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FULL-LENGTH ORIGINAL RESEARCH

Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analysis of three phase III studies

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Summary

Purpose: Three phase III studies (304 [ClinicalTrials.gov identifier: NCT00699972], 305 [NCT00699582], 306 [NCT00700310]) evaluated perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, as adjunctive therapy for refractory partial seizures. We report post hoc analyses of pooled study data by randomized dose.

Methods: Patients with partial seizures despite receiving 1–3 antiepileptic drugs were randomized to once-daily placebo, perampanel 8 or 12 mg (studies 304, 305), or placebo, perampanel 2, 4, or 8 mg (study 306). Studies included a 6-week baseline period and double-blind treatment phase (6-week titration; 13-week maintenance). Primary end points were median change in partial seizure frequency (baseline vs. double-blind phase) and percentage of patients achieving ≥50% reduction in seizure frequency (baseline vs. maintenance). Here, these end points, together with secondary, exploratory, and safety end points, were assessed using pooled study data.

Key Findings: The pooled intent-to-treat analysis set (randomized, treated patients with any seizure data) included 1,478 patients. Median changes in partial seizure frequency were greater with perampanel than placebo (perampanel 4 mg, −23.3%; 8 mg, −28.8%; 12 mg, −27.2%; placebo, −12.8%; $p < 0.01$, each dose vs. placebo), as were 50% responder rates (perampanel 4 mg, 28.5%; 8 mg, 35.3%; 12 mg, 35.0%; placebo, 19.3%; $p < 0.05$, each dose vs. placebo). In addition, median changes in complex partial plus secondary generalized seizure frequency were also greater with perampanel than placebo (perampanel 4 mg, −31.2%; 8 mg, −35.6%; 12 mg, −28.6%; placebo, −13.9%). Perampanel was generally well tolerated. The most frequent treatment-emergent adverse events (TEAEs) were dizziness, somnolence, and headache. Most TEAEs were mild/moderate; relatively few patients experienced severe TEAEs (placebo, 5.4%; perampanel, 8.9%) or serious TEAEs (placebo, 5.0%; perampanel, 5.5%). There were no deaths and no clinically important mean changes in laboratory values, electrocardiography (ECG) findings, or vital signs.

Significance: Perampanel reduced partial seizure frequency and improved responder rates compared with placebo, with an acceptable tolerability profile.

KEY WORDS: Antiepileptic drugs, Epilepsy, Glutamate, Perampanel, Pooled analysis.

Approximately 20–40% of patients with epilepsy are, or become, refractory to treatment, potentially resulting in impaired quality of life and an increased risk of injury or unexpected sudden death (French, 2007; Brodie, 2010). Consequently, there is a rationale for continued efforts to improve outcomes through the investigation of antiepileptic drugs (AEDs) with novel mechanisms of action. One such agent is perampanel, an orally active antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Hanada et al., 2011), which are required for the transduction of glutamate-mediated postsynaptic signaling in the brain (Rogawski, 2011). Perampanel was recently approved as an adjunctive treatment for partial seizures with or without secondary generalization, in patients aged ≥12 years, in both the European Union (EU) (European Medicines Agency, 2012) and the United States (Food & Drug Administration, 2012).

Preclinical studies indicated that perampanel binds to AMPA receptors at a noncompetitive site with high selectivity (Hanada et al., 2011; Ceolin et al., 2012). Therapeutic proof of concept was established in two phase II placebo-controlled, dose-escalation studies in patients with

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uncontrolled partial seizures (Fuseau et al., 2011; Krauss et al., 2012a). Pharmacokinetic and pharmacodynamic data from these studies were analyzed to predict the no-effect dose (2 mg), and minimum, middle, and high effective doses (4, 8, and 12 mg, respectively) of perampanel, for evaluation in phase III studies.

The phase III clinical program included three multinational, double-blind, placebo-controlled studies of adjunctive perampanel (2–12 mg) in adolescents and adults with uncontrolled partial seizures despite receiving 1–3 AEDs: studies 304 (perampanel 8 or 12 mg; ClinicalTrials.gov identifier NCT00699972; French et al., 2012), 305 (perampanel 8 or 12 mg; NCT00699582; French et al., 2013), and 306 (perampanel 2, 4, or 8 mg; NCT00700310; Krauss et al., 2012c). In these studies, the no-effect dose of perampanel (2 mg) provided similar outcomes to placebo, whereas the predicted effective doses (4–12 mg) were generally well tolerated and associated with reductions in seizure frequency.

Herein we report post hoc analyses of pooled efficacy and safety data from studies 304, 305, and 306 according to randomized dose.

Methods

Overall program

The designs of studies 304, 305, and 306 have been reported previously (French et al., 2012; Krauss et al., 2012c; French et al., 2013). The studies were conducted between April 2008 and January 2011, with patients enrolled from >40 countries in five continents. In brief, patients aged $\geq$12 years, experiencing partial seizures despite receiving 1–3 AEDs, were randomized to receive once-daily placebo, perampanel 8 or 12 mg (studies 304 and 305), or placebo, perampanel 2, 4, or 8 mg (study 306). Patients were permitted only one concomitant inducer AED, defined as carbamazepine, phenytoin, phenobarbital, or primidone. All studies included a 6-week baseline period and a double-blind treatment phase (6-week titration; 13-week maintenance period). Patients used daily diaries to record partial seizures and their types (simple partial seizures with/without motor signs, complex partial [CP] seizures, and partial seizures with secondary generalization [SG seizures]).

In all three studies, the primary end point for the intent-to-treat (ITT) analysis set (all randomized and treated patients with any seizure data) was median percentage change in the frequency of all partial seizures per 28 days (baseline vs. double-blind phase). For EU registration, the primary end point was the percentage of patients achieving a 50% reduction in the frequency of all partial seizures per 28 days (50% responder rate; baseline vs. maintenance). The median percentage changes in the frequencies of CP plus SG (CP + SG) seizures and SG seizures only (baseline vs. double-blind phase) were also assessed as secondary and exploratory end points, respectively. Other exploratory end points included 50% responder rates for CP + SG and SG seizures (baseline vs. maintenance); 75% responder rates for all partial seizures (baseline vs. maintenance); seizure-freedom rates for all partial seizures (percentage of patients with no seizures during the entire maintenance period); and the proportion of patients with a >50% increase in seizure frequency (baseline vs. maintenance).

Safety data were obtained from physical examinations, neurologic examinations, vital-sign measurements, electrocardiography (ECG) measurements, clinical laboratory tests, and telephone interviews. Any adverse events that were new or worsened during the double-blind treatment phases were recorded as treatment-emergent adverse events (TEAEs), and were classified according to the Medical Dictionary for Regulatory Activities (MedDRA; version 13.0 [studies 304 and 306] or 13.5 [study 305]).

All studies were performed in accordance with the Declaration of Helsinki, Good Clinical Practice ICH-E6 Guideline CPMP/ICH/135/95, European Clinical Trial Directive 2001/20/EC, and the U.S. Code of Federal Regulations Part 21. Trial protocols, amendments, and informed consent were reviewed by national regulatory authorities in each country and independent ethics committees or institutional review boards for each site. All patients gave written informed consent before participation.

Pooled analysis

For the current analyses, efficacy end points were evaluated using data from the ITT analysis sets of studies 304, 305, and 306, pooled according to randomized treatment: placebo or perampanel 2, 4, 8, or 12 mg. The impact of the four most commonly coadministered AEDs on seizure frequency and 50% responder rates was also assessed. Data are primarily reported for the effective doses of 4–12 mg. Outcomes and statistical significance were similar regardless of whether all three studies were pooled or only studies assessing the same dose range were pooled (i.e. study 306 only [perampanel 2, 4, or 8 mg], or studies 304 and 305 combined [perampanel 8 or 12 mg]).

Analyses of changes in seizure frequency and responder rates were conducted using the ITT analysis set with last observation carried forward (LOCF). Seizure-freedom rates reported the numbers of patients who were seizure-free during the complete maintenance period, either as a percentage of the population that completed the maintenance period or a percentage of the ITT analysis set: both approaches were used due to suggestions that completer analyses may overestimate seizure-freedom rates, as dropouts are not accounted for (Gazzola et al., 2007).

For analyses of change in seizure frequency, the baseline seizure frequency per 28 days and the percentage change during treatment were rank-transformed separately prior to regression analysis due to the skewed distribution of the seizure frequency data. An analysis of covariance was then conducted on the rank-transformed data with treatment as a

Table 1. Baseline patient demographics and clinical characteristics (safety analysis set)

	Placebo (n = 442)	Perampanel 2 mg (n = 180)	Perampanel 4 mg (n = 172)	Perampanel 8 mg (n = 431)	Perampanel 12 mg (n = 255)
ITT analysis set, n (%)	441 (99.8)	180 (100.0)	172 (100.0)	431 (100.0)	254 (99.6)
Completed, n (%)	392 (88.7)	154 (85.6)	158 (91.9)	367 (85.2)	193 (75.7)
Mean age (SD), years	34.3 (13.5)	33.8 (13.6)	33.6 (12.2)	35.6 (13.7)	36.1 (14.4)
Female, n (%)	222 (50.2)	95 (52.8)	84 (48.8)	224 (52.0)	136 (53.3)
Mean BMI (SD), kg/m^2	25.0 (5.4)	23.5 (4.6)	24.5 (4.7)	25.2 (5.5)	26.0 (6.1)
Mean time since epilepsy diagnosis (SD), years	21.0 (12.4)	19.7 (12.2)	20.0 (12.2)	22.1 (13.1)	22.6 (13.9)
Seizure type, n (%)					
Simple partial seizures, with/without motor signs	210 (47.5)	85 (47.2)	80 (46.5)	228 (52.9)	126 (49.4)
CP seizures	376 (85.1)	153 (85.0)	147 (85.5)	368 (85.4)	222 (87.1)
SG seizures	318 (71.9)	115 (63.9)	119 (69.2)	298 (69.1)	178 (69.8)
Seizure frequency per 28 days during the prerandomization phase, median (min, max)[a]					
All partial seizures	11.1 (3.3, 569.1)	10.1 (3.2, 429.6)	10.0 (2.9, 4503.9)	12.2 (2.4, 1030.8)	13.0 (1.4, 1083.1)
CP + SG seizures	7.8 (0.6, 569.1)	6.8 (0.7, 429.6)	7.5 (0.6, 303.9)	8.0 (0.7, 576.3)	9.8 (0.7, 598.4)
SG seizures	3.7 (0.6, 169.4)	3.4 (0.7, 31.4)	3.7 (0.7, 104.5)	3.4 (0.6, 158.7)	4.1 (0.6, 138.6)
No. of concomitant AEDs at baseline, n (%)					
1	60 (13.6)	30 (16.7)	19 (11.0)	69 (16.0)[b]	28 (11.0)
2	218 (49.3)	80 (44.4)	88 (51.2)	220 (51.0)[b]	145 (56.9)
3	164 (37.1)	70 (38.9)	65 (37.8)	141 (32.7)[b]	82 (32.2)
Received one or more of the four most common concomitant AEDs, n (%)					
Carbamazepine (inducer)	143 (32.4)	58 (32.2)	56 (32.6)	138 (32.0)	96 (37.6)
Valproic acid	140 (31.7)	80 (44.4)	75 (43.6)	120 (27.8)	63 (24.7)
Lamotrigine	125 (28.3)	56 (31.1)	68 (39.5)	146 (33.9)	63 (24.7)
Levetiracetam	125 (28.3)	48 (26.7)	45 (26.2)	130 (30.2)	87 (34.1)

AED, antiepileptic drug; BMI, body mass index; CP, complex partial; CP + SG, complex partial plus secondary generalized; ITT, intent-to-treat; SD, standard deviation; SG, secondarily generalized.
[a]Data shown for the ITT analysis set.
[b]AED information was not available for one patient in the 8 mg group.

factor and the ranked baseline seizure frequency per 28 days as a covariate. Hodges-Lehmann 95% confidence intervals (CIs) were constructed for median difference in percentage changes in seizure frequency. Responder rates were analyzed over the maintenance period (LOCF) using the chi-square test. Nominal p-values are reported to highlight effects of interest.

Results

Patient allocation and demographics

Overall, 1,480 patients were randomized and treated (safety analysis set). Of these, 143 were <18 years of age. No meaningful demographic differences were observed between groups (Table 1). Most patients were receiving two or more concomitant AEDs at baseline (one, n = 206, 13.9%; two, n = 751, 50.7%; three, n = 522, 35.3%), the most common being carbamazepine (n = 491, 33.2%), valproic acid (n = 478, 32.3%), lamotrigine (n = 458, 30.9%), and levetiracetam (n = 435, 29.4%). Concomitant valproic acid was more frequently administered in patients randomized to perampanel 2 mg (n = 80; 44.4%) or 4 mg (n = 75; 43.6%) than in those randomized to perampanel 8 mg (n = 120; 27.8%) or 12 mg (n = 63; 24.7%). This reflects the fact that a higher percentage of patients in study 306 (the only one of the three studies with perampanel 2 and 4 mg dose groups) were taking valproic acid than in studies 304 or 305. The median pre-randomization frequency of all partial seizures per 28 days was similar in the placebo (11.1) and perampanel (10.0–13.0) groups (Table 1).

The ITT analysis set included 1,478 patients from studies 304 (n = 387), 305 (n = 386), and 306 (n = 705). Of these, 178 (12.0%) had received prior epilepsy surgery and 93 (6.3%) had used vagus nerve stimulation.

Protocol-prespecified primary and secondary efficacy end points

Median percentage changes in the frequency of all partial seizures between baseline and the double-blind phase were greater with perampanel 4 mg (−23.3%), 8 mg (−28.8%), and 12 mg (−27.2%) than placebo (−12.8%; $p < 0.01$, each dose vs. placebo; Fig. 1). Median (95% CI) differences from placebo were −12.2% (−20.1 to −4.6), −17.9% (−24.1 to −11.8), and −15.8% (−23.0 to −8.7) for perampanel 4, 8, and 12 mg, respectively.

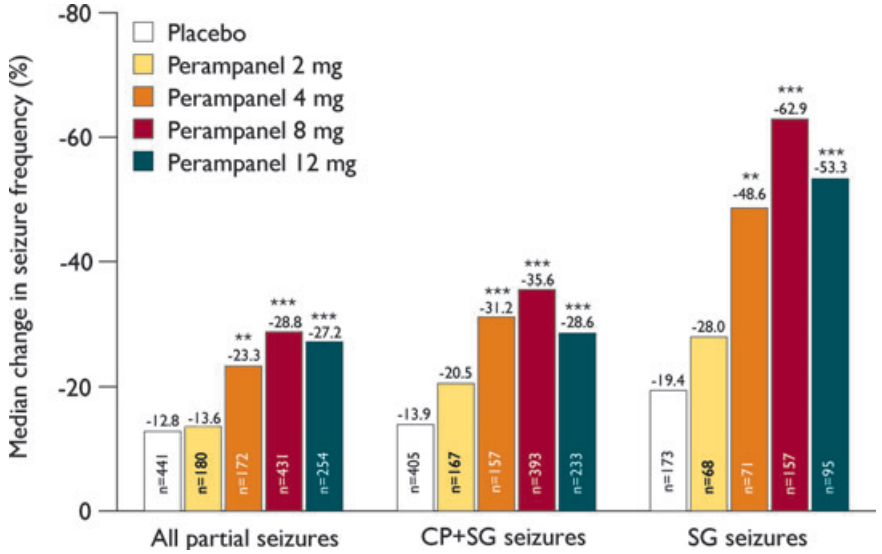

Figure 1.
Median percentage changes in the frequencies of all partial seizures, CP + SG seizures, and SG seizures only, between baseline and double-blind treatment phase (ITT analysis set). **p < 0.01; ***p < 0.001 versus placebo. CP + SG, complex partial plus secondary generalized; ITT, intent-to-treat; SG, secondarily generalized.
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For all partial seizures, 50% responder rates were greater with perampanel 4 mg (28.5%), 8 mg (35.3%), and 12 mg (35.0%) than placebo (19.3%; $p < 0.05$, each dose vs. placebo; Fig. 2).

Perampanel 4–12 mg was also associated with greater median reductions in the frequency of CP + SG seizures compared with placebo (Fig. 1).

Protocol-prespecified exploratory end points

Median percentage changes in the frequency of SG seizures between baseline and the double-blind phase were greater with perampanel 4 mg (−48.6%), 8 mg (−62.9%), and 12 mg (−53.3%) than placebo (−19.4%; $p < 0.01$, each dose vs. placebo; Fig. 1).

As for all partial seizures, 50% responder rates for CP + SG seizures and SG seizures alone were greater with perampanel 4–12 mg than placebo ($p < 0.05$ in all cases, except for the responder rate for SG seizures with perampanel 4 mg vs. placebo; Fig. 2). In addition, 75% responder rates for all partial seizures were greater with perampanel 4–12 mg than placebo ($p < 0.05$, 4 mg vs. placebo; $p < 0.001$, 8–12 mg vs. placebo; Fig. 3).

In patients who completed the maintenance period (n = 1,264), seizure-freedom rates during the maintenance period were greater with perampanel 4 mg (4.4%), 8 mg (3.5%), and 12 mg (4.1%) than placebo (1.0%; $p < 0.05$, each dose vs. placebo; seizure-freedom rate of 1.9% achieved with perampanel 2 mg [$p > 0.05$ vs. placebo]). Similar data were obtained in an analysis of the entire ITT analysis set, in which drop-outs were considered as nonresponders (n = 1,358; perampanel 4 mg 4.3%, 8 mg 3.3%, 12 mg 3.7%; placebo 1.0%; $p < 0.05$, each dose vs. placebo; seizure-freedom rate of 1.8% achieved with perampanel 2 mg [$p > 0.05$ vs. placebo]).

The proportion of patients in the ITT analysis set with a >50% increase in seizure frequency per 28 days was similar with perampanel (2 mg 10.6%; 4 mg 7.6%; 8 mg 8.4%; 12 mg 9.1%) and placebo (12.9%).

Impact of concomitant AEDs

Patients included in this subanalysis were receiving one or more of the four most commonly coadministered AEDs (carbamazepine, valproic acid, lamotrigine, and levetiracetam), alone or in combination with other AEDs. In subgroups of patients receiving each of these four AEDs, perampanel consistently provided greater reductions in seizure frequency and greater 50% responder rates than placebo for all partial seizures, CP + SG seizures, and SG seizures (statistical significance not evaluated; Tables 2 and 3). However, efficacy was lower when the inducer carbamazepine was coadministered compared with any of the other three noninducer AEDs (median percentage change in the frequency of all partial seizures with perampanel 12 mg and concomitant carbamazepine, −20.3%; valproic acid, −37.2%; lamotrigine, −31.2%; levetiracetam, −34.7%; 50% responder rates for all partial seizures with perampanel 12 mg and concomitant carbamazepine, 31.3%; valproic acid, 36.5%; lamotrigine, 30.6%; levetiracetam, 43.0%).

Safety

TEAEs occurred in 294 patients (66.5%) receiving placebo and 799 (77.0%) receiving perampanel (any dose). The majority were mild to moderate in intensity, with relatively few patients experiencing severe TEAEs (placebo 24 patients [5.4%]; perampanel 92 patients [8.9%]). The most frequently reported TEAEs were dizziness, somnolence, and headache (Table 4).

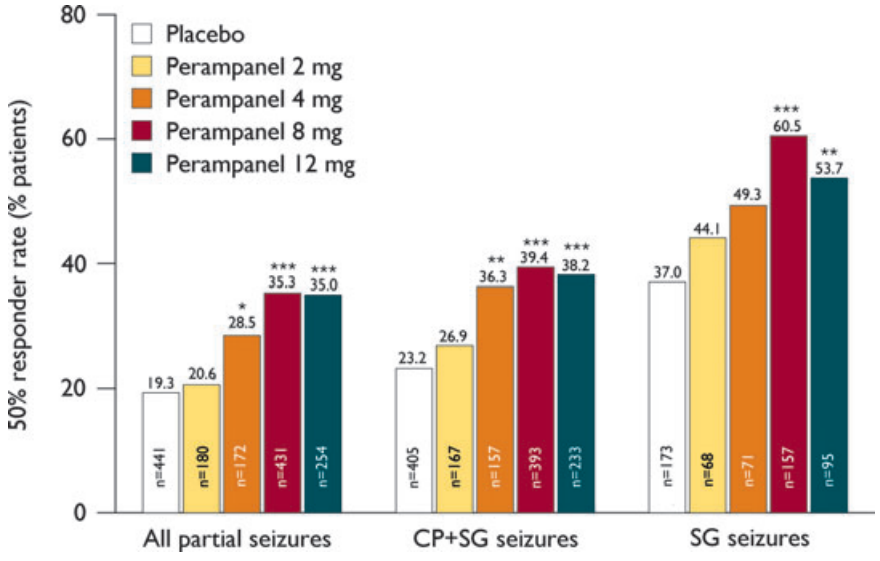

Figure 2.
Fifty percent responder rates for all partial seizures, CP + SG seizures, and SG seizures only (ITT analysis set). *p < 0.05; **p < 0.01; ***p < 0.001 versus placebo. CP + SG, complex partial plus secondary generalized; ITT, intent-to-treat; SG, secondarily generalized.
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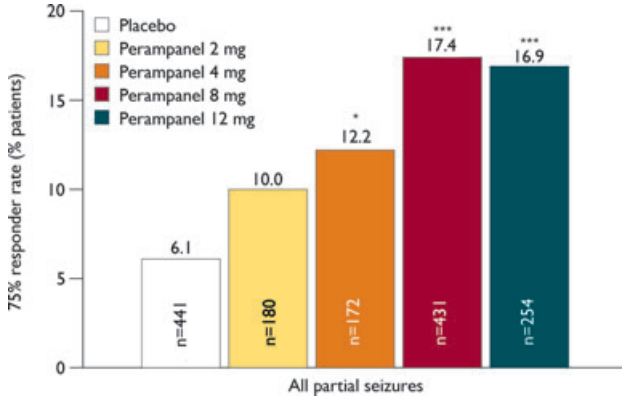

Figure 3.
Seventy-five percent responder rates for all partial seizures (ITT analysis set). *p < 0.05; ***p < 0.001 versus placebo. ITT, intent-to-treat.
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Although there were no deaths, other serious TEAEs were reported by 22 patients (5.0%) receiving placebo and 57 (5.5%) receiving perampanel at any dose (2 mg, n = 6 [3.3%]; 4 mg, n = 6 [3.5%]; 8 mg, n = 24 [5.6%]; 12 mg, n = 21 [8.2%]). One serious fall occurred in a patient treated with perampanel 12 mg. Serious cases of blood disorders, hepatobiliary disorders, and renal/urinary disorders have been observed with other AEDs, but were relatively rare in this pooled population: kidney stones (perampanel 2 mg, n = 1), gallstones (perampanel 4 mg, n = 1; perampanel 8 mg, n = 1), hemorrhagic cystitis (perampanel 12 mg, n = 1), urinary incontinence (perampanel 12 mg, n = 1), and thrombocytopenia (placebo, n = 1).

Serious psychiatric TEAEs were reported in four patients (0.9%) receiving placebo and 12 (1.2%) receiving perampanel, the most common being aggression (n = 3: one patient receiving perampanel 2 mg, two receiving perampanel 12 mg [no patients receiving placebo]). One serious case of suicidal ideation was reported in a patient treated with perampanel 8 mg.

TEAEs necessitated withdrawal of perampanel in 99 patients (9.5%; 2 mg, n = 12 [6.7%]; 4 mg, n = 5 [2.9%]; 8 mg, n = 33 [7.7%]; 12 mg, n = 49 [19.2%]) and placebo in 21 patients (4.8%). The TEAEs most frequently necessitating treatment withdrawal were dizziness (perampanel 2 mg, n = 1 [0.6%]; 4 mg, n = 1 [0.6%]; 8 mg, n = 9 [2.1%]; 12 mg, n = 11 [4.3%]; placebo, n = 4 [0.9%]), convulsion (perampanel 2 mg, n = 2 [1.1%]; 4 mg, n = 1 [0.6%]; 8 mg, n = 4 [0.9%]; 12 mg, n = 3 [1.2%]; placebo, n = 5 [1.1%]), and somnolence (perampanel 2 mg, n = 1 [0.6%]; 4 mg, n = 0 [0.0%]; 8 mg, n = 2 [0.5%]; 12 mg, n = 7 [2.7%]; placebo, n = 1 [0.2%]).

A further analysis of TEAEs was done using a broad and narrow MedDRA Standardized Medical Query (SMQ) for events suggestive of hostility/aggression. Events within this SMQ were reported as follows: 5%, 12%, and 20% with perampanel 4, 8, and 12 mg, respectively, versus 6% with placebo. The most common events within this SMQ were irritability (4 mg, 4%; 8 mg, 7%; 12 mg, 12%; vs. placebo, 3%) and aggression (4 mg, 1%; 8 mg, 2%; 12 mg, 3%; vs. placebo, 1%).

Adverse drug reactions occurring in $\geq$5% of patients receiving perampanel 4–12 mg were dizziness (16%, 32%, and 43% for 4, 8, and 12 mg, respectively, vs. 9% for placebo), somnolence (9%, 16%, and 18% vs. 7%), fatigue (8%, 8%, and 12% vs. 5%), irritability (4%, 7%, and 12% vs. 3%), nausea (3%, 6%, and 8% vs. 5%), and falls (2%, 5%, and 10% vs. 3%).

There were no clinically important mean changes in laboratory values, ECG results, or vital signs. Weight increase

Table 2. Median percentage changes in seizure frequency per 28 days (baseline vs. double-blind treatment phase), by seizure type and concomitant AEDs[a] (intent-to-treat analysis set)

	Median percentage change in seizure frequency per 28 days, % (no. of patients evaluated)				
	Placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg	Perampanel 12 mg
All partial seizures					
Concomitant carbamazepine	−12.7 (143)	−5.9 (58)	−19.7 (56)	−25.4 (138)	−20.3 (96)
Concomitant valproic acid	−17.2 (140)	−16.0 (80)	−26.2 (75)	−27.7 (120)	−37.2 (63)
Concomitant lamotrigine	−11.4 (125)	−21.3 (56)	−20.6 (68)	−29.6 (146)	−31.2 (62)
Concomitant levetiracetam	−18.2 (125)	−10.2 (48)	−19.0 (45)	−25.7 (131)	−34.7 (86)
CP + SG seizures					
Concomitant carbamazepine	−13.9 (131)	−7.6 (56)	−28.7 (51)	−25.5 (121)	−20.3 (86)
Concomitant valproic acid	−17.2 (127)	−21.5 (78)	−37.5 (69)	−36.3 (111)	−38.3 (58)
Concomitant lamotrigine	−11.5 (118)	−20.5 (53)	−40.3 (61)	−38.8 (133)	−31.8 (55)
Concomitant levetiracetam	−19.5 (116)	−11.1 (44)	−23.4 (42)	−36.8 (120)	−39.2 (79)
SG seizures					
Concomitant carbamazepine	−12.7 (51)	−30.1 (21)	−33.2 (20)	−53.8 (43)	−52.8 (33)
Concomitant valproic acid	−34.4 (64)	−19.7 (29)	−48.3 (30)	−65.4 (46)	−75.4 (24)
Concomitant lamotrigine	−22.9 (45)	−65.4 (22)	−60.5 (27)	−61.1 (54)	−75.5 (22)
Concomitant levetiracetam	−19.1 (43)	−26.9 (20)	−63.6 (15)	−61.1 (41)	−70.7 (27)

AED, antiepileptic drug; CP + SG, complex partial plus secondary generalized; SG, secondarily generalized.
No statistical analyses were performed on these data.
[a]Patients may have received more than one AED.

Table 3. Responder rate ($\geq$ 50% reduction in seizure frequency, maintenance period vs. baseline) by seizure type and concomitant AEDs[a] (intent-to-treat analysis set)

	Responder rate, % (no. of patients evaluated)				
	Placebo	Perampanel 2 mg	Perampanel 4 mg	Perampanel 8 mg	Perampanel 12 mg
All partial seizures					
Concomitant carbamazepine	23.1 (143)	13.8 (58)	19.6 (56)	29.7 (138)	31.3 (96)
Concomitant valproic acid	20.0 (140)	18.8 (80)	34.7 (75)	38.3 (120)	36.5 (63)
Concomitant lamotrigine	13.6 (125)	21.4 (56)	32.4 (68)	35.6 (146)	30.6 (62)
Concomitant levetiracetam	20.0 (125)	14.6 (48)	20.0 (45)	35.9 (131)	43.0 (86)
CP + SG seizures					
Concomitant carbamazepine	26.7 (131)	17.9 (56)	25.5 (51)	31.4 (121)	33.7 (86)
Concomitant valproic acid	24.4 (127)	28.2 (78)	43.5 (69)	40.5 (111)	48.3 (58)
Concomitant lamotrigine	16.1 (118)	28.3 (53)	42.6 (61)	42.1 (133)	32.7 (55)
Concomitant levetiracetam	26.7 (116)	25.0 (44)	28.6 (42)	39.2 (120)	45.6 (79)
SG seizures					
Concomitant carbamazepine	37.3 (51)	38.1 (21)	35.0 (20)	51.2 (43)	51.5 (33)
Concomitant valproic acid	42.2 (64)	27.6 (29)	43.3 (30)	67.4 (46)	62.5 (24)
Concomitant lamotrigine	35.6 (45)	54.5 (22)	63.0 (27)	55.6 (54)	68.2 (22)
Concomitant levetiracetam	39.5 (43)	45.0 (20)	66.7 (15)	61.0 (41)	66.7 (27)

AED, antiepileptic drug; CP + SG, complex partial plus secondary generalized; SG, secondarily generalized.
No statistical analyses were performed on these data.
[a]Patients may have received more than one AED.

>7% was observed in 14.6% of perampanel-treated patients (2 mg, 12.2%; 4 mg, 14.0%; 8 mg, 15.3%; 12 mg, 15.4%) versus 7.1% of placebo-treated patients. Over 19 weeks, mean weight gain was greater with perampanel (+1.2 kg) than placebo (+0.4 kg). As might be expected, these mean weight gains were greater in the 143 adolescents aged <18 years (perampanel [n = 98], +1.7 kg; placebo [n = 45], +1.2 kg).

Discussion

This pooled analysis of phase III data supports the efficacy and safety of perampanel as an adjunctive treatment for refractory partial seizures. At randomized doses of 4–12 mg, perampanel conferred significant improvements in seizure frequency and 50% responder rates for all partial seizures and CP + SG seizures compared with placebo.

Table 4. TEAEs occurring in ≥5% of patients in any treatment group

		Perampanel			
Adverse event, n (%)	Placebo (n = 442)	2 mg (n = 180)	4 mg (n = 172)	8 mg (n = 431)	12 mg (n = 255)
Any TEAE	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

TEAE, treatment-emergent adverse event.

Improvements in SG seizure end points and seizure-freedom rates were consistent, and efficacy was also demonstrated in patients receiving each of the four most commonly coadministered AEDs. The majority of TEAEs were mild to moderate in intensity, with relatively few patients experiencing severe TEAEs.

When patients were subgrouped by concomitant AEDs, percentage changes in seizure frequency and 50% responder rates for all partial seizures, CP + SG seizures, and SG seizures were generally dose-responsive up to 8 mg, and often continued to improve at 12 mg. However, in the overall population, perampanel 12 mg did not appear to offer additional benefit over 8 mg. When interpreting this observation, it should be noted that analysis of randomized dose may underestimate AED efficacy at higher doses. Specifically, data may have been confounded by patients who did not achieve the target randomized dose, for example, owing to poor tolerability. In contrast, pooled analyses of data from patients who completed the maintenance periods of studies 304 or 305 (only studies with a 12-mg dose group), based on actual dose received, indicate that perampanel 12 mg confers a greater seizure-freedom rate and greater median reduction in the frequency of SG seizures than perampanel 8 mg (seizure-freedom rate, 4.4% [12 mg] vs. 2.5% [8 mg]; median change in SG seizure frequency, −54.0% [12 mg] vs. −46.0% [8 mg]; Kramer et al., 2012). This observation is consistent with pooled pharmacokinetic/pharmacodynamic data from the phase III studies, which indicate a linear exposure-efficacy relationship across perampanel doses of 2–12 mg that is not affected by concomitant AEDs (Hussein et al., 2012). Perampanel should be titrated in each patient until an effective and tolerable dose is achieved. It is important to recognize that although some patients will benefit from a dose increase from 8 to 12 mg, not all patients will, and some may experience additional TEAEs. Perampanel dose may be increased up to 12 mg for patients who fail to achieve seizure reductions at lower doses.

Reductions in seizure frequency and responder rates were lower in patients receiving concomitant carbamazepine than in those receiving concomitant noninducer AEDs. This may be because perampanel exposure is reduced in the presence of inducer AEDs, such as carbamazepine (although the exposure-efficacy relationship remains unaffected) (Hussein et al., 2012). Due to this effect, patients receiving concomitant inducer AEDs may be expected to require higher doses of perampanel than other patients. This is reflected in the current U.S. prescribing information, which recommends a starting dose of perampanel 2 mg in patients not receiving concomitant inducer AEDs, and a starting dose of 4 mg in those who are (Food & Drug Administration, 2012). In addition, it is recommended that patients are closely monitored when switching from concomitant noninducer AEDs to inducer AEDs and vice versa: depending upon individual clinical response and tolerability, dose increases or decreases may be required (European Medicines Agency, 2012; Food & Drug Administration, 2012).

Perampanel was generally well tolerated: the majority of TEAEs were mild to moderate in intensity and there were no clinically important mean changes in laboratory values, ECG findings, or vital signs. Falls were more frequent with perampanel 8 or 12 mg than with placebo, although only one fall was considered a serious TEAE. Psychiatric and behavioral TEAEs within the broad and narrow SMQ of hostility/aggression were observed at a greater rate in the perampanel groups compared with the placebo group, and the rate increased with increasing dose. This finding was primarily driven by the TEAE of irritability. In addition, serious psychiatric TEAEs affected 12 patients (1.2%) receiving perampanel (vs. four patients [0.9%] receiving placebo) and included three cases of aggression and one case of suicidal ideation (there were no serious cases of aggression or suicidal ideation with placebo). Serious psychiatric and behavioral adverse events were also reported in open-label studies of perampanel and in studies of perampanel in other indications (Eisai Inc, 2013; Krauss et al.,

2013). Accordingly, the potential for increased risks of falls, aggression, and suicidal ideation are noted in the European and U.S. licenses (European Medicines Agency, 2012; Food & Drug Administration, 2012).

Withdrawal of perampanel was required in 9.5% of patients overall and 19.2% of patients in the 12 mg group. This is consistent with discontinuation rates reported for the highest approved doses of other recently approved AEDs in double-blind studies, such as lacosamide 400 mg/day (15.1%; Halász et al., 2009) and retigabine 1200 mg/day (26.8%; French et al., 2011). The incidence of serious TEAEs in the perampanel 12 mg group (8.2%) was similar to the rates reported with lacosamide 400 mg/day (9.4%; Halász et al., 2009) and retigabine 1,200 mg/day (12.4%; French et al., 2011).

When considering the incidence of TEAEs, it is important to note that patients participating in the three phase III trials were receiving fixed, and often high, doses of concomitant AEDs. This aspect of the trial design may not reflect standard clinical practice, in which doses of concomitant AEDs may be reduced during the introduction of a new treatment. However, this was accounted for in the design of an open-label extension to the three phase III trials, in which the doses of concomitant AEDs could be adjusted at the discretion of the investigator (Krauss et al., 2013).

Perampanel was efficacious and well tolerated, despite the observation that the patient population exhibited characteristics of highly refractory epilepsy. Of note, 35% of patients in the safety analysis set were receiving three concomitant AEDs at baseline. Approximately 69% of patients had a history of SG seizures and the baseline median seizure frequency per 28 days was 10.0–13.0 across the treatment groups. Moreover, 12% of patients in the ITT analysis set had undergone prior surgery and 6% had used vagal nerve stimulation.

A recent report (Krauss et al., 2012b) compared registration studies of perampanel with those of previously approved second- or third-generation AEDs. Patients in the perampanel studies generally had higher seizure frequencies, more often had histories of SG seizures, and were more often receiving three concomitant AEDs. Therefore, perampanel was effective in a treatment-refractory pool of patients, many of whom had previously not responded to newer generation AEDs, such as levetiracetam and lamotrigine.

There was a significant treatment-by-region interaction in the pooled population, characterized by a relatively high placebo response in patients from Central/South America (160/388 randomized and treated patients in study 304; French et al., 2012). This was postulated to reflect regional differences in patient selection or study conduct, and confounded data from the present pooled analysis. In addition, it is important to note that the pooled analysis compares data from perampanel 2 and 4 mg dose groups (only present in study 306) and 12 mg dose groups (only present in studies 304 and 305) with data from the pooled placebo group. Nevertheless, results from the pooled analyses were consistent with those from each individual study. Furthermore, data pooling enabled analysis of subgroups, where individual studies had insufficient patient numbers for such evaluation.

In summary, this large pooled analysis supports the efficacy of perampanel as an adjunctive treatment for refractory partial seizures. It also provides further evidence that perampanel is generally well tolerated.

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