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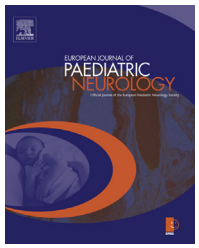

Original article

Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a combined extension study

William Rosenfeld [a,*], *Joan Conry* [b,h], *Lieven Lagae* [c,i], *Guntis Rozentals* [d,j], *Haichen Yang* [e,k], *Randi Fain* [f,l], *Betsy Williams* [f,l], *Dinesh Kumar* [e,k], *Jin Zhu* [g,m], *Antonio Laurenza* [e,k]

[a] *Comprehensive Epilepsy Care Center for Children and Adults, St Louis, MO, USA*
[b] *Children's National Medical Center, Washington, DC, USA*
[c] *University Hospitals KULeuven, Leuven, Belgium*
[d] *Children's Clinical University Hospital, Riga, Latvia*
[e] *Eisai Neuroscience Product Creation Unit, Woodcliff Lake, NJ, USA*
[f] *Eisai Medical and Scientific Affairs, Woodcliff Lake, NJ, USA*
[g] *Formerly Eisai Inc., Woodcliff Lake, NJ, USA*

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ABSTRACT

Objective: Assess perampanel's efficacy and safety as adjunctive therapy in adolescents (ages 12–17) with drug-resistant partial seizures.
Methods: Adolescent patients enrolled in multinational, double-blind, placebo-controlled, phase III core studies (studies 304, 305, or 306) completed 19-week, double-blind phase (6-week titration/13-week maintenance) with once-daily perampanel or placebo. Upon completion, patients were eligible for the extension (study 307), beginning with 16-week,

Abbreviations: AE, adverse event; AED, antiepileptic drug; ANCOVA, analysis of covariance; BMI, body mass index; CP, complex partial seizure; ECG, electrocardiogram; EU, European Union; ITT, intent to treat; LOCF, lastobservation carried forward; MedDRA, medical dictionary for regulatory activities; NONMEM, nonlinear mixed-effect modeling; SAE, serious adverse event; SG, secondarily generalized seizure; SP, simple partial seizure; TEAE, treatment-emergent adverse event.

* *Corresponding author*. Comprehensive Epilepsy Care Center for Children and Adults, 3009 North Ballas Road, Building A, Suite 129A, St. Louis, MO 63131, USA. Tel.: +1 314 453 9300; fax: +1 314 453 0163.
E-mail addresses: werosenfeld@msn.com (W. Rosenfeld), jconry@childrensnational.org (J. Conry), lieven.lagae@uzleuven.be (L. Lagae), dr.rozentals@inbox.lv (G. Rozentals), Haichen_Yang@eisai.com (H. Yang), Randi_Fain@eisai.com (R. Fain), Betsy_Williams@eisai.com (B. Williams), Dinesh_Kumar@eisai.com (D. Kumar), vgo329@yahoo.com (J. Zhu), Antonio_Laurenza@eisai.com (A. Laurenza).
[h] Children's National Medical Center, 222 South Woods Mill Road, Suite 610 North, St. Louis, MO 63017, USA.
[i] Department of Pediatric Neurology, University Hospitals KULeuven, Herestraat 49, B-3000 Leuven, Belgium.
[j] Children's Clinical Hospital, 45 vienibas gatve, Riga LV1004, Latvia.
[k] Eisai Neuroscience and General Medicine PCU, 155 Tice Blvd., Woodcliff Lake, NJ 07677, USA.
[l] Eisai Medical and Scientific Affairs, 100 Tice Blvd., Woodcliff Lake, NJ 07677, USA.
[m] 17 Hillsborough Ct., Rockaway, NJ 07866, USA.

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blinded conversion, during which placebo patients switched to perampanel. Patients then entered the open-label treatment.

Results: Of 1480 patients from the core studies, 143 were adolescents. Pooled adolescent data from these core studies demonstrated median percent decreases in seizure frequency for perampanel 8 mg (34.8%) and 12 mg (35.6%) were approximately twice that of placebo (18.0%). Responder rates increased with perampanel 8 mg (40.9%) and 12 mg (45.0%) versus placebo (22.2%). Adolescents receiving concomitant enzyme-inducing antiepileptic drugs (AEDs) had smaller reductions in seizure frequency (8 mg:31.6%; 12 mg:26.8%) than those taking non-inducing AEDs (8 mg:54.6%; 12 mg:52.7%). Relative to pre-perampanel baseline, seizure frequency and responder rates during the extension (Weeks 1–52) improved with perampanel. Most commonly reported adverse events in adolescents during the core studies were dizziness (20.4%), somnolence (15.3%), aggression (8.2%), decreased appetite (6.1%), and rhinitis (5.1%). Dizziness (13.2%), somnolence (11.6%), and aggression (6.6%) most often led to perampanel interruption/dose adjustment during the extension.

Significance: Data demonstrated adjunctive perampanel treatment in adolescents with drug-resistant partial seizures produced better seizure control versus placebo, sustained seizure frequency improvements, and a generally favorable safety profile. Results were comparable to the overall study population.

Clinical Trial Registration: clinicaltrials.gov Identifiers: Study 304: NCT00699972; 305: NCT00699582; 306: NCT00700310; Study 307: NCT00735397.

1. Introduction

Therapeutic advances over the past 20 years have led to the development of newer drugs for the treatment of epilepsy. Physicians can now choose from a number of antiepileptic drugs (AEDs), although many of these have unknown mechanisms of action.[1,2] Approximately 50% of patients achieve seizure control on their first AED.[3] For those whose seizures remain uncontrolled, further antiepileptic medications or combination regimens are prescribed.[3] Despite such attempts to manage uncontrolled seizures with poly-AED therapy, rates of drug resistance remain high.[1,4,5]

One longitudinal study of 525 children, adolescents, and adults with newly diagnosed epilepsy showed that 37% were considered drug-resistant even after adjunctive antiepileptic therapy.[5] Similar rates of drug resistance (25%–30%) have been found in pediatric-only populations.[2] Treatment-limiting adverse events (AEs) associated with antiepileptic therapy are common in the pediatric population, occurring in 26% of patients in one study involving 216 children and adolescents.[6] Thus the availability of novel AEDs that are effective and well tolerated in adolescents represents a significant unmet need.

Perampanel, the first in a novel class of AEDs, is a selective, noncompetitive AMPA-receptor antagonist.[7] The AMPA-type glutamate receptors, located largely on post-synaptic excitatory synapses in the central nervous system, bind glutamate and are key modulators in the generation and spread of epileptiform activity.[8] Perampanel is approved in more than 40 countries, including the United States (US) and in the European Union (EU), for adjunctive treatment of partial seizures with or without secondarily generalized seizures, in patients with epilepsy aged ≥12 years, and in Canada in patients aged ≥18 years.[9] Findings from several clinical studies demonstrate that perampanel administered once daily in doses up to 12 mg/day reduces partial seizure frequency (including simple partial seizures (with and without motor signs, complex partial [CP] seizures, and partial seizures with secondarily generalized [SG] seizures).[10–16] Perampanel was well tolerated by most patients aged ≥12 years old, despite the incidence of AEs being greater in patients treated with 8 mg/day or 12 mg/day,[10–12,15] highlighting that perampanel dosing should be based on clinical response and tolerability in order to provide adequate, individualized seizure control.

Here we report the results of an analysis in a subpopulation of adolescents (aged 12–17 years) with drug-resistant partial seizures, based on data from the perampanel clinical study program that were submitted to several regulatory agencies for approval of the drug. Data from the three phase III core studies and the combined extension study are pooled here to assess the efficacy, long-term safety, and tolerability of adjunctive perampanel in the adolescent population.

2. Materials and methods

2.1. *Registration, protocol approvals, and informed consent*

The three phase III core studies (study 304: NCT00699972; 305: NCT00699582; 306: NCT00700310) were conducted between April 2008 and January 2011 in more than 40 countries.[10–12] Study 307 (NCT00735397) was a long-term extension of studies 304, 305, and 306.[13] All studies were compliant with the Helsinki Declaration, European Medicines Agency