Movement Disorders
Vol. 25, No. 7, 2010, pp. 896–905

Safety and Efficacy of Perampanel in Advanced Parkinson's Disease: A Randomized, Placebo-Controlled Study

Karla Eggert, MD,[1] David Squillacote, MD,[2] Paolo Barone, MD,[3] Richard Dodel, MD,[4] Regina Katzenschlager, MD,[5] Murat Emre, MD,[6] Andrew J. Lees, MD,[7] Olivier Rascol, MD, PhD,[8,9] Werner Poewe, MD,[10] Eduardo Tolosa, MD,[11] Claudia Trenkwalder, MD,[12] Marco Onofrj, MD,[13] Fabrizio Stocchi, MD, PhD,[14] Giuseppe Nappi, MD,[15,16] Vladimir Kostic, MD,[17] Jagoda Potic, MD,[18] Evzen Ruzicka, MD, DSc,[19] Wolfgang Oertel, MD,[1]*
and in cooperation with the German Competence Network on Parkinson's Disease

[1]*German Competence Network on Parkinson's Disease, Department of Neurology, Philipps-University Marburg, Marburg, Germany*
[2]*Eisai Global Clinical Development, Eisai Medical Research Inc., Woodcliff Lake, New Jersey, USA*
[3]*Department of Neurological Sciences, University of Naples Federico II-IDC Hermitage-Capodimonte, Naples, Italy*
[4]*Department of Neurology, Rheinische Friedrich-Wilhelms-University, Bonn, Germany*
[5]*Department of Neurology, Donauspital, Vienna, Austria*
[6]*Department of Neurology, Istanbul Medical School, Istanbul, Turkey*
[7]*Reta Lila Weston Institute of Neurological Studies, University College London, London, United Kingdom*
[8]*Clinical Investigation Center, INSERM CIC9302, University Hospital Toulouse, Toulouse, France*
[9]*Departments of Clinical Pharmacology and Neurosciences, INSERM UMR825, University Hospital Toulouse, Toulouse, France*
[10]*Department of Neurology, Medical University Innsbruck, Innsbruck, Austria*
[11]*Neurology Service, Hospital Clinic, Universitat de Barcelona, CIBERNED, Barcelona, Spain*
[12]*Paracelsus-Elena Klinik, Kassel, Germany*
[13]*Clinica Neurologica, Universitàˋ Chieti-Pescara, Italy*
[14]*Department of Neurology, IRCCS San Raffaele, Rome, Italy*
[15]*Chair of Neurology, University "La Sapienza," Rome, Italy*
[16]*IRCCS "C. Mondino Institute of Neurology" Foundation, Pavia, Italy*
[17]*Institute of Neurology, Clinical Centre of Serbia, Belgrade, Serbia*
[18]*Clinic for Neurology and Psychiatry, Clinical Hospital Centre "Zvezdara," Belgrade, Serbia*
[19]*Department of Neurology, Charles University in Prague, 1st Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic*

*Correspondence to: Dr. Wolfgang Oertel, German Competence Network on Parkinson's Disease, Department of Neurology, Philipps-University Marburg, Rudolf-Bultmann-Str. 8, D-35033 Marburg, Germany. E-mail: oertelw@med.uni-marburg.de

Potential conflict of interest: This study and editorial support were sponsored by Eisai Co., Ltd. No compensation was provided to the authors for their work on this manuscript. All authors, except for Dr. Squillacote, received compensation from Eisai for their site's conduct of the study. Drs. Barone, Lees, and Oertel received honoraria from Eisai as members of the Advisory Board of this study. Dr. Rascol has received unrestricted scientific grant and honoraria from Eisai for his advice to the company on this project. Dr. Dodel received honoraria from Eisai for presenting the study at meetings. Drs. Katzenschlager, Poewe, Kostic, and Ruzicka received honoraria from Eisai for consulting in relation to this study. Dr. Emre has been on the Protocol Development and Advisory Committee for the study and received honoraria for his advice. Dr. Onofrj received honoraria from Eisai in his capacity as Principal Investigator.

Received 3 February 2009; Revised 19 November 2009; Accepted 20 November 2009

Published online 29 March 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22974

Abstract: Perampanel, a novel, noncompetitive, selective AMPA-receptor antagonist demonstrated evidence of efficacy in reducing motor symptoms in animal models of Parkinson's disease (PD). We assessed the safety and efficacy of perampanel for treatment of "wearing off" motor fluctuations in patients with PD. Patients (N = 263) were randomly assigned to once-daily add-on 0.5, 1, or 2 mg of perampanel or placebo. The primary objective was to determine whether there was a dose-response relationship for efficacy among the 3 perampanel doses and placebo. The primary efficacy endpoint for each treatment was measured as the least-squares (LS) mean change from baseline to week 12 in percent "off" time reduction during the waking day, as recorded by patient diaries. The primary efficacy analysis was a 1-sided Williams test for dose-response trend at the 0.025 level of significance. At week 12, dose-response trends, as determined by the Williams test, were not statistically significant for LS mean reduction in percent "off" time during the waking day ($P = 0.061$, with significance defined as $P \leq 0.025$). The 2 higher perampanel doses (ITT population; n = 258) produced nonsignificant reductions from baseline to week 12 in percent "off" time during the waking day versus placebo (7.59%, $P = 0.421$ [1 mg], 8.60%, $P = 0.257$ [2 mg] versus 5.05% [placebo]; significance for pairwise comparisons defined as $P \leq 0.05$). There were no significant changes in dyskinesia or cognitive function in any perampanel group versus placebo. Adverse events were similar across treatment groups. Perampanel treatment was well tolerated and safe, but failed to achieve statistical significance in primary and secondary endpoints. © 2010 Movement Disorder Society

Key words: Parkinson's disease; motor fluctuations; dyskinesia; perampanel; AMPA receptor antagonist

Treatment of advanced Parkinson's disease (PD) is a challenge because it must achieve control of motor and nonmotor disease symptoms without impairing cognitive function or inducing intolerable side effects. Levodopa (L-dopa) is the most efficacious therapy for treating symptoms,[1–3] but motor fluctuations and dyskinesias can compromise long-term therapeutic response.[1,2,4]

Several classes of antiparkinsonian therapies, including catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and dopamine agonists, have demonstrated beneficial effects as adjunctive therapy to improve the efficacy of L-dopa or to partially substitute for L-dopa.[5–9]

It is believed that dopamine depletion in patients with PD results in overactivation of glutamatergic brain pathways, such as the corticostriatal pathway. Reduction or blockade of excessive transmission in glutamatergic pathways may reduce PD symptoms and alleviate dopaminergic treatment-induced side effects.[10,11]

α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-type glutamate receptor antagonists have been reported to prolong the effect of L-dopa and reduce "wearing off" effects in PD rat models.[12,13] AMPA receptor antagonists have also increased locomotor activity after L-dopa administration and reduced L-dopa–induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys.[12,14] Perampanel, a potent, selective, noncompetitive AMPA-type glutamate receptor antagonist, has shown evidence of efficacy in reducing motor symptoms in PD animal models.[15–17] This article describes the first study of perampanel in patients with PD. This phase II dose-ranging study assessed the safety, tolerability, and efficacy of perampanel for the treatment of "wearing off" motor fluctuations and dyskinesias in patients with PD.

SUBJECTS AND METHODS

This double-blind, placebo-controlled, dose-ranging study enrolled 263 idiopathic patients with PD fulfilling the United Kingdom Brain Bank diagnostic criteria from 38 centers across Europe (Table 1). Subjects were men and women aged 30 to 75 years who were taking L-dopa at least three times daily. All study subjects fulfilled the following inclusion criteria: motor fluctuations of the "wearing-off type" with at least 2.5 hours of "off" time during the waking day; at least 90 minutes of "off' time during the 8-hour period following the morning dose of L-dopa; clinically relevant dyskinesias during the "on" period; and a Hoehn and Yahr score[18] from II to IV during the "off" periods.

Eligible subjects were randomly assigned to receive perampanel 0.5, 1, or 2 mg/d, or placebo in a 1:1:1:1 ratio. The study consisted of two screening visits, a baseline 2-day inpatient stay (day −1 to 1) and a double-blind treatment period of up to 12 weeks. Safety visits occurred at weeks 1, 2, 4, 6, and 8. Efficacy was assessed at weeks 2, 4, 6, and at week 12 (2-day inpatient stay). Blood samples for measurement of L-dopa concentration were taken at baseline and week 12, 30 minutes before the usual dose of L-dopa was given, and then 30 minutes and 2 and 3 hours after L-dopa and study medication intake. Follow-up visits occurred at weeks 14 and 16. During the treatment period, subjects took 1 tablet of the study medication daily, at the same time as the first usual morning dose of L-dopa. PD treatments remained stable for at least 4 weeks before the baseline visit and throughout the study, unless changes were medically indicated. All other concomitant medications remained at a constant dose during the study. Because plasma concentrations of perampanel appear to be higher in women than in

TABLE 1. *Demographics and baseline characteristics*

		Perampanel		
	Placebo (n = 66)	0.5 mg (n = 68)	1 mg (n = 65)	2 mg (n = 64)
Age (yr)				
Mean (SD)	63.4 (8.66)	61.5 (8.62)	62.8 (7.99)	63.2 (7.62)
Range	39, 77	39, 74	33, 76	45, 76
Sex, n (%)				
Men	37 (56.1)	39 (57.4)	36 (55.4)	35 (54.7)
Women	29 (43.9)	29 (42.6)	29 (44.6)	29 (45.3)
Race, n (%)				
White	66 (100)	68 (100)	65 (100)	64 (100)
Duration of PD (yr)				
Mean (SD)	10.2 (4.68)	10.1 (5.12)	11.7 (4.78)	10.8 (4.81)
Hoehn and Yahr score, n (%)				
Stage II	15 (22.7)	17 (25.0)	17 (26.2)	11 (17.2)
Stage III	36 (54.5)	34 (50.0)	34 (52.3)	33 (51.6)
Stage IV	15 (22.7)	17 (25.0)	14 (21.5)	20 (31.3)
Any parkinsonian medication,[a] n (%)	66 (100)	68 (100)	65 (100)	64 (100)
Levodopa and peripheral decarboxylase inhibitors				
Levodopa/carbidopa	40 (60.6)	39 (57.3)	34 (52.3)	36 (56.2)
Levodopa/benserazide	38 (57.6)	35 (51.5)	45 (69.2)	45 (70.4)
COMT inhibitors				
Entacapone	20 (30.3)	18 (26.5)	22 (33.8)	22 (34.4)
NMDA antagonists				
Amantadine hydrochloride	25 (37.9)	22 (32.4)	22 (33.8)	23 (35.9)
Amantadine sulfate	4 (6.1)	5 (7.4)	4 (6.2)	4 (6.3)
Dopamine receptor agonists				
Cabergoline	16 (24.2)	21 (30.9)	16 (24.6)	16 (25.0)
Pramipexole	17 (25.8)	19 (27.9)	22 (33.8)	14 (21.9)
Ropinirole	8 (12.1)	9 (13.2)	4 (6.2)	9 (14.1)
Pergolide	6 (9.1)	9 (13.2)	6 (9.2)	8 (12.5)
Bromocriptine	8 (12.1)	8 (11.8)	8 (12.3)	5 (7.8)
MAO inhibitors				
Selegiline hydrochloride	9 (13.6)	8 (11.8)	17 (26.2)	11 (17.2)

[a]Concomitant parkinsonian medications taken by at least 5% of subjects in any treatment group.

men, as observed in a previous study,[19] randomization was stratified by gender. Subjects were also stratified by concomitant amantadine use.

Primary Endpoint

The primary objective was to determine whether there was a dose-response relationship for efficacy among the 3 perampanel doses and placebo. The primary efficacy endpoint for each treatment was measured as the least-squares (LS) mean change from baseline to week 12 in percent "off' time reduction during the waking day, as recorded by subject diaries (intent-to-treat [ITT] population). The primary efficacy analysis was a 1-sided Williams test for dose-response trend at the 0.025 level of significance. Significance for pairwise comparisons between perampanel and placebo was defined as $P \leq 0.05$.

Subjects marked boxes in their diary every 30 minutes of the waking day for 3 consecutive days before baseline and before each of the efficacy visits indicating whether they spent that half-hour predominantly asleep, in an "off" state, or in an "on" state with no, mild, moderate, or severe dyskinesias.

Secondary Endpoints

Secondary endpoints (ITT population) included the following: change from baseline to week 12 in absolute "off" time; change from baseline to week 12 in dyskinesia severity (duration and disability) determined by the Unified Parkinson's Disease Rating Scale (UPDRS)[20] (Part IV: questions 32, 33); optimal dose of perampanel was determined according to the opinion of the physician based on the overall efficacy visit data showing improvement of the subject, the Clinical Global Impression (CGI) of change, and CGI of tolerability[21]; nature of dose- and concentration-response relationships; and effect of perampanel on L-dopa plasma level. At baseline and week 12, L-dopa peak-dose dyskinesias were assessed every 20 minutes for three times after onset of the first "on" state following

the first morning dose of L-dopa. A trained rater assessed the subjects using a modified Abnormal Involuntary Movement Scale (AIMS)[22] and Goetz scale.[23] Responder rates for the proportion of subjects who had a reduction in absolute "off" time at week 12 of ≥30, ≥60, ≥90, or ≥120 minutes compared with baseline were calculated.

Adverse events (AEs), physical and neurologic examinations, and laboratory tests were used to assess safety and tolerability of treatment throughout the study. Cognitive function was assessed using the Mini-Mental State Examination (MMSE),[24] Symbol Digit Modalities Test (SDMT),[25] and Adapted Digit Ordering Test (DOT-A).[26] CGI of Tolerability[21] was assessed using a 5-point scale at weeks 6, 12, 16, and at any early termination visit.

Statistical Analyses

The primary efficacy endpoint was analyzed using the Williams test for global trend at the 0.025 level of significance. The Williams test evaluates whether there is an increasing dose-response relationship. A mixed effects analysis of variance (ANOVA) model was performed with a random term for patient, a fixed term for treatment, and the covariates of gender, concomitant amantadine, baseline L-dopa dose, country, and age. Statistical tests were 2-sided at the 0.05 level of significance, unless otherwise noted (e.g., primary efficacy endpoint); final inferences were based on LS means, unless otherwise stated. The efficacy comparison of the individual perampanel doses with placebo were tested hierarchically as supportive analysis and no adjustments were made for multiplicity. The highest dose was tested first in the hierarchy. Point estimates of each of the perampanel dose versus placebo comparisons, with the appropriate 95% confidence intervals (CIs), were provided.

The primary statistical analyses were performed according to the ITT principle. The ITT population included subjects who took at least 1 dose of study medication and had at least 1 baseline and 1 postbaseline measure of the primary endpoint. For efficacy analyses, if data of a subject for a particular visit were missing, the last available postbaseline observation for that subject was carried forward for that visit to minimize bias due to withdrawals. In addition to the ITT population, the modified strictly stable evaluable (MSSE) population was analyzed, including those subjects who were kept on stable PD medication for the entire duration of the study. The safety population included all subjects who took at least 1 dose of study medication.

For secondary endpoints, perampanel and placebo comparisons followed a closed-testing procedure to adjust for multiple comparisons in making inferences for each dose.

Assuming a placebo response rate of 8% in the change from baseline "off" time, a common standard deviation (SD) of 20%, a type I error of 5%, a total of 180 patients (45 per dose group) were required to detect a clinically relevant difference of at least 12% between treatment with perampanel 1 mg and placebo in "off" time reduction. Assuming a dropout rate of 20%, a total of 225 randomly assigned patients would be needed. There was no correction for multiplicity in the calculation of the sample size.

A post hoc analysis was performed to assess the change from baseline in mean total daily "off" time across the treatment period. The mean of the "off" times at weeks 2, 4, 6, and 12 was used to calculate the mean total daily "off" time across the treatment period. The results of this analysis are discussed in the ONLINE section of this article.

Institutional Review Board (IRB) approval was obtained for all participating centers in this trial and informed consent was obtained from all study participants.

RESULTS

Of 263 subjects randomly assigned to treatment, 226 completed the study (Fig. 1). The most common reason for discontinuation was treatment-emergent AEs (TEAEs) that occurred in similar numbers of subjects across treatment groups: 0.5 mg, 6 (8.8%); 1 mg, 4 (6.2%); 2 mg, 5 (7.8%); and placebo, 5 (7.6%). Only 1 subject (1.5%) in the 0.5-mg group discontinued because of lack of therapeutic efficacy. Demographics and baseline characteristics are shown in Table 1.

Primary Efficacy Measure

At week 12, dose-response trends, as determined by the Williams test, were not statistically significant for LS mean reduction in percent "off" time during the waking day ($P = 0.061$, with significance defined as $P \leq 0.025$). The largest LS mean decrease from baseline was in the perampanel 2-mg group (8.6%), but the difference from placebo (5.05% decrease) was not statistically significant ($P = 0.257$, significance for pairwise comparisons defined as $P \leq 0.05$). At baseline, the mean percent "off" time was similar across treat-

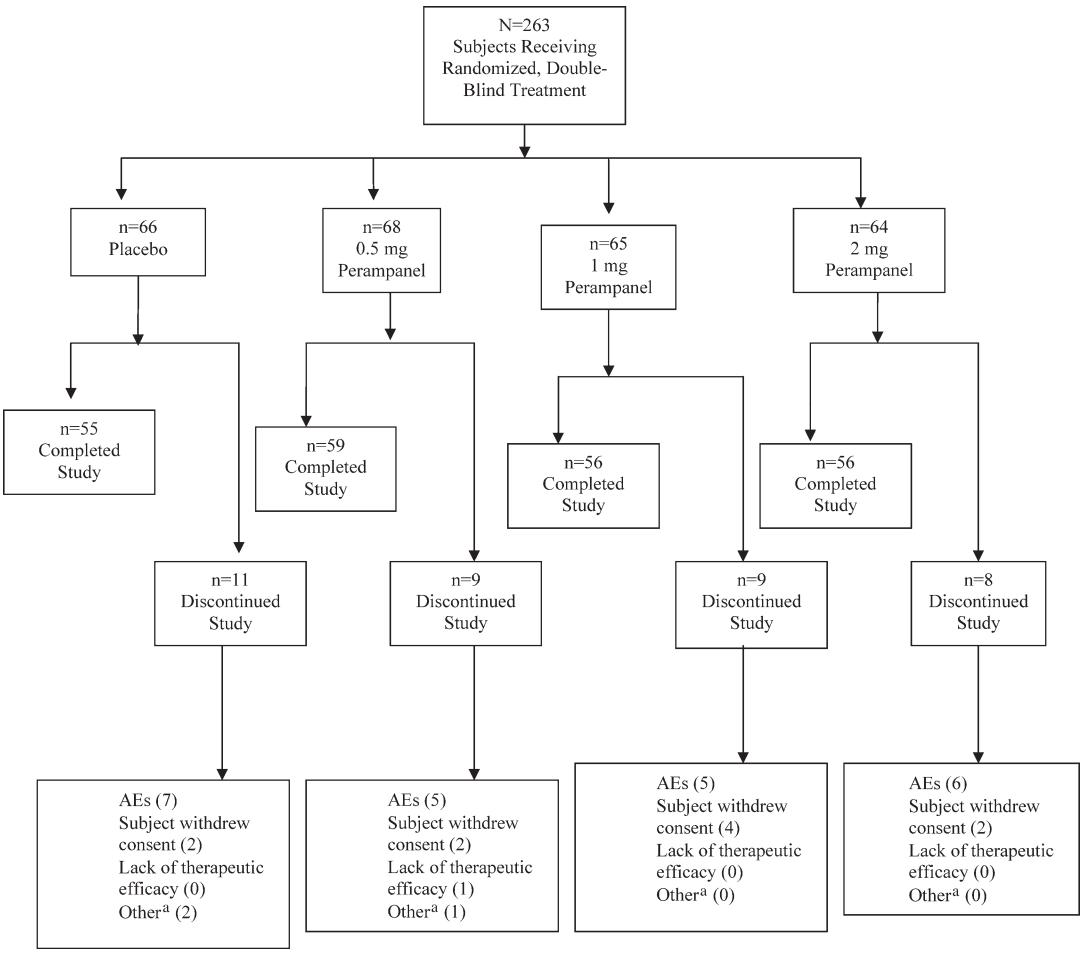

FIG. 1. Disposition of subjects.
[a]Other reasons were lost to follow-up (1 subject in the placebo group) and sponsor decision (1 subject each in the placebo and 0.5-mg groups).

ment groups in the ITT population (35–37% waking day). At week 12, the mean percent "off" time decreased from baseline for all treatment groups, including placebo (Table 2).

Review of the MSSE population (placebo, n = 47; 0.5 mg, n = 46; 1 mg, n = 47; 2 mg, n = 47) showed a greater reduction in the percent "off" time, namely −10.11% in the perampanel 2-mg group. The difference from placebo was nonsignificant, with −3.55% for the ITT ($P = 0.257$) and −4.47% for the MSSE population ($P = 0.183$). The Williams test for trend in dose response in the MSSE population was not statistically significant ($P = 0.065$).

There was no evidence that the perampanel treatment effect was different in amantadine users compared with nonusers for mean change from baseline to week 12 in percent "off" time: 0.5 mg (−2.30 versus −2.61), 1 mg (−6.28 versus −5.66), and 2 mg (−7.32 versus −8.98). The decrease in percent "off" time was greater in women than in men in most treatment groups, including the placebo group.

Secondary Efficacy Measures

At baseline, the mean absolute "off" time was 5.50 to 6.22 hours among the treatment groups (Table 2). The mean absolute "off" time at weeks 2, 4, 6, 12, 14, and 16 was generally lower than baseline for all treatment groups. Results were comparable to those for the primary endpoint. Dose-response trends in the perampanel treatment groups were apparent soon after dosing and were maintained throughout the study. At week 12, the Williams test for global trend approached statistical significance for a dose-response relationship ($P = 0.039$). The perampanel 2-mg treatment group showed the greatest reduction from baseline to week 12 in absolute "off" time, with an LS mean change of 1.39 hours, a difference of 0.7 hour versus placebo

TABLE 2. *Change from baseline to week 12 in percent and absolute "off" time, and change from baseline in mean total daily "off" time across treatment period (ITT population)*

		Perampanel			
	Placebo (n = 64)	0.5 mg (n = 67)	1 mg (n = 65)	2 mg (n = 62)	Trend *P* value
Percent off time (primary endpoint)					
Baseline mean (%)	35.03	34.76	37.00	37.35	0.061[a] (NS)
Week 12 mean (%)	31.49	31.27	31.35	29.00	
LS mean change	−5.05	−4.25	−7.59	−8.60	
LS mean change difference[b] (95% CIs)		0.81 (−5.33, 6.95)	−2.54 (−8.74, 3.66)	−3.55 (−9.70, 2.61)	
P value[c]		0.796 (NS)	0.421 (NS)	0.257 (NS)	
Absolute off time					
Baseline mean (hr)	5.50	5.80	5.98	6.22	0.039[a] (NS)
Week 12 mean (hr)	5.11	5.28	5.16	4.76	
LS mean change	−0.68	−0.53	−1.14	−1.39	
LS mean change difference[b] (95% CIs)		0.15 (−0.89, 1.19)	−0.46 (−1.51, 0.59)	−0.70 (−1.75, 0.34)	
P value[c]		0.771 (NS)	0.391 (NS)	0.185 (NS)	
Mean total daily off time[d]					
Baseline mean (hr)	5.50	5.80	5.98	6.22	0.007[a]
Mean across treatment period (hr)	5.14	5.06	5.02	4.90	
LS mean change	−0.48	−0.84	−1.04	−1.24	
LS mean change difference[b] (95% CIs)		−0.36 (−1.09, 0.38)	−0.56 (−1.30, 0.18)	−0.76 (−1.51, −0.01)	
P value[c]		0.342 (NS)	0.136 (NS)	0.046	

[a]Williams test for global trend (1-sided test; significance level at 0.025).
[b]LS mean difference in change from baseline between each perampanel group and placebo.
[c]*P* value for the pairwise comparison of change from baseline between each perampanel group and placebo (significance level at 0.05).
[d]Based on a post hoc analysis. The mean total daily off time was derived by calculating the mean of the "off" times across treatment period (i.e., weeks 2, 4, 6, and 12).
NS, nonsignificant.

(pairwise comparisons showed no statistically significant differences, $P = 0.185$). Of note, the analysis model for mean change from baseline in absolute "off" time did not indicate a significant effect of amantadine use in the perampanel-treated groups.

The proportions of subjects in the perampanel groups with mean reductions in absolute "off" time of ≥30, ≥60, ≥90, or ≥120 minutes were highest in the 2-mg group (60%, 52%, 44%, and 37%, respectively) versus placebo (39%, 34%, 31%, and 27%, respectively). The proportion of subjects having mean reductions in absolute "off" time ≥60 minutes was 52%, 43%, 39%, and 34% in the 2-mg, 1-mg, 0.5-mg, and placebo groups, respectively.

At baseline, approximately three-quarters of subjects had dyskinesias 1–50% of the waking day (Table 3).

TABLE 3. *Dyskinesias (duration and disability) at baseline and at week 12 measured using UPDRS (ITT population)*

			Perampanel					
	Placebo (n=64)		0.5 mg (n=67)		1 mg (n=65)		2 mg (n=62)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Dyskinesias Duration, n (% of day)								
None	0	2 (3.1)	0	1 (1.5)	0	1 (1.5)	0	3 (4.8)
1–25%	16 (25)	26 (40.6)	19 (28.4)	29 (43.3)	26 (40)	32 (49.2)	19 (30.6)	30 (48.4)
26–50%	29 (45.3)	20 (31.3)	32 (47.8)	22 (32.8)	23 (35.4)	12 (18.5)	28 (45.2)	16 (25.8)
51–75%	14 (21.9)	12 (18.8)	15 (22.4)	12 (17.9)	13 (20)	13 (20)	13 (21)	8 (12.9)
76–100%	5 (7.8)	1 (1.6)	1 (1.5)	0	3 (4.6)	2 (3.1)	2 (3.2)	3 (4.8)
Odds ratio vs. placebo (95% CI)			0.98 (0.45, 2.14)		1.06 (0.48, 2.36)		1.54 (0.71, 3.37)	
Dyskinesias Disability, n (%)								
None	4 (6.3)	10 (15.6)	4 (6.0)	12 (17.9)	9 (13.8)	16 (24.6)	6 (9.7)	16 (25.8)
Mild	24 (37.5)	32 (50)	24 (35.8)	27 (40.3)	25 (38.5)	26 (40)	19 (30.6)	23 (37.1)
Moderate	26 (40.6)	18 (28.1)	31 (46.3)	21 (31.3)	23 (35.4)	12 (18.5)	26 (41.9)	16 (25.8)
Severe	10 (15.6)	1 (1.6)	8 (11.9)	4 (6.0)	7 (10.8)	6 (9.2)	11 (17.7)	4 (6.5)
Completely disabled	0	0	0	0	1 (1.5)	0	0	1 (1.6)
Odds ratio vs. placebo (95% CI)			0.84 (0.43, 1.64)		1.10 (0.55, 2.18)		1.16 (0.58, 2.29)	

UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 4. *TEAE incidence in ≥3 subjects in any treatment group*[a]

	Placebo, n (%) (n = 66)	Perampanel, n (%)		
		0.5 mg (n = 68)	1 mg (n = 65)	2 mg (n = 64)
Akinesia	2 (3)	7 (10.3)	3 (4.6)	3 (4.7)
Bronchitis NOS	0	4 (5.9)	0	0
Constipation	1 (1.5)	3 (4.4)	2 (3.1)	0
Diarrhea NOS	1 (1.5)	2 (2.9)	0	3 (4.7)
Dyspnea	2 (3)	1 (1.5)	3 (4.6)	0
Fall	1 (1.5)	2 (2.9)	3 (4.6)	2 (3.1)
Hallucination NOS	4 (6.1)	1 (1.5)	2 (3.1)	1 (1.6)
Hypertension NOS	3 (4.5)	1 (1.5)	2 (3.1)	1 (1.6)
Nasopharyngitis	0	3 (4.4)	1 (1.5)	3 (4.7)
Edema peripheral	3 (4.5)	4 (5.9)	0	0
Urinary tract infection NOS	4 (6.1)	2 (2.9)	3 (4.6)	1 (1.6)
Vomiting NOS	0	0	0	3 (4.7)

[a]The Medical Dictionary for Regulated Activities (MedDRA), version 6.0, was used to report AE data.
NOS, not otherwise specified.

At week 12, in all treatment groups, the proportion of subjects in the 1–25% category increased, whereas the proportion of subjects in the 26–50% category decreased. There was no statistically significant difference between groups, although the odds ratio versus placebo was 1.54 for the perampanel 2-mg group compared with roughly 1 for the 0.5- and 1-mg groups (Table 3).

Similarly, at baseline, approximately three-quarters of subjects had mildly to moderately disabling dyskinesias (Table 3). Between baseline and week 12, the severity of dyskinesia improved for all treatment groups. Proportions of subjects with moderately disabling dyskinesias at week 12 were slightly lower than at baseline, whereas the proportions of subjects with mildly disabling dyskinesias increased for all treatment groups. There was no statistically significant difference between treatment groups. Odds ratios were close to 1 for the perampanel groups versus placebo. No statistically significant differences between perampanel and placebo treatment were observed in the Goetz score for all tasks and AIMS score at week 12.

Perampanel had no apparent effect on plasma concentrations of L-dopa, which were similar at baseline and at the end of week 12 in all treatment groups.

Findings of the post hoc analysis for mean total daily "off" time (ITT population) are shown in Table 2. At baseline, the mean total daily "off" time was 5.50 to 6.22 hours across treatment groups. The largest LS mean decrease of 1.24 hours from baseline in mean total daily "off" time across the treatment period was in the 2-mg group, with a statistically significant difference from placebo of 0.76 hour ($P = 0.046$). The pairwise comparisons of the 1- and 0.5-mg groups versus placebo were not significant. However, the Williams test for global trend indicated a statistically significant dose-response relationship ($P = 0.007$).

Safety and Tolerability

Compared with placebo, perampanel was generally well tolerated at all doses tested. TEAEs were reported in 52.9% (36 of 68), 49.2% (32 of 65), 42.2% (27 of 64), and 37.9% (25 of 66) of subjects in the 0.5-mg, 1-mg, 2-mg, and placebo groups, respectively. In all treatment groups, TEAEs were mostly mild to moderate. Table 4 lists the TEAEs occurring in ≥3 subjects in any treatment group. The most common TEAEs were akinesia, urinary tract infection not otherwise specified (NOS), hallucination NOS, and peripheral edema (Table 4). A total of 8 subjects experienced treatment-related serious AEs (SAEs): 4 in the placebo group (6.1%), 1 in the perampanel 0.5-mg group (1.5%), 1 in the 1-mg group (1.5%), and 2 in the 2-mg group (3.1%). Most SAEs that were possibly or probably related to treatment with study drug were resolved during the study.

Results of the cognitive function tests, DOT-A and SDMT, showed no evidence of treatment affecting working memory performance and accuracy in a code transcription task.

DISCUSSION

Perampanel was safe and well tolerated at the doses studied. Although the primary endpoint in this study was not met, there was a nonsignificant reduction in percent "off" time in the 2-mg perampanel group compared with placebo (with a difference of 3.55%, $P =$

0.257 for pairwise comparison). This treatment effect of 3.55% corresponded to an absolute "off" time difference of 0.7 hour in the perampanel 2-mg group versus placebo at week 12. Secondary efficacy analyses also failed to demonstrate a statistically significant benefit in the perampanel groups versus placebo, although reduction in absolute "off" time in the 2-mg group, including the change from baseline to week 12, was consistently greater than that in the other groups. Reduction in absolute "off" time was noted as early as week 2 from baseline and was maintained throughout the study for all treatment groups. Perampanel had a safety and tolerability profile similar to placebo.

The greater percent and absolute "off" time reductions observed in the 2-mg and 1-mg groups versus placebo, although not statistically significant, provided support for the existence of a potential treatment effect. The analyses of the MSSE population indicated that changes in PD medications during the study may have impacted the treatment effect size. Furthermore, the sample size determination had accounted for an 8% placebo response rate. However, the actual placebo response in the study was about 14%. The high placebo response rate is consistent with the placebo response rate of 16% (range: 0–55%) reported by Goetz et al. in a meta-analysis of 11 studies.[27] The high placebo response rate observed in our study may be attributed to a highly increased patient care that included full-time clinical and laboratory assessments during the inpatient stay of the study.

A gender effect was observed in the primary analysis, with women experiencing greater reductions from baseline in percent "off" time than men. Although these observations may be partly due to higher plasma concentrations of perampanel in women,[19] greater reductions were also observed in women taking placebo.

One of the study objectives was to examine the effect of perampanel on dyskinesias. Review of direct investigator observation (Goetz, UPDRS Part IV, and AIMS) revealed no improvement in dyskinesias in the perampanel-treated groups versus placebo, but also no significant worsening. This observation is encouraging, because previous studies found that other agents successful in reducing "off" time generally did so partly at the expense of increased dyskinesia.[5–9]

The numerical superiority of the 2 mg and 1 mg perampanel doses compared with placebo on the primary efficacy endpoints and the excellent safety and tolerability of all perampanel doses in this study suggested the need for further studies with higher doses of perampanel. Two global phase III studies were conducted at 2- and 4-mg versus placebo. Perampanel did not show a significant difference in "off" time reduction, and subsequently, the perampanel Parkinson's disease program was terminated.

Acknowledgments: We wish to thank Cynthia Pereira, MSc, MA, of Ogilvy Healthworld Medical Education for providing editorial assistance.

Financial Disclosures: Karla Eggert: Has worked as a consultant for Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Valeant Pharmaceuticals International, and Desitin. She has served on the advisory board of Orion Pharma, Schwarz Pharma Neuroscience (UCB), and Valeant Pharmaceuticals International. Dr. Eggert has received honoraria from Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Valeant Pharmaceuticals International, Desitin, Boehringer Ingelheim, and GlaxoSmithKline. She receives scientific grants from the German Ministry of Education and Health, Pitzer Foundation, and Rhön Foundation. David Squillacote: Is an employee of Eisai Co., Ltd., and has received contracts from the company. Paolo Barone: Is a consultant for Novartis, Schwarz Pharma/UCB, and Merck Serono, Eisai, Solvay, General Electric, and Lundbeck. He has served on the advisory board of Novartis, Schwarz Pharma/UCB, Merck Serono, and Eisai. Dr. Barone has also received grants from Boehringer Ingelheim, Novartis, Schwarz Pharma/UCB, and Merck Serono, Solvay, and Lundbeck. He is employed at the Department of Neurological Sciences-University of Napoli. Richard Dodel: Is a consultant for Rentschler and Lilly. He has received honoraria from Baxter, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Lundbeck, Merz, Novartis, Octapharma, Pfizer, and Solvay. He has also received grants from MJ Fox Foundation for Parkinson's Research, Rentschler, and ZLB Behring. Dr. Dodel is employed by Phillipps-University Marburg and has contracts with several pharmaceutical companies through the University of Marburg. He owns two patents not related to the present manuscript topic. Regina Katzenschlager: Is a consultant for Santhera Pharmaceuticals. She is on the advisory board of and has received honoraria from Boehringer Ingelheim, Novartis, UCB Pharma, and Cephalon Germany. In addition, she has also received honoraria from GlaxoSmithKline, Teva, Lundbeck, and Merz. Murat Emre: Is a consultant for Novartis-Orion and Boehringer Ingelheim. He is on the advisory board of Novartis-Orion and Schering-Plough. Dr. Emre has also received honoraria from Novartis-Orion, Boehringer Ingelheim, and Schering Plough. Andrew Lees: Is on the advisory board of and has received honoraria from Novartis, Teva, Meda, Boehringer Ingelheim, GlaxoSmithKline, Ipsen, Lundbeck, Allergan, and Orion. He is also a consultant for Genus Pharmaceuticals and has received grants from PSP Association and Weston Trust—The Reta Lila Howard Foundation. Dr. Lees is employed by UCL/UCLH. Olivier Rascol: Has received consulting fees from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Schering, Solvay, Teva Neuroscience, Lundbeck, and UCB. He has also received scientific grants from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Solvay, Teva Neuroscience, and Lundbeck. Werner Poewe: Has served on the advisory board of and has received consultancy and lecture fees (including honoraria) from Eisai, Teva, Novartis, GlaxoSmithKline, Boehringer-Ingelheim, UCB, Orion Pharma, Merck Serono,

and Schering Plough in relation to clinical drug development programs for Parkinson's disease. Eduardo Tolosa: Has served on the advisory board of Novartis, Merck Serono, and Teva. He has also received honoraria from Boehringer Ingelheim, Lundbeck, Solvay, and UCB. Claudia Trenkwalder: Is a consultant for Novartis, Orion Pharma, and Mundipharma. She is on the advisory board of UCB and Boehringer Ingelheim, and has received honoraria from UCB, Boehringer Ingelheim, GlaxoSmithKline, and Teva. Dr. Trenkwalder has also provided expert testimony for Mundipharma. Marco Onofrj: Has served on the advisory board of Novartis, GlaxoSmithKline, and Newron Pharmaceuticals. He has received honoraria from Novartis, GlaxoSmithKline, Newron Pharmaceuticals, and Boehringer Ingelheim as well as grants from Novartis and royalties from Springer-Verlag, Italy. Dr. Onofrj is employed by the University G.D'Annunzio, Chieti-Pescara, Italy. Fabrizio Stocchi: Is a consultant for Novartis, GlaxoSmithKline, Pfizer, Teva, Vernalis, Valeant, BI, KV, IMPAX, Merck Sorono, and Solvay. He has received grants/research support from Novartis, Valeant, and GlaxoSmithKline and honoraria from Novartis, GlaxoSmithKline, Pfizer, and Valeant. Giuseppe Nappi: Has nothing to disclose. Vladimir Kostic: Has served as a consultant to Solvay Pharmaceuticals and Biogen Idec and on the advisory board of Boehringer Ingelheim. He has received honoraria for lectures from Novartis, Boehringer Ingelheim, Libra (Merck), Lundbeck, and GlaxoSmithKline. Jagoda Potic: Has nothing to disclose. He is employed by the University Clinical Centre "Zvezdara" and at the Department of Neurology, Medical Faculty University of Belgrade, both located in Belgrade, Serbia. Evzen Ruzicka: Has served on the advisory board of GlaxoSmithKline. He has also received honoraria from GlaxoSmithKline, Medtronic, Solvay, and Boehringer Ingelheim. Dr. Ruzicka receives grant from the Czech Ministry of Health, Czech Ministry of Education, and the Grant Agency of the Czech Republic. Wolfgang Oertel: Owns stocks in Roche. He has worked as a consultant for ProteoSys, Novartis, Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Desitin, and Synosia. He has served on the advisory board of Bayer-Schering, Bioprojet, Boehringer Ingelheim, Eisai (until 2007), Meda Pharmaceuticals International, Merck Serono, NeuroSearch, Novartis, Orion Pharma, Schering Plough, Schwarz Pharma Neuroscience (UCB), and Teva. Dr. Oertel has received honoraria from Novartis, Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Meda Pharmaceuticals International, Desitin, Boehringer Ingelheim, GlaxoSmithKline, and Teva. He also receives scientific grants from the German Ministry of Education and Health.

Author Roles: Wolfgang Oertel—conception and design; acquisition of data; analysis and interpretation of data; drafting of all or part of the submitted publication; critical revision of all or part of the submitted publication material for important intellectual content; statistical expertise; obtaining funding; administrative, technical, or material support; supervision. Karla Eggert—conception and design; acquisition of data; analysis and interpretation of data; drafting of all or part of the submitted publication; critical revision of all or part of the submitted publication material for important intellectual content; administrative, technical, or material support; supervision. David Squillacote—conception and design; acquisition of data; analysis and interpretation of data; drafting of all or part of the submitted publication; critical revision of all or part of the submitted publication material for important intellectual content; statistical expertise; administrative, technical, or material support; supervision. Paolo Barone—acquisition of data; critical revision of all or part of the submitted publication material for important intellectual content; no additional contributions. Richard Dodel—conception and design; acquisition of data; critical revision of all or part of the submitted publication material for important intellectual content; statistical expertise; administrative, technical, or material support. Regina Katzenschlager—conception and design; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; no additional contributions. Murat Emre—conception and design; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Andrew Lees—conception and design; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Olivier Rascol—analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; no additional contributions. Werner Poewe—conception and design; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; no additional contributions. Eduardo Tolosa—conception and design; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Claudia Trenkwalder—acquisition of data; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Marco Onofrj—acquisition of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Fabrizio Stocchi—acquisition of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Giuseppe Nappi—conception and design; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Vladimir Kostic—acquisition of data; analysis and interpretation of data; drafting of all or part of the submitted publication; critical revision of all or part of the submitted publication material for important intellectual content; administrative, technical, or material support; supervision. Jagoda Potic—acquisition of data; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; supervision. Evzen Ruzicka—acquisition of data; analysis and interpretation of data; critical revision of all or part of the submitted publication material for important intellectual content; no additional contributions.

REFERENCES

1. Fahn S, Oakes D, Shoulson I, et al. on behalf of the Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498–2508.
2. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards

Subcommittee of the American Academy of Neurology. Neurology 2002;58:11–17.
3. Schapira AH. Present and future drug treatment for Parkinson's disease. J Neurol Neurosurg Psychiatry 2005;76:1472–1478.
4. Blanchet PJ, Allard P, Gregoire L, Tardif F, Bedard PJ. Risk factors for peak dose dyskinesia in 100 levodopa-treated parkinsonian patients. Can J Neurol Sci 1996;23:189–193.
5. Deane KHO, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev 2004;4:CD004554.
6. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005;62: 241–248.
7. Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM; Zydis Selegiline Study Group. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord 2004;19:426–432.
8. Clarke CE, Deane KH. Ropinirole for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev 2000;3:CD001516.
9. Clarke CE, Speller JM, Clarke JA. Pramipexole for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev 2000;3:CD002261.
10. Metman LV, Del DP, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. Arch Neurol 1999;56:1383–1386.
11. Crosby NJ, Deane KH, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. Cochrane Database Syst Rev 2003;2: CD003467.
12. Klockgether T, Turski L, Honore T, et al. The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann Neurol 1991;30: 717–723.
13. Marin C, Jimenez A, Bonastre M, Chase TN, Tolosa E. Non-NMDA receptor-mediated mechanisms are involved in levodopa-induced motor response alterations in parkinsonian rats. Synapse 2000;36:267–274.
14. Konitsiotis S, Blanchet PJ, Verhagen L, Lamers E, Chase TN. AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys. Neurology 2000;54:1589–1595.
15. Tokuhara N, Hatakeyama S, Amino H, Hanada T, Nishizawa Y. Pharmacological profile of perampanel: a novel, non-competitive selective AMPA receptor antagonist. Abstract and poster presented at 60th Annual Meeting of the American Academy of Neurology, Chicago, IL, April 12–19, 2008. Poster PO2.112.
16. Hashizume Y, Ohgoh M, Ueno M, Hanada T, Nishizawa Y. Effect of perampanel, a selective AMPA receptor antagonist, on L-dopa-induced rotational behavior in L-dopa primed 6-OHDA Hemiparkinsonian rats. Abstract and poster presented at 60th Annual Meeting of the American Academy of Neurology, Chicago, IL, April 12–19, 2008. Poster PO6.102.
17. Mizuta E, Ueno M, Hanada T, Kuno S. Effects of perampanel, a selective AMPA receptor antagonist, on L-dopa-induced dyskinesia in MPTP-treated cynomolgus monkeys. Abstract and poster presented at 60th Annual Meeting of the American Academy of Neurology, Chicago, IL, April 12–19, 2008. Poster PO6.101.
18. Hoehn NM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–442.
19. Data on File. Eisai Inc. Woodcliff Lake, New Jersey, USA. A randomized, open-label, single-dose, two-way crossover, food effect study of E2007 in healthy male and female volunteers. Protocol No. E2007-E044–003. Final Report July 19, 2002; Addendum July 30, 2003.
20. Fahn S, Elton RL; UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors. Recent developments in Parkinson's disease, Vol 2. Florham Park, NY: Macmillan Healthcare Information; 1987. p 153–163.
21. Guy W. ECDEU assessment manual for psychopharmacology, revised. Bethesda, MD: US Dept of Health, Education, and Welfare and National Institute of Mental Health; 1976. Publication ADM 76–338:218–222.
22. May PR, Lee MA, Bacon RD. Quantitative assessment of neuroleptic induced extrapyramidal symptoms: clinical and nonclinical approaches. Clin Neuropharmacol 1983;6 Suppl 1:35–51.
23. Goetz CG, Stebbins GT, Shale HM, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intra-rater reliability assessment. Mov Disord 1994;9:390–394.
24. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:939–944.
25. Smith A. Symbol digit modalities test (SDMT). Manual (revised). Los Angeles: Western Psychological Services; 1982.
26. Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 1991;114:2095–2122.
27. Goetz CG, Wuu J, McDermott MP, et al. on behalf of the Parkinson Study Group. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. Mov Disord 2008;23:690–699.