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FULL-LENGTH ORIGINAL RESEARCH

Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: Interim results from phase III, extension study 307

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Summary

Purpose: To evaluate safety, tolerability, and seizure outcome data during long-term treatment with once-daily adjunctive perampanel (up to 12 mg/day) in patients with refractory partial-onset seizures.

Methods: Study 307 was an extension study for patients completing the double-blind phase of three pivotal phase III trials (studies 304, 305, and 306). The study consisted of two phases: an open-label treatment phase (including a 16-week blinded conversion period and a planned 256-week maintenance period) and a 4-week follow-up phase. Patients were blindly titrated during the conversion period to their individual maximum tolerated dose (maximum 12 mg/day). Adverse events (AEs) were monitored throughout the study and seizure frequency recorded. The interim data cutoff date for analyses was December 1, 2010.

Key Findings: In total, 1,218 patients were enrolled in the study. At the interim cutoff date, 1,186 patients were in the safety analysis set; 1,089 (91.8%) patients had >16 weeks of exposure to perampanel, 580 (48.9%) patients had >1 year of exposure, and 19 (1.6%) patients had >2 years of exposure. At the interim analysis, 840 (70.8%) patients remained on perampanel treatment. The large majority of patients (n = 1,084 [91%]) were titrated to 10 mg or 12 mg/day. Median (range) duration of exposure was 51.4 (1.1–128.1) weeks. Treatment-emergent AEs were reported in 87.4% of patients. The most frequent were dizziness (43.9%), somnolence (20.2%), headache (16.7%), and fatigue (12.1%). Serious AEs were reported in 13.2% of patients. In the intent-to-treat analysis set (n = 1,207), the frequency of all seizures decreased over the first 26 weeks of perampanel treatment in patients with at least 26 weeks of exposure to perampanel (n = 1,006 [83.3%]); this reduction was maintained in patients with at least 1 year of exposure (n = 588 [48.7%]). The overall median percent changes in seizure frequency in patients included in each 13-week interval of perampanel treatment were −39.2% for weeks 14–26 (n = 1,114), −46.5% for weeks 40–52 (n = 731), and −58.1% for weeks 92–104 (n = 59). Overall responder rates in patients included in each 13-week interval of perampanel treatment were 41.4% for weeks 14–26 (n = 1,114), 46.9% for weeks 40–52 (n = 731), and 62.7% for weeks 92–104 (n = 59). During the blinded conversion period, the reduction in seizure frequency in patients previously randomized to placebo (−42.4%, n = 369) was similar to that in patients previously randomized to perampanel (−41.5%, n = 817).

Significance: Consistent with pivotal phase III trials, these interim results demonstrated that perampanel had a favorable tolerability profile in patients with refractory partial-onset seizures over the longer term. The decrease in seizure frequency was consistent and maintained in those patients over at least 1 year of perampanel exposure.

KEY WORDS: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, Long-term, Open-label, Partial epilepsy, Perampanel, Safety.

Despite the availability of >20 antiepileptic drugs (AEDs) (Perucca & Tomson, 2011), approximately one third of patients with epilepsy are treatment resistant (French, 2007; Perucca et al., 2007). There is a need for AEDs with novel

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mechanisms to help patients who continue to have inadequate seizure control despite treatment with current agents.

Excessive glutamate release is observed during seizure activity, and glutamate binding to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)–type glutamate receptor plays an important role in the generation and spread of epileptic seizures (During & Spencer, 1993; Rogawski & Donevan, 1999; Rogawski, 2011). Perampanel is a selective, noncompetitive antagonist of AMPA-type glutamate receptors, currently in clinical development as adjunctive therapy for the treatment of refractory partial-onset seizures. In vitro, perampanel selectively inhibits AMPA receptors with high potency and reduces neuronal excitability (Hanada et al., 2011), an action that is expected to have beneficial effects in epilepsy (Meldrum & Rogawski, 2007; Rogawski, 2011).

In phase II studies, perampanel was well tolerated at doses up to 12 mg/day in patients with refractory partial-onset seizures (Krauss et al., 2012a). More recently, the efficacy and tolerability of adjunctive perampanel in this patient population has been demonstrated in three phase III, randomized, double-blind, placebo-controlled trials (study 304, NCT00699972; study 305, NCT00699582; and study 306, NCT00700310) (French et al., 2012a,b; Krauss et al., 2012b). These studies showed that once-daily perampanel, at doses up to 12 mg/day, significantly reduced seizure frequency and increased responder rate in treatment-resistant patients. Herein we present interim results from study 307 (NCT00735397), an extension to studies 304, 305, and 306. The primary objective of this study was to evaluate the long-term safety and tolerability of perampanel (up to 12 mg/day) when given as adjunctive treatment in patients with refractory partial-onset seizures. The secondary objective was to evaluate the maintenance effect of perampanel for the treatment of refractory partial-onset seizures.

Methods

Patients

Patients who completed the double-blind phase of studies 304, 305, and 306 (French et al., 2012a,b; Krauss et al., 2012b) were eligible to participate. The initial studies enrolled patients aged ≥12 years with uncontrolled simple or complex partial-onset seizures, with or without secondary generalization, despite treatment with 1–3 approved AEDs. Following a 6-week baseline, patients were randomized to once-daily double-blind treatment with placebo, perampanel 8 mg or 12 mg in studies 304 and 305; and placebo, perampanel 2 mg, 4 mg, or 8 mg in study 306.

Study design

This extension study consisted of a 16-week blinded conversion period, a planned 256-week open-label maintenance period, and a 4-week follow-up phase. The first patient entered the study in October 2008, and patients were enrolled from 249 centers in 39 countries. The interim data cutoff date for this analysis was December 1, 2010; at that time, patients still enrolled in the study were in the blinded conversion period, continuing with open-label treatment, or had entered the follow-up phase.

Patients entered the extension study on the same concomitant AED regimen they received during the core double-blind study. During the blinded conversion period, patients who had received placebo or doses <12 mg/day in the double-blind phase of the core trials had their perampanel dose blindly titrated upward in 2-mg increments every 2 weeks, to the maximum tolerated dose (MTD; up to 12 mg/day). Titration rate in the extension study was slower compared with the core phase III studies (every 2 weeks vs. weekly) and dose adjustment to an individual's MTD was permitted based on tolerability. Patients who achieved 12 mg/day in the double-blind phase of the core phase III studies maintained this dose throughout the extension. Patients remained on the MTD achieved during the blinded conversion period throughout the maintenance period unless further dose titration for tolerability and/or efficacy reasons was necessary. Adjustment of dose, discontinuation, or change of concomitant AEDs was permissible at the investigator's discretion. Patients who could not tolerate perampanel doses of at least 2 mg/day were discontinued. All doses were given once daily at bedtime with food, and visits occurred every 4 weeks during the conversion period and every 3 months thereafter.

This trial was performed in accordance with the International Conference on Harmonization/Good Clinical Practice guidelines and the Declaration of Helsinki. 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. All patients provided informed consent prior to participating in the study.

Safety assessments

Adverse events (AEs) were recorded throughout the study. AEs were considered treatment-emergent if they started on or after the first perampanel dose (core phase III or extension study) and prior to 30 days after the last dose; or if they were present prior to treatment but worsened in severity during the study. Other safety investigations included assessments of clinical laboratory parameters, vital signs, body weight, and electrocardiography studies (ECGs). Markedly abnormal laboratory values were defined as a laboratory result that worsened in severity to meet modified National Cancer Institute toxicity criteria of grade 2 or higher on treatment; notably high or low systolic or diastolic blood pressure was defined as changes of ≥20 mm Hg or ≥15 mm Hg, respectively; clinically notable changes in weight were defined as an increase or decrease of >7% from baseline; and assessment of clinically important changes in ECG were based on investigator assessment.

Seizure frequency assessments

Patients recorded seizure frequency and type in daily diaries. All simple partial seizures (with or without motor signs), complex partial seizures, and secondarily generalized seizures were recorded. Seizure-related end points included the following: percent change in seizure frequency (all seizure types) per 28 days during treatment relative to pre-perampanel baseline and responder rate (proportion of patients who experienced a ≥50% reduction in seizure frequency during treatment per 28 days relative to pre-perampanel baseline).

Statistical analyses

The safety analysis set was defined as all patients who received at least one dose of perampanel in the extension study and had at least one postdose safety assessment during the extension. All seizure-related analyses were performed in the intent-to-treat (ITT) analysis set (all patients who received at least one dose of perampanel in the extension and had valid seizure data during the perampanel treatment duration [double-blind and/or extension]).

For patients randomized to placebo in the core phase III studies, the pre-perampanel baseline was defined using all data from the double-blind study prior to perampanel treatment. The duration of treatment therefore consisted of the extension phase for these patients. For patients randomized to perampanel in the core studies, pre-perampanel baseline was computed from the baseline period of these studies. In these patients, perampanel treatment duration consisted of the double-blind phase plus the extension phase for patients with a ≤14-day gap in exposure between the two studies, and the extension phase for those patients with a >14-day gap in exposure. A protocol amendment designated rollover into the extension as a ≤14-day gap, in light of updated information on the steady state of perampanel.

Safety data are presented by maximum daily dose and include data from the entire perampanel treatment duration. For AE analyses, this was defined as all exposure to perampanel in the double-blind and extension studies. For other safety analyses, treatment duration was similar to that defined above for efficacy analyses, except for those patients with a >14-day gap in exposure between the studies. In these patients, treatment duration was defined as the longer of either the double-blind phase or extension treatment phase.

Results

Patient characteristics and disposition

Of 1,264 patients who completed the double-blind phase of the three core phase III trials, 1,218 (96.4%) continued into study 307. These included 380 patients previously randomized to placebo and 838 previously randomized to perampanel in the phase III studies (n = 147 previously randomized to 2 mg/day; n = 154 to 4 mg/day; n = 356 to 8 mg/day, and n = 181 to 12 mg/day). Ten patients had a >14-day gap in exposure between the double-blind studies and the extension study. Of the patients enrolled, 1,186 were included in the safety analysis set and 1,207 in the ITT analysis set. Thirty-two patients enrolled and treated in this study had no extension phase postdose safety data at the interim cutoff date and were thus excluded from the safety analysis set. Inclusion of patients in the ITT analysis set was dependent on availability of seizure data during the perampanel treatment period (double-blind and/or extension). As a consequence, the number of patients included in the ITT analysis set is higher than the safety analysis set. At the interim data cutoff, 840 patients (70.8%) in the safety analysis set remained on perampanel treatment.

The most common reasons for discontinuation were AEs (10.5%), subject choice (9.0%), and inadequate therapeutic effect (7.4%) (Table 1). Overall, 41.3% of patients who discontinued early listed a secondary reason; for discontinuations due to subject choice, inadequate therapeutic effect was listed by 27 patients, and AE by 18 patients. The proportion discontinuing perampanel treatment was similar for patients who had previously been randomized to placebo (27.6%) in the initial phase III studies and for patients previously randomized to perampanel (27.9%).

Baseline characteristics, seizure history, and concomitant AED use are summarized in Table 2. The majority (86.6%) of patients were taking two or more AEDs at baseline, and the mean number of AEDs at baseline was 2.2. At the date of interim analysis cutoff or study discontinuation, most patients (94.9%) remained on the same number of concomitant AEDs that they were receiving at the start of the extension study. One patient who entered the blinded conversion period on one concomitant AED discontinued all AEDs

Table 1. Patient disposition (safety analysis set)

	Total (n = 1,186)
Therapy, n (%)	
Discontinued	346 (29.2)
Ongoing	840 (70.8)
Primary reason for discontinuation from therapy,[a] n (%)	
Adverse event(s)	125 (10.5)
Subject choice	107 (9.0)
Inadequate therapeutic effect	88 (7.4)
Administrative/other	9 (<1.0)
Reason missing	9 (<1.0)
Lost to follow-up	8 (<1.0)
Secondary reason for discontinuation from therapy, n (%)	
Adverse event(s)	31 (2.6)
Subject choice	66 (5.6)
Inadequate therapeutic effect	47 (4.0)
Administrative/other	5 (<1.0)
None provided	203 (17.1)

[a]Only one primary reason was recorded. Subjects with a missing reason had not had a final visit to fill out an end of study (subject disposition) case report form.

except perampanel. Eighteen patients (1.5%) decreased their number of concomitant AEDs and 44 (3.6%) increased their number of concomitant AEDs.

Exposure to open-label perampanel

The large majority of patients in the safety analysis set (n = 1,089, 91.8%) received >16 weeks of treatment with perampanel; 580 (48.9%) patients received perampanel for >52 weeks, and 250 (21.1%) for >76 weeks (Table S1).

Table 2. Baseline patient demographics and clinical characteristics (safety analysis set)

	Total (n = 1,186)
Mean age (SD), years	34.3 (13.4)
Gender, n (%)	
Male	598 (50.4)
Race, n (%)	
Black or African American	23 (1.9)
Asian	250 (21.1)
White	881 (74.3)
Other	32 (2.7)
Mean body mass index (SD), kg/m^2	25.0 (5.4)
Pre-perampanel seizure frequency per 28 days, median (range)	11.2 (1.2–4503.9)
No. concomitant AEDs at baseline (double-blind), n (%)	
1 AED	159 (13.4)
2 AEDs	596 (50.3)
3 AEDs	431 (36.3)
Mean number of AEDs at baseline (double-blind)	2.2
Most common concomitant AEDs at baseline (double-blind), n (%)[a]	
Carbamazepine	400 (33.7)
Valproic acid	399 (33.6)
Lamotrigine	374 (31.5)
Levetiracetam	344 (29.0)
Topiramate	239 (20.2)
Oxcarbazepine	213 (18.0)

[a]Data shown for AEDs used in ≥10% of all patients.
AED, antiepileptic drug; SD, standard deviation.

The median (range) duration of exposure to perampanel for the safety analysis set was 51.4 (1.1–128.1) weeks and mean exposure (±standard deviation [SD]) was 52.5 ± 25.6 weeks. Most patients (n = 1,084, 91.4%) were exposed to perampanel doses of 10 mg or 12 mg/day; the mean ± SD dose of perampanel across the entire extension treatment phase in the safety analysis set was 10.1 ± 2.3 mg. Among the 840 patients remaining on perampanel treatment at the interim cutoff date, no patients were still receiving 2 mg/day, eight were receiving 4 mg/day, 45 were receiving 6 mg or 8 mg/day, and 787 were receiving 10 mg or 12 mg/day (92 patients in the conversion period and 695 in the maintenance period).

Tolerability and safety

One thousand thirty-seven patients (87.4%) reported at least one treatment-emergent AE (TEAE) in the core phase III studies and/or the extension study (Table 3). TEAEs were considered treatment-related in 78.2% of all patients and were described as mild or moderate in 73.0% of patients. The proportion of patients with TEAEs was similar among those taking one, two, or three AEDs at baseline (one AED, n = 140 [88.1%]; two AEDs, n = 515 [86.4%]; and three AEDs, n = 382 [88.6%]). TEAEs leading to withdrawal, dose reduction, or dose interruption occurred in 157 (13.2%), 428 (36.1%), and 39 (3.3%) patients respectively. AEs leading to dose adjustment or interruption in ≥2% of patients were dizziness (20.7%), somnolence (7.3%), ataxia (3.3%), fatigue (2.9%), headache (2.3%), and gait disturbance (2.0%). Dizziness (3.0%), irritability (1.2%), and aggression (1.1%) were the only AEs to result in discontinuation in ≥1% of patients.

TEAEs occurring in ≥5% of patients are shown in Table 4. The most commonly reported TEAEs were dizziness, somnolence, headache, and fatigue. As duration of exposure to each dose of perampanel varied in this study, it was not possible to determine if the incidence of TEAEs was dose-related. TEAEs related to depression were reported in 59 (5.0%) patients (depression n = 46, depressed

Table 3. Incidence of TEAEs (safety analysis set)

	Extent of exposure, n (%)				
	<4 mg/day[a] (n = 1)	4 mg/day[a] (n = 15)	>4–8 mg/day[a] (n = 86)	>8–12 mg/day[a] (n = 1,084)	Total (n = 1,186)
Any TEAE	1 (100)	13 (86.7)	83 (96.5)	940 (86.7)	1,037 (87.4)
Severe TEAEs	0	2 (13.3)	16 (18.6)	153 (14.1)	171 (14.4)
Any treatment-related TEAE	0	13 (86.7)	82 (95.3)	832 (76.8)	927 (78.2)
Any serious TEAE	0	2 (13.3)	11 (12.8)	144 (13.3)	157 (13.2)
Any TEAE leading to discontinuation of study or study drug	1 (100)	6 (40.0)	23 (26.7)	127 (11.7)	157 (13.2)
Any TEAE leading to dose reduction	0	10 (66.7)	69 (80.2)	349 (32.2)	428 (36.1)
Any TEAE leading to dose interruption	0	0	2 (2.3)	37 (3.4)	39 (3.3)

[a]Maximum daily dose of perampanel exposed.
TEAE, treatment-emergent adverse event.

Table 4. Incidence of TEAEs occurring in ≥5% of patients (safety analysis set)

	Extent of exposure, n (%)				
	<4 mg/day[a] (n = 1)	4 mg/day[a] (n = 15)	>4–8 mg/day[a] (n = 86)	>8–12 mg/day[a] (n = 1,084)	Total (n = 1,186)
Dizziness	0	9 (60.0)	51 (59.3)	461 (42.5)	521 (43.9)
Somnolence	0	3 (20.0)	23 (26.7)	214 (19.7)	240 (20.2)
Headache	0	2 (13.3)	24 (27.9)	172 (15.9)	198 (16.7)
Fatigue	0	2 (13.3)	13 (15.1)	128 (11.8)	143 (12.1)
Irritability	0	1 (6.7)	8 (9.3)	107 (9.9)	116 (9.8)
Nasopharyngitis	0	0	2 (2.3)	85 (7.8)	87 (7.3)
Fall	0	1 (6.7)	5 (5.8)	75 (6.9)	81 (6.8)
Nausea	0	2 (13.3)	7 (8.1)	72 (6.6)	81 (6.8)
Weight increased	0	0	3 (3.5)	78 (7.2)	81 (6.8)
Ataxia	0	0	10 (11.6)	63 (5.8)	73 (6.2)
Gait disturbance	0	0	7 (8.1)	62 (5.7)	69 (5.8)
Convulsion	0	0	3 (3.5)	62 (5.7)	65 (5.5)
Vertigo	0	1 (6.7)	7 (8.1)	57 (5.3)	65 (5.5)
Balance disorder	0	0	5 (5.8)	59 (5.4)	64 (5.4)
Vomiting	0	2 (13.3)	0	61 (5.6)	63 (5.3)
Upper respiratory tract infection	0	1 (6.7)	5 (5.8)	56 (5.2)	62 (5.2)

[a]Maximum daily dose of perampanel exposed.
TEAE, treatment-emergent adverse event.

mood n = 11, depressive symptom n = 1, and major depression n = 1). Anxiety and confusional state were reported in 46 (3.9%) and 20 (1.7%) patients, respectively. Worsening seizures were defined as a >50% increase in seizure frequency compared with baseline. At the end of the conversion period (n = 1,207), the percentages of patients with worsening seizures for those previously randomized to placebo, 2, 4, 8, and 12 mg were 8.7%, 4.8%, 5.8%, 7.6%, and 11.0%, respectively. At the end of 1 year of the extension maintenance period (n = 239), the percentages were 4.7%, 0%, 2.5%, 8.3%, and 10.7%, respectively.

Serious AEs (SAEs) occurred in 157 patients (13.2%). The only SAEs to occur in >1% of patients were those related to seizures, which were reported by 24 (2%) patients. These included increased seizure frequency (n = 7/24), breakthrough seizures (n = 3/24), exacerbation of seizures (n = 4/24), seizure clusters (n = 2/24), recurrent seizures (n = 4/24), convulsions (n = 3/24), and uncontrolled or intractable seizures (n = 2/24). Status epilepticus was reported as an SAE in nine (<1%) patients. Other SAEs that occurred in more than five patients were aggression (n = 10, <1%), psychotic disorder (n = 6, <1%), and suicidal ideation (n = 6, <1% [four patients required hospitalization and four discontinued from perampanel treatment]). Three deaths occurred: one due to a road traffic accident; one due to sudden unexpected death in epilepsy; and one due to cerebral hemorrhage. None of the deaths were considered to be related to study treatment.

The incidence of markedly abnormal laboratory values during the study was low (0–4.5%). Alanine aminotransferase or aspartate aminotransferase levels >3× upper limit of normal (ULN) were <1%, and creatine phosphokinase levels >5× ULN were 1.7%. The majority of markedly abnormal values occurred in patients taking concomitant carbamazepine, oxcarbazepine, or valproic acid: 34/34 with abnormally low sodium values, 41/50 with low neutrophil values, and 14/24 with a markedly low white blood cell count.

The incidence of notably high or low systolic or diastolic blood pressure (changes of ≥20 or ≥15 mm Hg, respectively) was <2%. After 50 weeks of treatment, the mean (SD) change from baseline in weight was 0.9 (3.0) kg in patients exposed to a maximum perampanel dose of 4 mg/day, 1.7 (4.1) kg in patients exposed to 6 mg or 8 mg/day, and 2.3 (4.6) kg in patients exposed to 10 mg or 12 mg/day. Overall, clinically notable increases or decreases in body weight (>7%) were observed in 29.5% and 7.6% of patients, respectively. There were no clinically important changes in ECG parameters and no patients had a QTcF or QTcB value >500 msec during perampanel treatment. Less than 1% of patients had a >60 msec change from baseline in QTcF or QTcB (two patients and seven patients, respectively).

Seizure frequency data

The percent change in seizure frequency per 28 days in perampanel-treated patients over 2 years, relative to the pre-perampanel baseline, is shown in Fig. 1A for four subsets of patients; those with at least 26, 39, 52, and 104 weeks of perampanel exposure. Seizure frequency decreased over the first 26 weeks with adjunctive perampanel treatment, and was maintained over the duration of the study. The median pre-perampanel seizure frequency per 28 days was 11.2 overall, and 11.5 during the phase III baseline period for patients receiving placebo in the double-blind studies. At the end of the 16-week blinded conversion period, there was no difference in the median percent change in seizure frequency between patients previously randomized to placebo

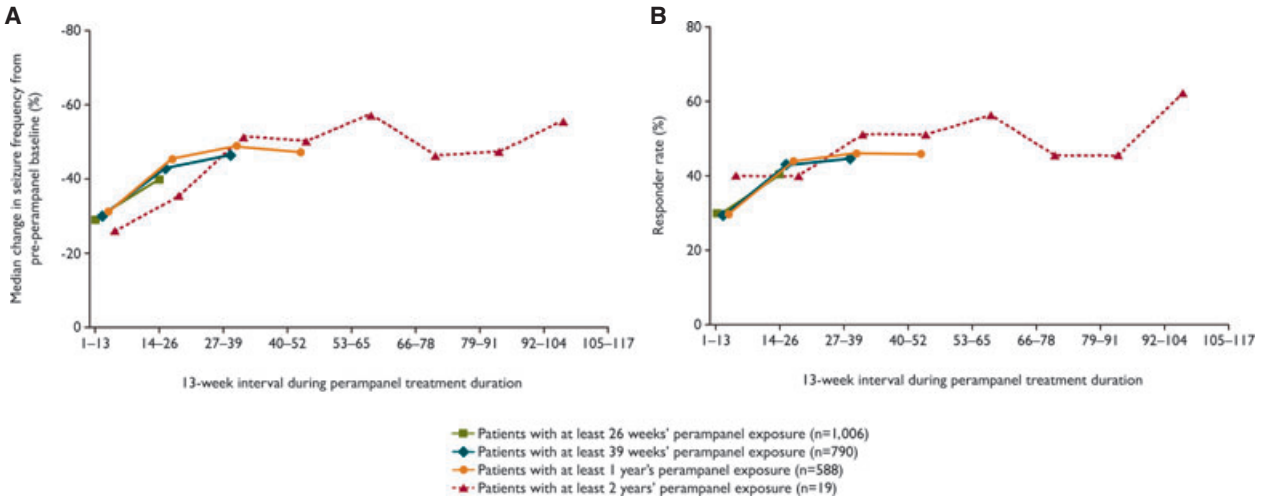

Figure 1.
(**A**) Median percent change in seizure frequency per 28 days (relative to pre-perampanel baseline) and (**B**) responder rate, by 13-week interval during open-label perampanel treatment (intent-to-treat analysis set).
Epilepsia © ILAE

in the double-blind studies (−42.4%, n = 369) and those randomized to perampanel (−41.5%, n = 817). This decrease in seizure frequency at the end of the conversion period was maintained in both groups of patients during the open-label maintenance period (Fig. 2A).

The sustained reduction in seizure frequency was observed in patients who had at least 26 weeks, 39 weeks, 1 year, and 2 years of perampanel exposure (Fig. 1A). In the 588 patients with at least 1 year of exposure to perampanel, the median percent change in seizure frequency per 28 days in the last 13-week interval was −47.2%. In the 19 patients with at least 2 years of exposure to perampanel, the median percent change in seizure frequency per 28 days in the last 13-week interval was −56.0%. The overall median percent changes in seizure frequency by each 13-week interval of perampanel treatment were the following: −29.1% for weeks 1–13 (n = 1,207); −39.2% for weeks 14–26 (n = 1,114); −44.0% for weeks 27–39 (n = 979); −46.5% for weeks 40–52 (n = 731); −51.2% for weeks 53–65 (n = 495); −52.3% for weeks 66–78 (n = 323); −51.2% for weeks 79–91 (n = 176); and −58.1% for weeks 92–104 (n = 59).

Figure 1B shows the proportion of patients experiencing a ≥50% reduction in seizure frequency (all types) over time. Responder rates increased in the first 26 weeks following perampanel treatment and were then generally stable across time. Responder rates at the end of the blinded conversion period were 44.2% (n = 369) and 43.3% (n = 817) for patients previously randomized to placebo and for those receiving perampanel in the double-blind studies, respectively. Improvements in responder rates at the end of the blinded conversion period were also maintained in both groups throughout the open-label maintenance period (Fig. 2B).

In patients with at least 1 year of exposure to perampanel (n = 588), the responder rate at the end of 1 year was 47.6%. In patients with at least 2 years of exposure to perampanel (n = 19), the responder rate at the end of 2 years was 63.2%. The overall responder rates by each 13-week interval of perampanel treatment were: 31.1% for weeks 1–13 (n = 1,207); 41.4% for weeks 14–26 (n = 1,114); 45.3% for weeks 27–39 (n = 979); 46.9% for weeks 40–52 (n = 731); 50.7% for weeks 53–65 (n = 495); 51.1% for weeks 66–78 (n = 323); 51.7% for weeks 79–91 (n = 176); and 62.7% for weeks 92–104 (n = 59), respectively. An analysis of seizure-free patients in the extension study with at least 6 (n = 586), 9 (n = 410), and 12 (n = 238) months of data was performed. Of the patients with 6 months of data, 16.4% were seizure-free for the last 3 months and 8.9% for the entire 6 months. For the patients with 9 and 12 months of data, the seizure-free rates for the entire 9 or 12-month period were 7.6% and 7.1%, respectively.

There were only three patients with data for weeks 79–91 of the open-label maintenance period and only one for weeks 92–104.

For both efficacy end points, improvements were greater at the end of the blinded conversion period compared with the end of the maintenance period in the double-blind studies (Fig. 2A,B).

Discussion

The interim results from this extension study of three pivotal phase III trials demonstrated that long-term adjunctive treatment with once-daily perampanel, at an average daily dose of approximately 10 mg, and over a dose range of 2–12 mg/day, had a favorable tolerability profile in patients

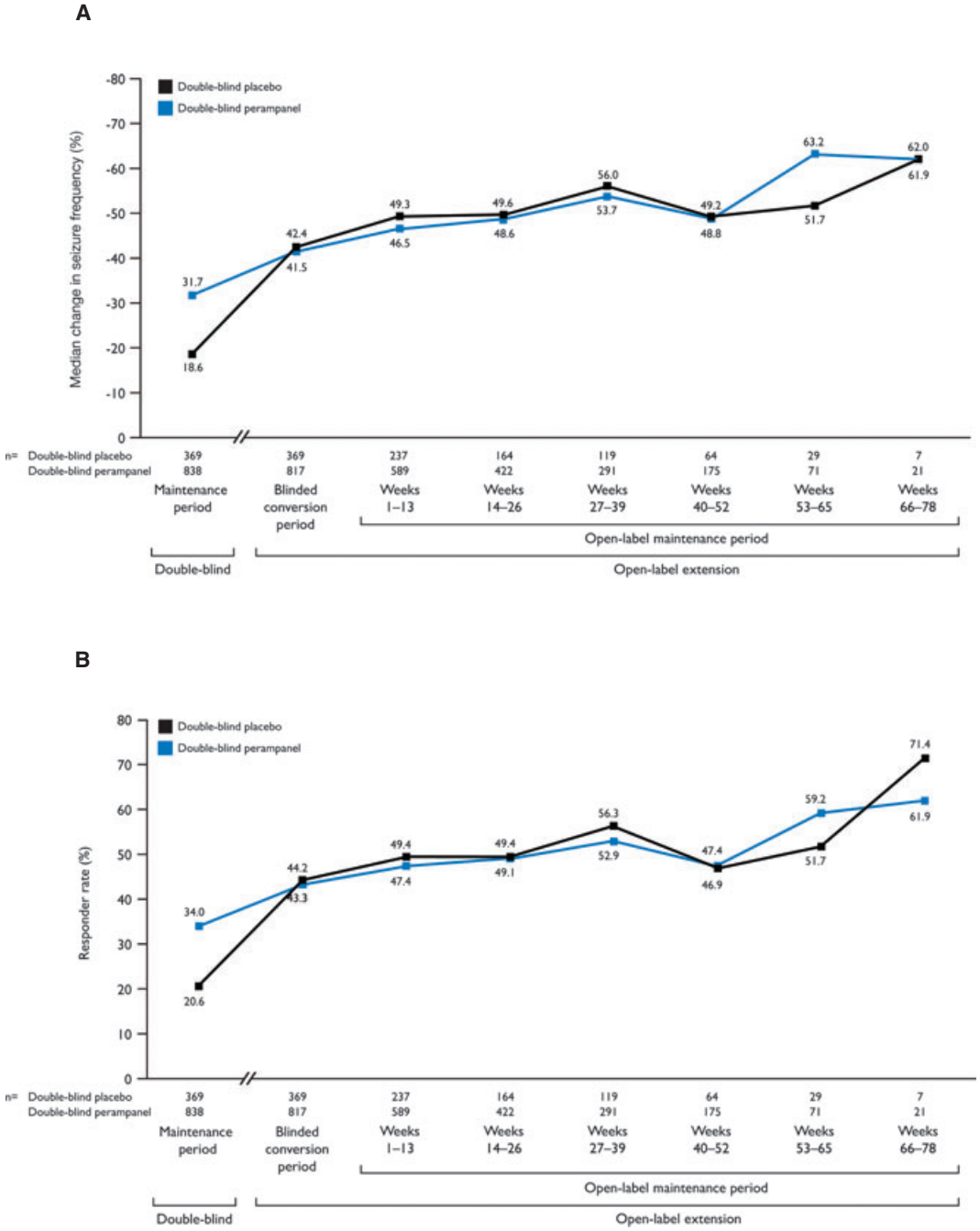

Figure 2.
(**A**) Median percent change in seizure frequency per 28 days (relative to pre-perampanel baseline) and (**B**) responder rate, at the end of the double-blind maintenance period, the end of the blinded conversion period, and by each 13-week interval during the open-label maintenance period (intent-to-treat analysis set).
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with refractory partial-onset seizures. This was reflected by relatively low rates of discontinuations due to AEs and a retention rate on treatment of >70% after an average exposure period of approximately 1 year. Furthermore, the reduction in seizure frequency and increase in responder rates achieved at the end of the phase III studies were also achieved by patients who converted from placebo to perampanel treatment during the blinded conversion period of the extension study. Patients' seizure frequencies were stable during the 1- to 2-year monitoring period.

As perampanel is the first selective AMPA receptor antagonist agent developed as an AED in large pivotal trials

(Hanada et al., 2011), this study is important to evaluate the safety and tolerability of a new class of AEDs. The vast majority (>91%) of patients in this study were titrated to doses of 10–12 mg/day, with close to 50% of patients having >1 year of exposure in this dose range. Discontinuation rates during the extension study were similar in patients who had been randomized to perampanel in the initial phase III studies and those who had not been previously exposed to perampanel. The safety of perampanel in patients following long-term treatment was consistent with the results from the phase II and III clinical trials (French et al., 2012a,b; Krauss et al., 2012a,b). Specifically, no new safety signals were identified. The most frequent AEs reported were dizziness, somnolence, headache, and fatigue, which are central nervous system (CNS) effects commonly seen with other AEDs (St Louis, 2009) and are consistent with common AEs reported in other long-term studies of AED safety (Beydoun et al., 2003; Wroe et al., 2008; Halász et al., 2010). Despite data in preclinical studies demonstrating that injection of an AMPA antagonist directly into the CNS reduced food intake (Zheng et al., 2002), clinically notable decreases (>7%) in weight were observed in only 7.6% of patients in this study. Clinically notable increases (>7%) in weight occurred in 29.5% of patients. Although patients aged 12–17 years were included in the current study, the safety and tolerability of perampanel specifically in adolescents will be reported separately.

In the initial phase III core studies, with a maximum treatment period of 19 weeks, perampanel significantly reduced seizure frequency and increased responder rates in refractory patients with partial-onset seizures compared with placebo. In this large long-term extension study, changes in seizure frequency remained stable during a 1- to 2-year period of perampanel treatment. However, the extension study did not include a placebo comparison and did not limit patients from receiving changes in concomitant therapies that may have maintained efficacy. Patients who were randomized to placebo in the double-blind studies achieved the same seizure reduction during the conversion period of the extension study as those who were randomized to perampanel. Similarly, improvements in both end points at the end of the blinded conversion period of the extension study compared with the maintenance period of the phase III studies are also likely to reflect the up-titration of dose in patients randomized to lower doses in the phase III studies.

All patients enrolled in this study were taking between one and three concomitant AEDs at study entry; >86% of patients were taking two or three AEDs at baseline. The incidence of TEAEs was similar in patients taking one, two, or three AEDs, suggesting that perampanel tolerability is not adversely affected by concomitant intake of multiple AEDs.

In conclusion, these interim results demonstrated that once-daily adjunctive perampanel, at doses up to 12 mg/day, had a good tolerability profile in patients with partial-onset seizures. Furthermore, reduced seizure frequency and improved responder rates were consistent and maintained during 1–2 years of continued perampanel therapy.

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Supporting Information

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

Table S1. Cumulative extent of exposure to perampanel up to date of interim data cutoff (safety analysis set).

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