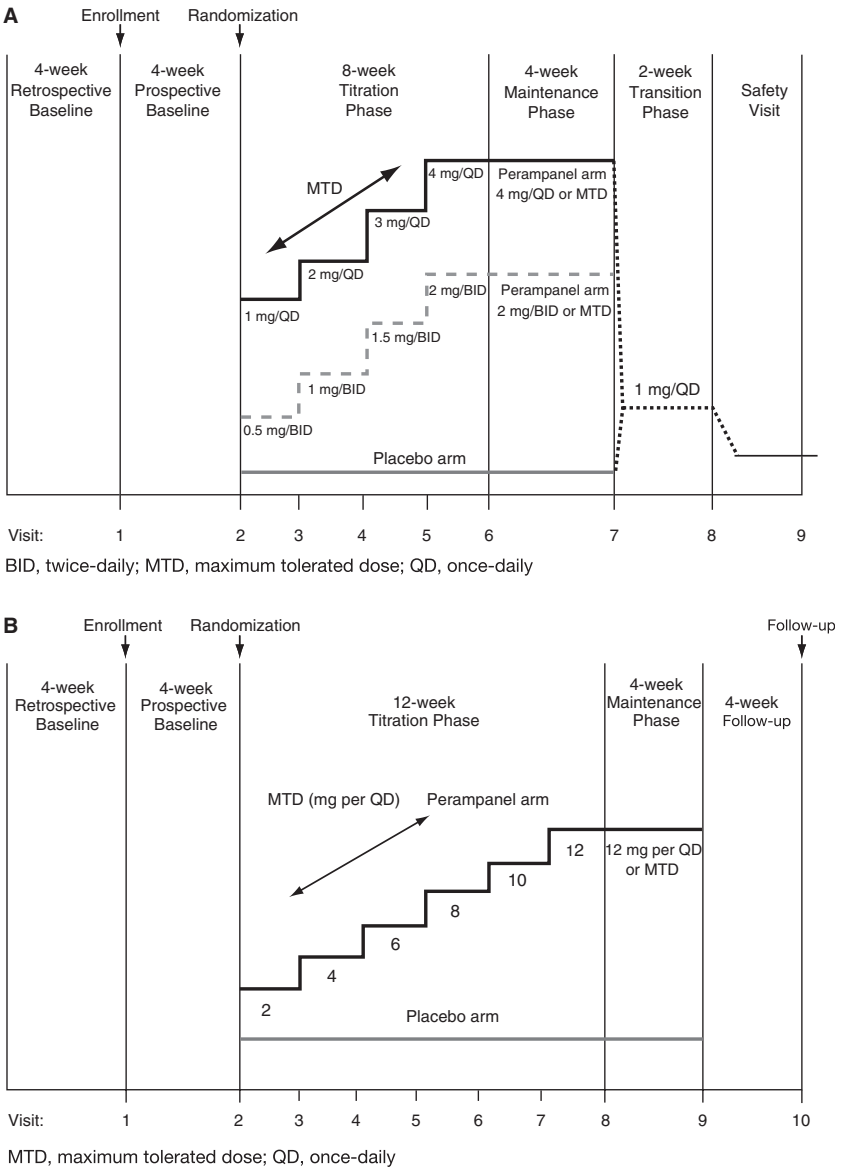


Figure 1. Study designs: (A) study 206 (B) study 208.

Patients continued on the final dose achieved during titration in the 4-week maintenance phase.

Dose-escalation, dosing and seizure-recording procedures – Placebo/perampanel doses were increased according to individual tolerability during the titration phases of both studies. If a patient did not tolerate treatment during titration, the dose could be reduced to the previous level. Patients requiring more than one dose reduction, or those unable to tolerate the lowest tested doses, were withdrawn. No dose reductions were permitted during the maintenance phases. In study 206, patients in the placebo and perampanel BID groups took placebo or perampanel, respectively, in the morning and also in the evening with food; in the perampanel QD group, perampanel was given as the morning dose and placebo as the evening dose. Patients from study 208 took placebo/perampanel in the evening with food. Throughout both studies, patients continued on their current AED regimens, and seizure frequency data were prospectively collected in patient diaries. To aid with determination of patient eligibility for the studies, these data were also collected retrospectively for the 4-week period before each study (Fig. 1).

Study assessments and endpoints

The primary endpoint of both studies was tolerability of perampanel up to the maximum dose evaluated in each study. Tolerability/safety was

assessed by monitoring AE frequency and severity (mild, moderate or severe), serious AE monitoring, physical and neurological examinations, 12-lead ECG, and clinical laboratory evaluations (including hematology, clinical chemistry and urinalysis). Preliminary efficacy endpoints included responder rate, defined as the proportion of patients experiencing a ≥50% reduction in seizure frequency (maintenance vs baseline phases [study 206], or overall treatment phase [titration plus maintenance] vs baseline [study 208]). The percent change in seizure frequency was also assessed (maintenance vs baseline [study 206]; overall treatment phase vs baseline [study 208]). Efficacy was assessed in the intent-to-treat (ITT) study populations (all patients in the safety populations with seizure-frequency data for ≥2 weeks at baseline and ≥1 week post-baseline).

Statistical analyses

The sample size for study 206 was based on anticipated responder rates. A Fisher's exact test (two-sided significance level <0.05) was estimated to provide 80% power to detect a 20% proportional difference between placebo and active treatment. Accounting for a dropout rate of 18%, the estimated required sample size was approximately 144 patients (BID or QD perampanel n = 96; placebo n = 48). Sample size calculations for study 208 were not based on any statistical criteria. In study 206, efficacy data were assessed using a last-observation carried forward method for patients who discontinued before study end. The statistical significance of efficacy assessments was calculated in study 206 only; responder rates and the percent change in seizure frequency were analysed using a Cochran–Mantel–Haenszel test (two-sided significance level <0.05) and ranked analysis of variance, respectively. In study 208, a Kaplan–Meier analysis was used to estimate the proportion of patients tolerating each perampanel dose. For this analysis, a patient was considered not to have tolerated a dose if, at that dose, he/she discontinued the study due to an AE considered possibly or probably drug-related, or was down-titrated to a lower dose.

Results

Patients

In study 206, 153 patients were randomized to placebo (n = 51), perampanel BID (n = 51) or perampanel QD (n = 51). All patients were included in the safety population; one patient (perampanel BID group) provided less than 1 week of post-baseline seizure-frequency data and was excluded from the ITT population. Overall, 138 patients completed study 206 (n = 46, 47 and 45 for placebo, perampanel BID and perampanel QD, respectively). Reasons for study discontinuation were AEs (n = 3, 2 and 4), protocol deviations (n = 1, 1 and 1), investigator request (n = 1, 0 and 0), subject withdrawn consent (n = 0, 1 and 0) and other (n = 0, 0 and 1).

Forty-eight patients were randomized and included in the safety population in study 208 (placebo n = 10; perampanel QD n = 38). One patient (placebo group) was excluded from the ITT population due to an invalid baseline seizure diary. Forty-two patients completed the study (n = 8 and 34 for placebo and perampanel QD, respectively). Discontinuations were due to AEs (n = 1 and 2), protocol violations (n = 1 and 1) or other reasons (n = 0 and 1).

Table 1 shows patient demographics and clinical characteristics at baseline by treatment group for both studies (Table 1). The mean time since onset of epilepsy was 18.0–25.1 years and most patients were treated with two or three concomitant AEDs.

Study 206 results

Dose titration – The highest dose tested in study 206 (4 mg/day) was tolerated by the majority of patients (Table 2). The proportion of patients who reached and tolerated 4 mg/day was the same in the placebo group and both perampanel groups (82.4%).

Tolerability and safety – The proportion of patients who experienced at least one AE was similar with placebo (62.7% [32/51]) and perampanel (BID and QD groups combined: 66.7% [68/102]). The most commonly reported AEs are shown by treatment group in Table 3. In both placebo- and perampanel-treated patients, the maximum severity for the majority of AEs was mild or moderate. The incidence of serious AEs was low, with five serious AEs experienced by four patients (placebo n = 2 [3.9%]; perampanel n = 2 [2.0%]). All serious AEs were considered possibly related to treatment and were associated with seizure activity (status epilepticus: placebo n = 1, perampanel n = 1; mental status changes and post-ictal state: perampanel n = 1; convulsive seizure: placebo n = 1). There were no deaths during the study, and no clinically significant differences between placebo and perampanel in clinical laboratory values, ECG, or any other safety variable. Overall, the dose-titration, tolerability and safety data described above

Table 1 Study 206 and study 208: baseline patient demographics and clinical characteristics (safety populations)

Variable	Study 206			Study 208	
	Placebo (N = 51)	Perampanel BID (N = 51)	Perampanel QD (N = 51)	Placebo (N = 10)	Perampanel QD (N = 38)
Mean age (SD), years	38.1 (11.62)	40.0 (11.38)	42.5 (12.06)	45.5 (12.05)	40.7 (11.99)
Gender, *N* (%)					
Female	28 (54.9)	29 (56.9)	29 (56.9)	5 (50.0)	20 (52.6)
Race, *N* (%)					
Caucasian	43 (84.3)	40 (78.4)	45 (88.2)	10 (100)	38 (100)
Black	3 (5.9)	7 (13.7)	4 (7.8)	0 (0)	0 (0)
Hispanic	3 (5.9)	1 (2.0)	1 (2.0)	0 (0)	0 (0)
Asian/Pacific	1 (2.0)	2 (3.9)	1 (2.0)	0 (0)	0 (0)
Other	1 (2.0)	1 (2.0)	0 (0)	0 (0)	0 (0)
Mean time since onset of epilepsy (SD), years	22.9 (13.69)	25.1 (13.45)	23.0 (12.99)	18.0 (9.27)	22.3 (15.07)
Seizure type at baseline, *N* (%)					
Simple partial	26 (51.0)	23 (45.1)	27 (52.9)	-	-
Simple partial without motor signs	-	-	-	2 (20.0)	5 (13.2)
Simple partial with motor signs	-	-	-	1 (10.0)	7 (18.4)
Complex partial	49 (96.1)	51 (100.0)	48 (94.1)	9 (90.0)	32 (84.2)
Secondarily generalized	30 (58.8)	30 (58.8)	32 (62.7)	10 (100.0)	31 (81.6)
Mean seizure frequency/28 days (SD)	19.6 (25.77)	26.4 (47.60)	16.6 (24.96)	17.3 (14.19)	17.6 (23.53)
No. concomitant AEDs, *N* (%)[a]					
1	9 (17.6)	34 (33.3)		1 (10.0)	1 (2.6)
2	42 (82.4)	67 (65.7)		7 (70.0)	24 (63.2)
3	0 (0)	(0)		2 (20.0)	13 (34.2)
AED classification, *N* (%)[a]					
CYP-inducer	24 (47.1)	45 (44.6)		3 (30)	19 (50)
Non-inducer	27 (52.9)	56 (55.4)		7 (70)	19 (50)

AED, antiepileptic drug; BID, twice-daily; CYP, cytochrome P450; QD, once-daily; SD, standard deviation.
[a]Data combined for BID and QD perampanel groups (N = 101).

Table 2 Study 206: dose-escalation (safety population)

Dose (mg/day)	Patients, *N* (%)		
	Placebo (N = 51)	Perampanel BID (N = 51)	Perampanel QD (N = 51)
1	3 (5.9)	4 (7.8)	1 (2.0)
2	1 (2.0)	2 (3.9)	3 (5.9)
3	4 (7.8)	2 (3.9)	3 (5.9)
4	42 (82.4)	42 (82.4)	42 (82.4)
NA*	1 (2.0)	1 (2.0)	2 (3.9)

Data show the maximum dose patients received for at least 2 weeks without dose reduction/treatment discontinuation. *Patients in this category did not receive the 2 weeks of dosing required to be included in the analysis. BID, twice-daily; NA, not applicable; QD, once-daily.

Table 3 Study 206: adverse events occurring in ≥5% of all patients (safety population)

Adverse event	Patients, *N* (%)			
	Placebo (N = 51)	Perampanel BID (N = 51)	Perampanel QD (N = 51)	Total (N = 102)
Dizziness	8 (15.7)	5 (9.8)	9 (17.6)	14 (13.7)
Headache	7 (13.7)	3 (5.9)	7 (13.7)	10 (9.8)
Somnolence	5 (9.8)	5 (9.8)	3 (5.9)	8 (7.8)
Contusion	2 (3.9)	3 (5.9)	4 (7.8)	7 (6.9)
Fatigue	3 (5.9)	3 (5.9)	3 (5.9)	6 (5.9)
Nausea	7 (13.7)	2 (3.9)	0 (0)	2 (2.0)
Nasopharyngitis	6 (11.8)	1 (2.0)	1 (2.0)	2 (2.0)

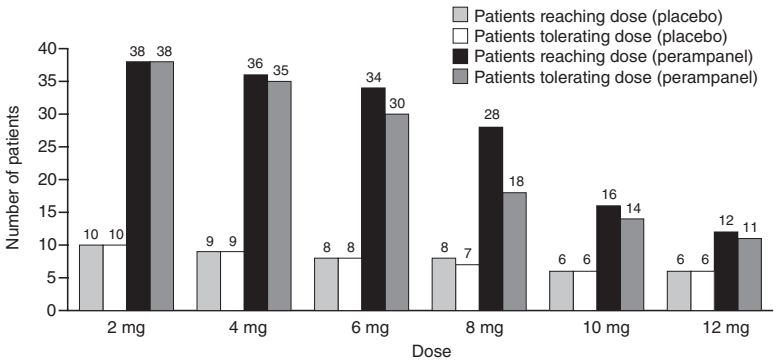
BID, twice-daily; QD, once-daily.

showed that the majority of patients tolerated 4 mg/day and the MTD of perampanel was not reached.

Preliminary efficacy – The responder rate in study 206 (maximum dose 4 mg/day) was 30.7% (31/101) with perampanel and 21.6% (11/51) with placebo (P = 0.19). In the BID and QD perampanel groups, the responder rate was 28.0% (14/50) and 33% (17/51), respectively. The median reduction in seizure frequency was 25.7% in all perampanel-treated patients and 19.5% in the placebo group (P = 0.43).

Study 208

Dose-titration – As the perampanel MTD was not reached in study 206, higher doses were investigated in study 208. Figure 2 shows the number of patients reaching and remaining on each dose



	Estimated proportion of patients tolerating dose (95% CI)*					
Placebo	1.00 (1.000, 1.000)	1.00 (1.000, 1.000)	1.00 (1.000, 1.000)	0.88 (0.387, 0.981)	0.88 (0.387, 0.981)	0.88 (0.387, 0.981)
Perampanel	1.00 (1.000, 1.000)	0.97 (0.819, 0.996)	0.86 (0.692, 0.938)	0.55 (0.369, 0.701)	0.48 (0.304, 0.641)	0.44 (0.265, 0.606)

CI, confidence interval
*Estimated (cumulative) probabilities from Kaplan-Meier analysis considering discontinuation due to a study drug-related adverse event or down-titration to a lower dose (after 2 mg) for any reason as events leading to non-tolerability, all other events were censored (allows for patients who did not reach their maximum tolerated dose).

Figure 2. Study 208 dose-escalation (safety population): number of patients tolerating each dose and Kaplan–Meier estimated probabilities of patients tolerating each dose. CI, confidence interval *Estimated (cumulative) probabilities from Kaplan -Meier analysis considering discontinuation due to a study drug-related adverse event or down-titration to a lower dose (after 2 mg) for any reason as events leading to non-tolerability, all other events were censored (allows for patients who did not reach their maximum tolerated dose).

during titration and maintenance treatment in this second study. Twelve (32%) perampanel-treated patients reached the highest tested dose (12 mg QD), with 11 of these patients remaining on this dose thereafter. In the placebo group, six (60%) patients reached the highest dose level; all six patients remained on this dose. The estimated cumulative probabilities for patients tolerating each perampanel dose, as estimated by the Kaplan–Meier analysis, are shown in the table beneath Fig. 2. The three highest doses of perampanel (8, 10 and 12 mg QD) were tolerated by substantial proportions of patients (Kaplan–Meier probabilities of 0.55, 0.48 and 0.44, respectively).

Table 4 Study 208: adverse events occurring in ≥10% of patients in the perampanel group (safety population)

	Patients, *N* (%)			
		Perampanel QD		
Adverse event	Placebo (N = 10)	All doses (N = 38)	≤6 mg* (N = 38)	>6 mg* (N = 28)
Dizziness	1 (10.0)	22 (57.9)	16 (42.1)	12 (42.9)
Somnolence	0 (0)	12 (31.6)	8 (21.1)	6 (21.4)
Headache	1 (10.0)	7 (18.4)	4 (10.5)	4 (14.3)
Fatigue	2 (20.0)	4 (10.5)	2 (5.3)	2 (7.1)
Diarrhea	1 (10.0)	4 (10.5)	4 (10.5)	1 (3.6)
Rhinitis	0	4 (10.5)	4 (10.5)	0 (0)

QD, once-daily. *Only data for AEs occurring in ≥10% of all perampanel-treated patients are shown.

Tolerability and safety – Similar proportions of placebo- and perampanel-treated patients experienced one or more AE (8/10 [80.0%] and 32/38 [84.2%], respectively). Table 4 shows data for the most common AEs in the perampanel group. Data for these AEs are also shown grouped by perampanel dose (≤6 mg vs >6 mg QD). AEs that were considered related to treatment and were only observed at perampanel doses >6 mg QD were nausea, gait disturbance, dysarthria and insomnia. The majority of AEs in study 208 were mild to moderate. Three patients in the perampanel group experienced severe drug-related dizziness; no severe AEs were reported in the placebo group. Serious AEs occurred in 1/10 (10%) and 1/38 (2.6%) of placebo- and perampanel-treated patients, respectively; no serious AEs were considered related to treatment. There were no deaths. No differences between placebo and perampanel were revealed in the other safety assessments.

Preliminary efficacy – In study 208, responder rates in the overall treatment phase were 22.2% (2/9) and 39.5% (15/38) in the placebo and perampanel groups, respectively. The median reduction in seizure frequency with perampanel was 39.6%; a median increase of 2.1% was observed in the placebo group.

Discussion

These two multicenter Phase IIa studies showed that the selective, non-competitive AMPA-receptor

antagonist perampanel is well tolerated as adjunctive therapy in adult patients with refractory partial-onset seizures. Study 206 – a large, well controlled, dose-escalation study – showed that the MTD of perampanel is higher than 4 mg/day, the maximum dose tested, in this study population. Tolerability profiles were broadly comparable in placebo- and perampanel-treated patients participating in study 206, with dizziness, headache and somnolence among the most common AEs. Identical proportions of placebo- and perampanel-treated patients (82%) tolerated the highest tested dose (4 mg/day) and there were no differences in the ability of patients to tolerate BID and QD perampanel dosing regimens. Dose selection for study 206 was based in part on data from preclinical and Phase I clinical studies (Eisai, data on file). The results of this study, however, suggest that doses of perampanel above 4 mg/day might be tolerable in patients with refractory partial-onset seizures.

Since most patients tolerated 4 mg/day, study 208 explored higher doses (up to 12 mg/day). Most patients were able to tolerate perampanel doses of 6 mg QD or above in this dose-escalation study, with Kaplan–Meier analyses providing a probability estimate that 44% of patients tolerated the highest tested dose (12 mg QD). The small sample size in study 208, however, was reflected in the wide confidence intervals associated with the estimates of tolerability (Fig. 2) and these data should therefore be explored in larger populations. As observed in the first study, most AEs in study 208 were common CNS-related symptoms found with other AED therapies and may be partially related to concomitant AED dosing (13, 14).

Preliminary evidence of perampanel efficacy was observed in both studies, even though studies 206 and 208 employed low doses and a small sample size, respectively. In study 206, responder rate and seizure frequency data favored perampanel over placebo, but these differences did not reach statistical significance. Responder rate trends observed in study 206 were similar to those reported for lower doses of some current AEDs (15, 16). The primary endpoint of this study was tolerability of perampanel at doses up to 4 mg/day. The study did not reach MTD, suggesting that the trend towards efficacy compared to placebo treatment required evaluation at higher doses. Indeed, treatment-group differences in efficacy endpoints were more marked in study 208, which investigated higher doses of perampanel. However, no assessment of the statistical significance of efficacy endpoints was possible in this dose-escalation study due to the small numbers of patients in each group.

Reductions in the frequency of partial-onset seizures have also been observed in a preliminary study with talampanel, another non-competitive AMPA receptor antagonist, which is structurally unrelated to perampanel (17). These results, however, were not explored in larger controlled studies. The preliminary anti-seizure effects of perampanel and the tolerability results observed in the current studies provided justification for more rigorous evaluations of efficacy in Phase III studies.

These two studies provide tolerability findings which, together with population pharmacokinetic/pharmacodynamic analyses of data from the studies (18), provide possible dosing ranges and a titration schedule for testing perampanel in larger trials. The studies showed that the highest tolerable dose of perampanel in this patient population was considerably higher than that originally hypothesized, and that use of flexible titration schedules for perampanel is feasible with no initial evidence of safety problems in the small groups treated. These Phase IIa studies show preliminary evidence of safety and tolerability of a novel selective AMPA antagonist and, despite not being powered to provide definite conclusions on efficacy, support Phase III evaluation of perampanel in larger groups of patients. A preliminary signal of efficacy at a low dose (study 206) and primary safety of higher doses (study 208) led to the start of Phase III studies with doses up to 12 mg/day. The efficacy and safety of perampanel at doses up to 12 mg QD are being investigated in the global Phase III trial program, EXPLORE (*Ex*amining *P*erampane*l* *O*bservations from *R*esearch *E*xperience). These studies will determine whether AMPA receptor modulation is a feasible therapeutic approach for treating drug-resistant epilepsy.

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Conflict of interest and sources of funding statement

G. Krauss is a study investigator and consultant for Eisai. V. Biton is a study investigator for Eisai. M. Bar, J. Klapper, I. Rektor and N. Vaiciene-Magistris have no disclosures to report. D. Squillacote and D. Kumar are salaried employees of Eisai.

Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1. Inclusion and exclusion criteria

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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