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FULL-LENGTH ORIGINAL RESEARCH

Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305

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Summary

Purpose: To assess the efficacy and safety of once-daily doses of perampanel 8 and 12 mg when added to 1–3 concomitantly administered, approved antiepileptic drugs (AEDs) in patients with uncontrolled partial-onset seizures.

Methods: Study 305 was a multicenter, double-blind, placebo-controlled trial in patients aged 12 years and older with ongoing seizures despite prior therapy with at least two AEDs, and currently receiving 1–3 AEDs. Equal randomization to once-daily oral perampanel 8 or 12 mg, or placebo was performed. Patients entered a 19-week double-blind treatment phase comprising a 6-week titration period, with weekly 2-mg dose increments, followed by a 13-week maintenance period. Primary efficacy end points were the responder rate (proportion of patients who had a ≥50% reduction in seizure frequency during treatment per 28 days relative to baseline), and the percent change in seizure frequency per 28 days relative to pre-perampanel baseline. A secondary end point was percent change in the frequency of complex partial plus secondarily generalized seizures. Adverse events (AEs) were monitored throughout the study.

Key Findings: Three hundred eighty-six patients were randomized and treated with study medication. Of these, 321 patients completed the study. The 50% responder rates (intent-to-treat analysis) were 14.7%, 33.3%, and 33.9%, respectively, for placebo, perampanel 8 mg, and perampanel 12 mg, with significant improvements over placebo for both perampanel 8 mg ($p = 0.002$) and 12 mg ($p < 0.001$). The median percent change from baseline in seizure frequency per 28 days (intent-to-treat analysis) was −9.7%, −30.5%, and −17.6% for placebo, 8 mg, and 12 mg, respectively, with significant reductions compared with placebo for both 8 mg ($p < 0.001$) and 12 mg ($p = 0.011$). For complex partial seizures plus partial seizures that secondarily generalized, the median percent change in frequency was −32.7% (8 mg), −21.9 (12 mg), and −8.1% (placebo), with significant reductions for both 8 mg ($p < 0.001$) and 12 mg ($p = 0.005$). The most frequent (occurring in ≥10% of patients in any treatment group) treatment-emergent AEs were dizziness, somnolence, fatigue, and headache, with an apparent dose effect suggested for all except headache.

Significance: This phase III trial demonstrated that adjunctive treatment with once-daily perampanel at 8 mg and 12 mg was effective in improving seizure control in patients 12 years and older with refractory partial-onset seizures. These study results also demonstrated that once-daily doses of 8 mg and 12 mg were safe and acceptably tolerated in this study. Perampanel demonstrated a favorable risk/benefit ratio in this population.

KEY WORDS: Antiepileptic drugs, Epilepsy, Glutamate, LOCF analysis, Postsynaptic, Randomized controlled trials.

Perampanel is a potent, orally active, noncompetitive and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist currently under development for the treatment of epilepsy (Hanada et al., 2011). AMPA receptors are found at the postsynaptic membrane of excitatory synapses in the brain, binding glutamate and transducing glutamate-mediated postsynaptic signaling (Rogawski, 2011). Perampanel has not been shown to interact with other ionotropic glutamate receptors, including *N*-methyl-D-aspartate (NMDA) and kainate receptors (Hanada et al., 2011; Rogawski, 2011), and is without the behavioral phencyclidine-like adverse events (AEs) that may be observed with some NMDA-receptor antagonists

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(Rogawski, 2011). Another AMPA receptor antagonist, talampanel, has been reported to be efficacious in a small phase II trial (Chappell et al., 2002).

Two phase II dose-escalation, placebo-controlled studies demonstrated therapeutic proof-of-concept in partial-onset seizures and the maximum tolerated dose of perampanel (Krauss et al., 2012a). In these studies, additional pharmacokinetic (PK) and pharmacodynamic (PD) analyses were used to predict efficacy, which was classified into four categories: no effect and minimum, middle, and high effect. Three multinational, multicenter, double-blind, placebo-controlled randomized phase III trials (study 304, study 305, study 306), including both adults and adolescents, were then initiated to establish the minimum effective dose and establish the dose range (2–12 mg) of perampanel for efficacy. Patients were receiving one to three first-, second-, and third-generation approved antiepileptic drugs (AEDs) at baseline but were still having uncontrolled partial-onset seizures despite the availability of second- and third-generation AEDs. Study 306 evaluated the minimum to middle dose range (2–8 mg) (Krauss et al., 2012b). The two other phase III studies, 304 and 305, had identical methodology and assessed the higher daily doses of 8 and 12 mg (French et al., 2012). Herein we present results from the second of these, and the only one of the high-dose trials also to have European and Asian patients.

Methods

Standard protocol approvals, registration, and patient consents

This trial (Eisai Inc. protocol E2007-G000-305, Clinical Trials.gov identifier: NCT00699582, study 305) was conducted between May 2008 and January 2011 at 78 centers in Australia, Austria, Belgium, Germany, Finland, France, United Kingdom, Greece, India, Israel, Italy, The Netherlands, Russia, Sweden, United States, and South Africa. Study 305 was performed in accordance with the Declaration of Helsinki, ICH-E6 Guideline CPMP/ICH/135/95, European Directive 2001/83/EC, and the U.S. Code of Federal Regulations Part 21. The trial protocol, amendments, and informed consent were reviewed by national regulatory authorities in each country and Independent Ethics Committees or Institutional Review Boards for each site. Before trial participation, all patients gave written informed consent.

Patients

Male and female patients were eligible if they were 12 years of age or older. The study was performed prior to the publication of the 2009 revised classification of seizures and epilepsy (Berg et al., 2010), and therefore the seizure definitions from the 1981 classification were employed. Patients had a diagnosis of simple or complex partial seizures, with or without secondary generalization according to the 1981 International League Against Epilepsy Classification of Epileptic Seizures (ILAE, 1981), were able to give informed consent, had at least five partial seizures in the 6-week baseline phase without a 25-day seizure-free period, had failed at least two AEDs in the previous 2 years, and were taking stable doses of up to three approved AEDs. Patients were permitted only one inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) and must have been on a stable dose of any concomitant benzodiazepines. A vagus nerve stimulator was allowed but it must have been implanted for ≥5 months prior to the study. Patients must have had a diagnosis of localization-related epilepsy established by clinical history and electroencephalography, with a computed tomography or magnetic resonance imaging scan within the past 10 years that ruled out a progressive cause of epilepsy. Nonpregnant, nonlactating female patients of child-bearing potential could be included but were required to be on medically acceptable contraception throughout the entire study period.

Key exclusion criteria were the following: clinically significant medical or psychiatric condition or evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal, hepatic, or hematologic disease), suicide attempt(s) within the past 2 years, clinically significant electrocardiography (ECG) abnormality, presence of a progressive central nervous system (CNS) disease, drug or alcohol dependence within the previous 2 years, history of nonepileptic or psychogenic seizures, seizure clusters in which individual seizures could not be counted, nonmotor simple partial seizures only, primary generalized seizures, status epilepticus in the past 12 months, Lennox-Gastaut syndrome, and scheduled epilepsy surgery.

Trial design

Study 305 was a multicenter, multinational, randomized, double-blind, placebo-controlled trial conducted over 29 weeks and consisting of four study periods: baseline, titration, maintenance, and follow-up. Patients enrolled in the trial were entered into a 6-week monitoring phase (baseline) to obtain baseline data and determine their eligibility for the double-blind phase of the trial. Patients who met eligibility criteria were randomized in a 1:1:1 ratio to one of three once-daily treatments: placebo, perampanel 8 mg, or perampanel 12 mg. Randomization was performed using a computer-generated random allocation sequence that was approved and locked after blinded review by an independent statistician. Kit numbers were generated for blinded study drug/kit dispensing by the investigator to each patient at each visit. Throughout the study, all patients and personnel involved with the conduct and interpretation of the study remained blinded to the treatment codes. The 19-week double-blind treatment phase consisted of a 6-week titration period and a 13-week maintenance period. Seizure frequency data were captured in a daily diary maintained by the patient or their caregiver. A 4-week follow-up period at the end of the trial was used to collect safety and efficacy data without treatment.

At the start of the blinded titration period, patients were provided with supplies of perampanel and/or placebo tablets. Perampanel daily doses were increased in weekly 2-mg increments until the respective randomized doses of 8 or 12 mg were reached. Placebo patients were given matching placebo pills. According to the investigator's clinical judgment, patients with AEs could stay on the same dose or have their dose reduced. More than one 2 mg downtitration was discouraged, and patients could have doses increased when tolerability improved. Patients not tolerating at least 2 mg of perampanel or placebo once daily by the end of the titration period were discontinued from study drug treatment.

During the maintenance period, patients continued treatment with the dose of perampanel achieved during titration. Patients completing the maintenance period were offered entry into a long-term, extension trial of perampanel. Patients who discontinued treatment during maintenance or who chose not to participate in the extension trial were entered into the follow-up period.

Measurement of efficacy

Efficacy assessments included seizure counts from patient diaries, Clinical and Patient Global Impression of Change (CGI-C/PGI-C), and the Quality of Life in Epilepsy questionnaire (QOLIE-31-P). Site personnel were given standardized training on seizure identification (simple partial with and without motor signs, complex partial with and without generalization) to ensure that patients were educated in the same standardized fashion at each visit. Training was reinforced at the investigator meetings and, as a follow-up, with a teaching video using scripted actors. Seizure frequency was recorded in patient diaries and reviewed with the site neurologist at visits 1 and 2. The primary end points, secondary end points, and many of the exploratory end points were based on seizure counts from patient diaries.

For registration in the European Union (EU), the 50% responder rate (percentage of patients who had a 50% or greater reduction in seizure frequency in the maintenance period relative to baseline) was designated as the primary end point according to EU guidelines. Percent change in seizure frequency per 28 days in the double-blind phase compared with baseline was the primary efficacy end point for the United States and was a secondary end point for the European Union. Other secondary efficacy end points included percent change in the frequency of complex partial plus secondarily generalized seizures in the double-blind phase relative to baseline.

Assessment of tolerability and safety parameters

Tolerability and safety assessments included prior and concomitant medication use, AEs, discontinuations, clinical laboratory parameters, vital signs, ECG studies, physical and neurologic examinations, Photosensitivity Questionnaire, and Withdrawal Questionnaire. At each study visit, patients were asked to describe any AEs, including symptoms and physical findings. All AEs were recorded, regardless of relationship to the study drug.

Statistical analysis

Sample size determination was based on the mean reduction in seizure frequency for patients treated with placebo and perampanel in previous dose-ranging studies (Krauss et al., 2012a). A sample of 125 patients in each treatment group was calculated to be sufficient to have >80% power to detect a treatment difference of 22% (assuming a common standard deviation of 56%) for percent change in seizure frequency between placebo and each of the active treatment arms. This sample size had 90% power to detect a treatment difference of 16% in responder rate proportions.

Efficacy analyses were based on the intent-to-treat (ITT) analysis set and were prespecified in the protocol. The ITT analysis set consisted of all randomized patients who received study drug and had any seizure frequency data collected during the double-blind phase. Available seizure data during the double-blind phase were converted to ''seizure frequency per 28 days.'' For the analysis of percent change in seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately prior to regression analysis due to the skewed distribution of the seizure frequency data. Countries were used as factors separately, except those with small numbers of patients, which were pooled into larger sets for analysis purposes (Austria was pooled with Finland and The Netherlands was pooled with Italy). An analysis of covariance (ANCOVA) was then conducted on the rank-transformed data, with treatment and countries (or pooled countries, as appropriate) as factors and the ranked baseline seizure frequency per 28 days as a covariate. Log transformation–based ANCOVA was conducted to assess the robustness of the results.

Responder rates were analyzed in the ITT analysis set over the maintenance period using the Cochran-Mantel-Haenszel test, adjusting for pooled countries. Missing data for patients with <2 weeks of data in the maintenance period were imputed from the titration period.

A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary efficacy end point for different dose groups (8 mg followed by 12 mg).

Results

Patient allocation and demographics

In total, 496 patients were screened between May 2008 and January 2011; 386 were randomized and received treatment (placebo, n = 136, perampanel 8 mg, n = 129, and perampanel 12 mg, n = 121). The most common reasons for screen failure were the following: insufficient number

of seizures during baseline, clinically significant ECG abnormalities, and the use of two or more inducing AEDs. Subsequently, 321 patients (83.2%) completed the trial, with 38 patients (9.8%) discontinuing due to AEs. Completion rates were 88.2%, 83.7%, and 76.9% for the placebo, 8 mg, and 12 mg groups, respectively, and the numbers of completer patients achieving each dose were placebo, n = 120; perampanel 2 mg, n = 1; 4 mg, n = 3; 6 mg, n = 19; 8 mg, n = 99; 10 mg, n = 9; 12 mg, n = 70. Patient disposition is further outlined in Fig. 1.

There were only minor differences in patient demographics and epilepsy characteristics (Table 1). Concomitant medications included approved second- and third-generation AEDs available in 2008–2009. Overall, 10.9% of patients were taking one AED, 50.5% were taking two AEDs, and 38.6% were taking three AEDs at baseline. The mean number of AEDs at baseline was 2.3 per patient. The median number of seizures ranged from 11.8 to 13.7 per 28 days during the 6-week baseline period.

Efficacy

The 50% responder rates were 33.3% for once-daily perampanel 8 mg ($p = 0.002$) and 33.9% for 12 mg ($p < 0.001$) versus 14.7% for placebo (Fig. 2). The median percent change in seizure frequency over the double-blind phase was −30.5% for once-daily perampanel 8 mg, −17.6% for 12 mg, and −9.7% for placebo ($p < 0.001$ and $p = 0.011$ for perampanel 8 and 12 mg, respectively, based on the rank ANCOVA versus placebo; $p = 0.001$ and $p = 0.025$ based on the log transformation-based ANCOVA; Fig. 3). Median differences (95% confidence interval) in percent change in seizure frequency compared with placebo were −19.1% (−29.2, −8.4) with once-daily perampanel 8 mg and −13.7% (−25.2, −2.3) with 12 mg. The mean compliance (ascertained from counts of tablets dispensed and tablets returned) was ≥98% in each treatment group.

For the secondary outcome measure of percent change in complex partial plus secondarily generalized seizures, the median percent changes in seizure frequency/28 days were −32.7% ($p < 0.001$) for once-daily perampanel 8 mg and −21.9% ($p = 0.005$) for 12 mg versus −8.1% for placebo.

Among patients who completed the maintenance period, the percentages who achieved seizure reductions of 75–100% were 15.5% and 16.5% for once-daily perampanel 8 and 12 mg, respectively, versus 4.4% for placebo. Overall, 2.3% (8 mg) and 5.0% (12 mg) of all patients enrolled in the trial (ITT population) were seizure-free during the entire maintenance period, versus 1.5% of placebo patients (Gazzola et al., 2007). Using only patients who entered the maintenance period (excluding dropouts during titration), similar results are seen, with 1.7%, 2.8%, and 6.5% seizure freedom in the placebo, 8 mg, and 12 mg groups, respectively.

The CGI-C responses at the end of treatment showed that more investigators assessed patients as ''much'' or ''very much'' improved with once-daily perampanel treatment compared with placebo: 28.8% ($p = 0.037$) for perampanel 8 mg and 27.3% ($p = 0.049$) for 12 mg versus 17.2% for placebo. The PGI-C responses at the end of treatment also showed more patients considered themselves ''much'' or ''very much'' improved with once-daily perampanel treat-

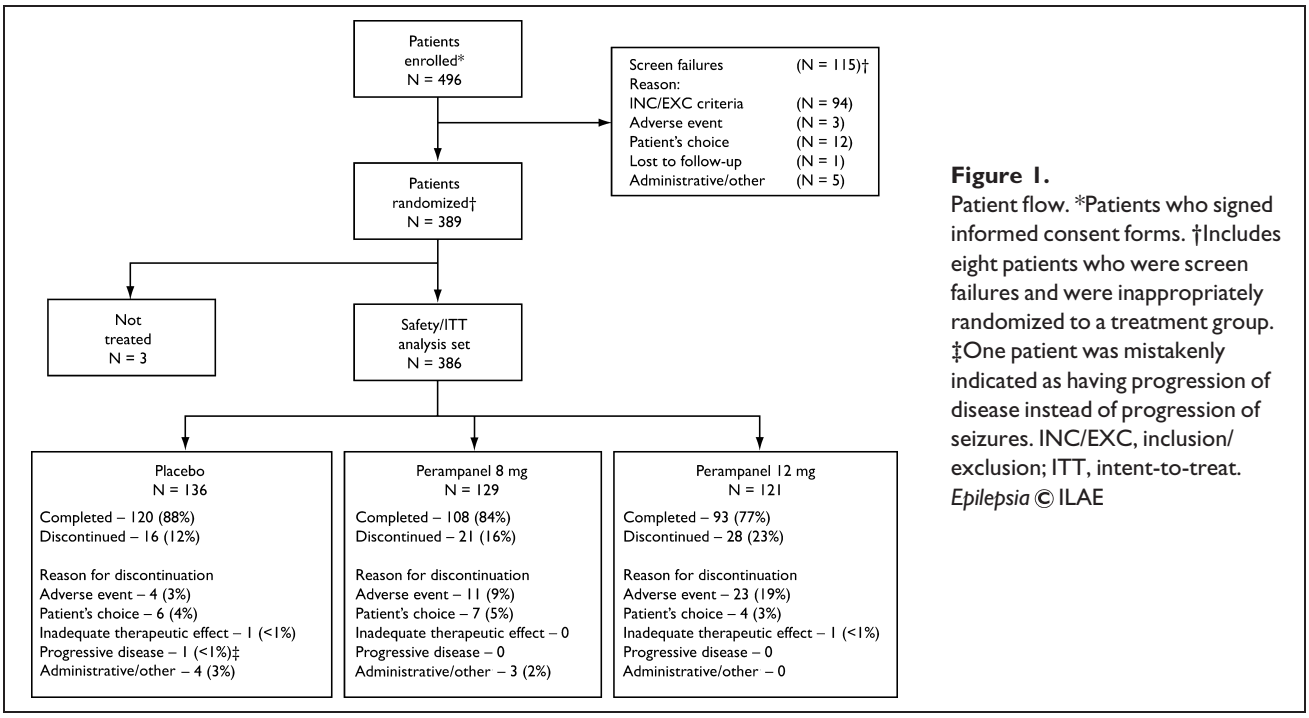

Figure 1.
Patient flow. *Patients who signed informed consent forms. †Includes eight patients who were screen failures and were inappropriately randomized to a treatment group. ‡One patient was mistakenly indicated as having progression of disease instead of progression of seizures. INC/EXC, inclusion/exclusion; ITT, intent-to-treat.

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

		Perampanel	
	Placebo (n = 136)	8 mg (n = 129)	12 mg (n = 121)
Mean age, years (SD)	34.4 (13.6)	36.7 (14.4)	35.5 (14.1)
Female gender, n (%)	65 (47.8)	64 (49.6)	71 (58.7)
Race, n (%)			
Asian	12 (8.8)	14 (10.9)	16 (13.2)
Black or African American	1 (<1)	2 (1.6)	1 (<1)
White	115 (84.6)	107 (82.9)	100 (82.6)
Other	8 (5.9)	6 (4.7)	4 (3.3)
Mean time since epilepsy diagnosis, months (SD)	264.2 (155.3)	270.3 (163.4)	255.9 (158.6)
Seizure type, n (%)			
Simple partial without motor signs	48 (35.3)	49 (38.0)	36 (29.8)
Simple partial with motor signs	30 (22.1)	39 (30.2)	38 (31.4)
Complex partial	114 (83.8)	114 (88.4)	100 (82.6)
Complex partial with secondary generalization	95 (69.9)	90 (69.8)	77 (63.6)
Seizure frequency per 28 days during the baseline phase, median (min, max)[a]	11.8 (3.4, 358.4)	13.0 (3.3, 652.2)	13.7 (1.4, 598.4)
No. of concomitant AEDs at baseline			
Only one AED, n (%)	17 (12.5)	16 (12.4)	9 (7.4)
Exactly two AEDs, n (%)	64 (47.1)	68 (52.7)	63 (52.1)
Exactly three AEDs, n (%)	55 (40.4)	45 (34.9)	49 (40.5)
Perampanel-inducing AEDs[b]	71 (52.2)	83 (64.3)	80 (66.1)
Most common concomitant AEDs, n (%)[c]			
Levetiracetam	52 (38.2)	49 (38.0)	46 (38.0)
Carbamazepine	43 (31.6)	43 (33.3)	47 (38.8)
Lamotrigine	37 (27.2)	40 (31.0)	27 (22.3)
Valproic acid	32 (23.5)	25 (19.4)	26 (21.5)
Oxcarbazepine	23 (16.9)	25 (19.4)	24 (19.8)
Topiramate	24 (17.6)	25 (19.4)	22 (18.2)
Clobazam	18 (13.2)	14 (10.9)	17 (14.0)
Zonisamide	19 (14.0)	12 (9.3)	11 (9.1)

AED, antiepileptic drug; SD, standard deviation.
[a]Data shown for the intent-to-treat population.
[b]Number of patients (%) taking perampanel clearance-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin).
[c]AEDs used in ≥10% of all patients.

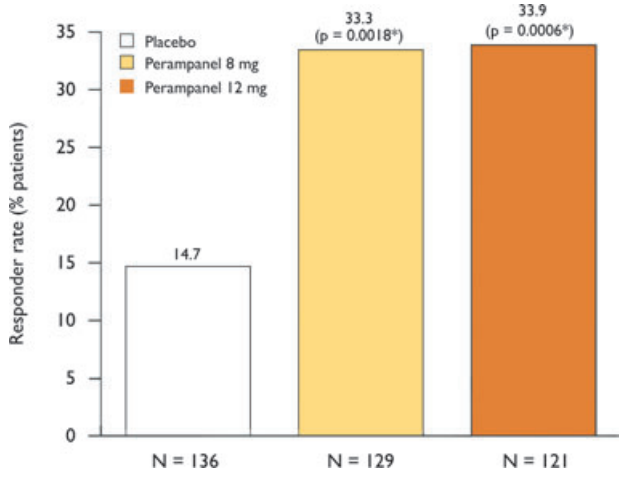

Figure 2.
Responder rates (percentage of patients who had a ≥50% reduction in seizure frequency in the maintenance period relative to baseline). *p-values are based on Cochran-Mantel-Haenszel analysis (intent-to-treat analysis set).
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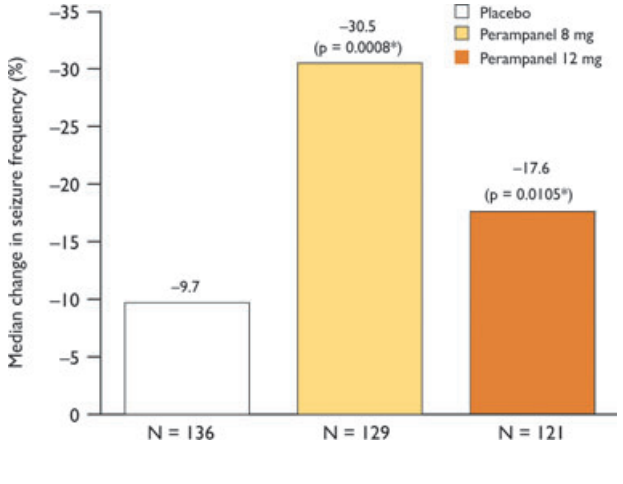

Figure 3.
Median percentage change in seizure frequency per 28 days during the double-blind phase compared with baseline. *p-values are based on analysis of covariance on rank-transformed percent change data (intent-to-treat analysis set).
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ment compared with placebo: 36.7% (p = 0.021) for perampanel 8 mg and 30.6% (p = 0.089) for 12 mg versus 21.8% for placebo, whereas 11.3% on placebo, 12.5% (p = 0.981) on perampanel 8 mg, and 20.4% (p = 0.839) on perampanel 12 mg considered themselves ''minimally,'' ''much,'' or ''very much'' worse. There were no differences in the changes in quality of life (as determined by response to QOLIE-31-P) between the placebo and perampanel-treated groups.

Safety

During the double-blind treatment phase, at least one treatment-emergent AE (TEAE) was reported in 86.8% and 86.0% of perampanel 8 mg and 12 mg-treated patients, versus 68.4% of patients in the placebo group. The most frequently reported TEAEs (occurring in ≥10% of patients) were headache in the placebo group; and dizziness, somnolence, fatigue, and headache in the perampanel 8 mg and 12 mg treatment groups (Table 2). The following TEAEs (reported in >5% of perampanel-treated patients) occurred in at least twice the number of patients in one of the perampanel groups, compared with the placebo group: dizziness (40.0% of perampanel-treated patients), somnolence (15.2%), fatigue (14.8%), irritability (9.2%), nausea (9.2%), fall (6.0%), and weight increase (5.6%). All but weight increase and irritability demonstrated an apparent dose–response relationship. Although the maintenance period was more than twice the duration of the titration period, the incidence of TEAEs in perampanel-treated patients was no greater during the maintenance period than the titration period, possibly indicating a relationship of TEAEs to the fast, blinded titration in the trial. Overall, 76.4% of perampanel-treated patients had a TEAE that was mild or moderate, compared with 61.7% of patients in the placebo group. Worsening seizures, defined as a >50% increase in seizures compared with baseline, occurred in 10%, 8%, and 9% of patients treated with placebo, 8 mg, and 12 mg.

The only TEAEs leading to discontinuation in ≥2% of total perampanel-treated patients were dizziness (<1%, 2.3%, 5.0%) and somnolence (0%, <1%, 3.3% each for placebo, 8 mg, and 12 mg treated patients, respectively) (Table 3). Overall, TEAEs were more likely to lead to dose adjustment, reduction, and/or interruption in patients receiving perampanel 8 mg and 12 mg (20.9%, 28.1%) than placebo (3.7%). The TEAEs associated with study drug interruption or dose adjustment in ≥2% of total perampanel-treated patients were dizziness (0%, 7.8%, 17.4%), somnolence (0%, 3.9%, 4.1%), fatigue (0%, 3.9%, 2.5%), and ataxia (0%, 1.6%, 2.5% each for placebo, 8 mg, and 12 mg treated patients, respectively).

Psychiatric TEAEs varied little by treatment group: 14.0% of placebo patients, 14.0% on perampanel 8 mg, and 17.4% on perampanel 12 mg. Psychiatric TEAEs occurring more frequently than placebo and in >1% of patients were few and included sleep disorder (<1%, 2.3%, 1.7%, for placebo, 8 mg, and 12 mg, respectively), anxiety (0%, 1.6%, 1.7%), aggression (<1%, 1.6%, <1%), confusional state (0%, 0%, 2.5%), and anger (0%, 0%, 1.7%). One patient in the placebo group had a TEAE related to suicidality (suicidal ideation). Rash led to discontinuation in four perampanel patients (1.6%) versus none in the placebo group, but there were no dermatologic serious AEs (SAEs) and no reports of Stevens-Johnson syndrome.

More falls occurred in the perampanel groups than in the placebo group. Thirty-one falls were reported in 19 patients during the double-blind phase: four falls in 4 (2.9%) placebo patients and 27 falls in 15 (6.0%) perampanel patients. An exposure-adjusted analysis of falls by treatment phase showed 0.0036 falls/subject-months during baseline, 0.0072 falls/subject-months for the double-blind placebo patients, and 0.0256 falls/subject-months for the double-blind perampanel patients. The exact timing of the falls was not recorded in the case report forms, but 3 of the 4 falls in placebo patients and 9 of the 27 falls in perampanel patients occurred on the same day as secondarily generalized seizures. Multiple episodes of fall (up to five in total) occurred only in the perampanel group, and occurred in 7 of 15 patients. Many of the patients with falls also complained of other CNS side effects such as unsteady gait, ataxia, dizziness, and slurred speech. Five perampanel patients experienced falls at daily doses lower than 8 mg. There were no discontinuations related to falls or injury. AEDs in patients with falls had a similar distribution to those in the overall trial population. A PK/PD analysis showed that the probability of occurrence of fall, grouped with gait disturbance and balance disorder, increased with increasing average plasma concentration of perampanel (Laurenza et al., 2012). This analysis was performed using the plasma exposure of perampanel at the time of the AE, and in patients taking an average of 2.3 concomitant AEDs.

Table 2. Incidence of treatment-emergent adverse events (TEAEs) (safety population)

	Patients, n (%)		
	Placebo (n = 136)	8 mg (n = 129)	12 mg (n = 121)
Any TEAE	93 (68.4)	112 (86.8)	104 (86.0)
Any treatment-related TEAE	65 (47.8)	89 (69.0)	94 (77.7)
TEAE severity			
Mild	43 (31.6)	51 (39.5)	35 (28.9)
Moderate	41 (30.1)	49 (38.0)	56 (46.3)
Severe	9 (6.6)	12 (9.3)	13 (10.7)
Any serious TEAE	7 (5.1)	10 (7.8)	12 (9.9)
TEAEs in ≥10% (any treatment group)			
Dizziness	10 (7.4)	42 (32.6)	58 (47.9)
Somnolence	4 (2.9)	16 (12.4)	22 (18.2)
Fatigue	11 (8.1)	17 (13.2)	20 (16.5)
Headache	18 (13.2)	11 (8.5)	16 (13.2)

Table 3. Incidence of treatment-emergent adverse events (TEAEs) leading to discontinuation from study or study drug adjustment interruption/reduction (safety analysis set)

	Patients, n (%)			
	Placebo (n = 136)	8 mg (n = 129)	12 mg (n = 121)	Total perampanel (n = 250)
Discontinuation due to TEAEs	6 (4.4)	12 (9.3)	23 (19.0)	35 (14.0)
Most common TEAEs leading to discontinuation (>2% patients in any treatment group)				
Dizziness	1 (<1)	3 (2.3)	6 (5.0)	9 (3.6)
Somnolence	0	1 (<1)	4 (3.3)	5 (2.0)
Convulsion	3 (2.2)	2 (1.6)	1 (<1)	3 (1.2)
Dose interruption/reduction due to TEAEs	5 (3.7)	27 (20.9)	34 (28.1)	61 (24.4)
Most common TEAEs leading to dose interruption/reduction (>2% patients in any treatment group)				
Dizziness	0	10 (7.8)	21 (17.4)	31 (12.4)
Somnolence	0	5 (3.9)	5 (4.1)	10 (4.0)
Headache	0	0	4 (3.3)	4 (1.6)
Fatigue	0	5 (3.9)	3 (2.5)	8 (3.2)
Ataxia	0	2 (1.6)	3 (2.5)	5 (2.0)
Asthenia	0	3 (2.3)	1 (<1)	4 (1.6)

There were no cases of sudden unexpected death in epilepsy or deaths due to other causes in this study. The number of patients who experienced SAEs was 7 (5.1%) for placebo, 10 (7.8%) for perampanel 8 mg, and 12 (9.9%) for 12 mg. The only SAEs occurring in more than one patient in any treatment group were those related to epilepsy and causing hospitalization (i.e., convulsion, epilepsy, partial seizures with secondary generalization, and status epilepticus), which occurred in six patients: 2 patients (1.5%) in the placebo group, 3 (2.3%) patients in the perampanel 8 mg group, and 1 (<1%) patient in the 12 mg group. However, six patients (three patients each in the perampanel 8 and 12 mg groups) had individual SAEs related to injury (lacerations, bone fractures) versus none in the placebo group. These were reported to be a result of fall (n = 3) or seizure with fall (n = 3). Psychiatric SAEs were uncommon (five patients, <2%) and were evenly distributed between placebo and perampanel patients. SAEs led to discontinuation in four patients in the perampanel 8 mg group (psychotic disorder, ischemic stroke, convulsion, and dizziness/nausea/somnolence) and three patients in the 12 mg group (status epilepticus/urinary incontinence, somnolence, and belligerence). With the exception of two SAEs of convulsion in the 8 mg group, no specific event was consistently considered related to perampanel by the investigators. Apart from the epilepsy-related SAEs, there were 29 other SAEs reported in 25 patients (5, 8, and 12 patients in the placebo, 8 mg, and 12 mg groups, respectively). The seven SAEs of injury were the only SAE seen more than twice.

There were no reports of abuse or diversion of perampanel. There were two reported overdoses in the placebo group (with no associated TEAEs), five in the 8 mg group (two associated TEAEs: nausea and vomiting), and three in the 12 mg group (six associated TEAEs: dizziness [three], somnolence, ataxia, and dysarthria). All 10 overdoses were accidental; eight were associated with blister pack errors by the patients. The highest dose taken was 36 mg in a patient in the 12 mg group.

No clinically important changes from baseline in mean laboratory values, ECG studies, vital signs, or physical or neurologic examinations were observed at the end of treatment. The large majority of patients with markedly abnormal laboratory values (leukopenia, thrombocytopenia, hyponatremia) were taking concomitant carbamazepine, oxcarbazepine, or valproic acid. These abnormalities were present at baseline and persisted throughout the study without any significant change. Weight increase of >7% during the double-blind treatment phase was seen in 11.6% of perampanel-treated patients (4.4% in the placebo group), without any apparent dose effect. The mean changes in weight from baseline were −0.1, 1.1, and 1.3 kg for placebo, 8 mg, and 12 mg, respectively.

The Withdrawal Questionnaire was intended to compare potential withdrawal-like symptoms observed during the trial versus the month after the end of therapy. More than 80% of patients did not complete the postbaseline Withdrawal Questionnaire per protocol because the majority of patients were rolled over into the extension. Although the numbers are small, most patients rated each symptom as ''none'' or ''mild.'' The Withdrawal Questionnaire results will be addressed at the end of the extension study. Positive responses on the Photosensitivity Questionnaire (skin rash/reaction/change in pigmentation/skin complaint) were reported for eight patients: 2 (2.2%) in the placebo group, 4 (4.9%) in the 8 mg group, and 2 (2.4%) in the 12 mg group. None of these eight patients required dose changes/discontinuations.

Discussion

These phase III results showed that adjunctive therapy with perampanel at daily doses of 8 mg or 12 mg led to statistically significant reductions in seizures with very few withdrawals for unacceptable AEs in patients with refractory partial-onset seizures. Furthermore, seizure freedom was attained in a small number of patients, with a suggestion that this might have occurred in a dose-dependent manner, although the numbers were too small to establish statistical significance for this trend. This was supported by an additional ''pragmatic ITT'' analysis of seizure freedom, in which the number of patients who completed the study seizure-free was the numerator and the ITT population was denominator (Gazzola et al., 2007).

The exploratory efficacy end points reported here were based both on variables related to seizure frequency, such as number of seizure-free days, and on more subjective measurements, such as the Global Impressions of Change. These results showed general improvement associated with perampanel and further support the findings of the primary and secondary efficacy end points.

In analyses of the ITT population at the randomized doses, the median percent changes from baseline in seizure frequency per 28 days at once-daily perampanel 8 mg and 12 mg, respectively, were −30.5% and −17.6%, whereas discontinuations due to AEs were 8.5% and 19.0%.

The incidence rates of discontinuations due to AEs and also SAEs associated with the perampanel 12 mg dose are consistent with the rates reported for the highest approved doses used in double-blind clinical trials evaluating other recently approved AEDs such as lacosamide and retigabine—discontinuation rates were lacosamide 400 mg/day, 15.1% vs. placebo, 4.9% (Halász et al., 2009) and retigabine 1,200 mg/day, 26.8% vs. placebo, 8.6% (French et al., 2011); SAE rates were lacosamide 400 mg/day, 9.4% vs. placebo, 3.7% (Halász et al., 2009) and retigabine 1,200 mg/day, 12.4% versus placebo, 5.3% (French et al., 2011).

This is the second of two double-blind, placebo-controlled trials of identical design, and with identical doses, to be completed. The first study included only patients from the Americas, whereas this one included multiple geographic regions including Europe, North America, and Australia. The availability of these two data sets allows comparison of efficacy findings as well as safety signals. Both studies demonstrated improvements in seizures, as measured by percent seizure reduction and number of responders (French et al., 2012). Both studies also demonstrated an increase in seizure freedom over the maintenance period in perampanel-treated patients, which seemed to have a dose-response relationship in this present study, but not the other (French et al., 2012). The two studies also identified similar AEs, increasing the likelihood that these are truly drug-related. These included dizziness, somnolence, fall, irritability, and ataxia. Other AEs were conspicuously absent or occurred at a low rate, not significantly greater than placebo in both studies. These included depression, psychosis, and rash.

Falls occurred at a greater rate in perampanel-treated patients, although the exposure adjusted rates were generally low. Falls were often multiple, appeared to occur more frequently at the higher doses of perampanel that patients achieved in the maintenance period, and were related to injury in some patients. These seemed to occur in combination with other CNS symptoms suggestive of drug-related intoxication. However, the absence of a multiple drug intoxication effect is clarified by examining the actual plasma exposure of perampanel at the time of the AE, as opposed to the randomized dose (the randomized dose analysis is unable to account for both the failure to reach/maintain the assigned dose and early termination). A PK/PD analysis showed that the probability of occurrence of falls increased with increasing plasma concentration of perampanel, irrespective of concomitant AEDs. Finally, generalized seizures occurred on the same day in almost half of patients with falls, but it is unknown if they occurred simultaneously.

Neither trial indicated a greater benefit in aggregate for perampanel 12 mg as compared with 8 mg (French et al., 2012). However, in this study, there were more patients with 75% as well as 100% seizure reductions (seizure-free) at perampanel 12 mg than 8 mg, indicating that some patients may benefit from doses up to 12 mg, but the numbers are too small to enable any firm conclusions to be drawn. Whereas some patients will experience increased AEs with the 12 mg dose, there may be an additional benefit for a meaningful proportion of patients. The 12 mg dose may be an important option in achieving the goal of greater seizure reduction and seizure freedom in those patients who can tolerate it and who have not achieved an optimal response at 8 mg.

The efficacy and safety results shown in this study were consistent with those in an identically designed study of patients with treatment-resistant epilepsy (French et al., 2012). The current study also provides further encouraging clinical evidence for the potential value of AMPA receptor antagonists in the epilepsy armamentarium.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 51:676–685.

Chappell AS, Sander JW, Brodie MJ, Chadwick D, Lledo A, Zhang D, Bjerke J, Kiesler GM, Arroyo S. (2002) A crossover, add-on trial of talampanel in patients with refractory partial seizures. *Neurology* 58:1680–1682.

French JA, Abou-Khalil BW, Leroy RF, Yacubian EMT, Shin P, Hall S, Mansbach H, Nohria V. (2011) Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 76:1555–1563.

French J, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, Kumar D, Rogawski MA. (2012) Adjunctive perampanel for refractory partial-onset seizures: randomized Phase III study 304. *Neurology* 79:589–596.

Gazzola DM, Balcer LJ, French JA. (2007) Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. *Epilepsia* 48:1303–1307.

Halász P, Kälviäinen R, Mazurkiewicz-Beldzinska M, Rosenow F, Doty P, Hebert D, Sullivan T. (2009) Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. *Epilepsia* 50:443–453.

Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, Hatakeyama S, Ohgoh M, Ueno M, Nishizawa Y. (2011) Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* 52:1331–1340.

ILAE. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 22:489–501.

Krauss GL, Bar M, Biton V, Klapper JA, Rektor I, Vaiciene-Magistris N, Squillacote D, Kumar D. (2012a) Tolerability and safety of perampanel: two randomized dose-escalation studies. *Acta Neurol Scand* 125:8–15.

Krauss GL, Serratosa JM, Villanueva VE, Endziniene M, Hong Z, French J, Yang H, Squillacote D, Edwards HB, Zhu J, Laurenza A. (2012b) Randomized Phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 78:1408–1415.

Laurenza A, Ferry J, Hussein Z. (2012) Population pharmacokinetics and pharmacodynamics of perampanel: a pooled analysis from three phase III trials. *Epilepsy Curr* 12(Suppl. 1):abs 2.231.

Rogawski MA. (2011) Revisiting AMPA receptors as an antiepileptic drug target. *Epilepsy Curr* 11:56–63.