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Long-term effects of adjunctive perampanel on cognition in adolescents with partial seizures

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ABSTRACT

Objective: The aim of this study was to evaluate long-term effects of adjunctive perampanel on cognition, efficacy, growth, safety, and tolerability in adolescents with inadequately controlled partial seizures.
Methods: Study 235, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase II study with an open-label extension phase (NCT01161524), was primarily designed to assess the effects of adjunctive perampanel on cognition. Patients (aged ≥12 to <18 years) had a diagnosis of epilepsy with inadequately controlled partial seizures, with or without secondary generalization, despite receiving 1–3 antiepileptic drugs. During the double-blind phase, adjunctive perampanel or placebo was administered over a 6-week titration period and a 13-week maintenance period up to 12 mg/day. During the extension phase, all patients received perampanel. Data from the extension phase are presented here. Study endpoints included change from baseline in Cognitive Drug Research (CDR) measures of cognition, seizure frequency, growth, development, the occurrence of treatment-emergent adverse events (TEAEs), and laboratory values.
Results: A total of 114 patients entered the extension phase (prior double-blind treatment: placebo, n = 41; perampanel, n = 73). Perampanel had no effect on the CDR system global cognition score, continuity of attention, quality of episodic memory, quality of working memory, or speed of memory but was associated with a significant decline in power of attention at end of treatment compared with baseline ($p = 0.03$). There were no effects on language skills or manual dexterity from baseline to end of treatment. At Weeks 40–52, median reduction in seizure frequency was 74.1%, and 50% responder rate was 66.0%. There were no clinically relevant effects of perampanel on growth or development at end of treatment compared with baseline. Overall, 84.2% of patients experienced at least one TEAE and 70.2% experienced at least one treatment-related TEAE. The most common TEAEs were dizziness (29.8%) and somnolence (19.3%). The TEAEs resulted in the discontinuation of treatment in 6.1% of patients.
Conclusions: In keeping with the 19-week double-blind phase, long-term adjunctive treatment with perampanel did not have any significant overall effects on the CDR system global cognition score in adolescent patients with inadequately controlled partial seizures. Similar trends were observed across the individual CDR system domains. Adjunctive perampanel showed sustained long-term seizure control and had a safety and tolerability profile similar to that observed in prior clinical studies.

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CDR, Cognitive Drug Research; COWAT, Controlled Oral Word Association; EIAED, enzyme-inducing antiepileptic drug; IGF-1, insulin-like growth factor-1; LGPT, Lafayette Grooved Pegboard Test; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

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1. Introduction

Both epileptic seizures and treatment with antiepileptic drugs (AEDs) can have a detrimental impact on cognition [1–4]. The impact of AEDs may be more prominent in the developing brain of children and adolescents compared with the mature adult brain [5]. Furthermore, long-term use of some AEDs has been associated with negative effects on bone health, including an increased risk of fractures, and reduced statural growth [6,7]. When evaluating a new AED, it is important to investigate both neurophysiological and bone physiological profiles, particularly in children and adolescents [5,7,8].

Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of partial seizures with or without secondarily generalized seizures, and primary generalized tonic-clonic seizures in patients with epilepsy ≥12 years of age [9,10]. Perampanel is also approved for monotherapy use for partial seizures in the United States and Philippines, and for conversion to monotherapy in Switzerland in patients with epilepsy ≥12 years of age. The short-term cognitive effects of adjunctive perampanel were assessed in Study 235, a randomized, double-blind, placebo-controlled, Phase II study in adolescent patients (aged ≥12 to <18 years) with inadequately controlled partial seizures. At the end of the double-blind phase, there were no significant differences between perampanel and placebo in the Cognitive Drug Research (CDR) system global cognition score or in the subdomains of working memory and power of attention; there were small differences in the subdomains of quality of episodic memory (improvement with perampanel versus placebo), continuity of attention, and speed of memory (both worsening with perampanel versus placebo). There were also no differences versus placebo in measures of motor or language skills [11].

Here, we report results from the open-label extension phase of Study 235, which examined the long-term effects of adjunctive perampanel on cognition in adolescent patients with inadequately controlled partial seizures. The study also assessed the long-term effects of perampanel on efficacy and safety, including effects on growth and development.

2. Materials and methods

2.1. Study design and patients

In the double-blind phase of Study 235 (ClinicalTrials.gov identifier: NCT01161524), adolescent patients (aged ≥12 to <18 years), who experienced partial seizures despite receiving a stable dose of 1–3 AEDs, were randomized (2:1) to receive once-daily perampanel or placebo during a 6-week titration period (perampanel initiated at 2 mg/day and up-titrated in weekly 2-mg increments to a target dosage of 8–12 mg/day) and a 13-week maintenance period (maximum perampanel dosage of 12 mg/day). The study was conducted at 39 centers across 11 countries in Asia, Australia, North America, and Europe. Full eligibility criteria for the study have been published previously [11].

Patients who completed all scheduled visits in the double-blind phase were eligible to participate in the open-label extension phase conducted at 37 centers (12 in Asia, one in Australia, 10 in North America, and 14 in the European Union). The extension phase comprised Part A (a 6-week double-blind conversion period and a 27-week open-label maintenance period) and Part B (additional open-label extension of 15–52 weeks for countries without commercially available perampanel or an activated extended-access program; patients ended the study if perampanel became commercially available or an extended-access program was activated during this period). During the conversion period, patients randomized to perampanel continued at the dose achieved at the end of the double-blind phase; those assigned to placebo switched to perampanel 2 mg/day, which was up-titrated weekly in 2-mg increments. All titrations were based on tolerance; any patients not tolerating the minimum 2-mg/day dose were discontinued from the study. In the maintenance period of the extension phase, all patients and investigators were unblinded to treatment; patients continued with their optimal perampanel dosage up to a maximum of 12 mg/day. Dose adjustments were permitted during the maintenance period of the Extension Phase if medically necessary.

Throughout the study, patients continued treatment with 1–3 approved AEDs without dose adjustment. Benzodiazepine administration (maximum of once per week) was allowed as rescue medication for worsening seizures. Neurocognitive testing was rescheduled if benzodiazepines were administered within 7 days prior to neurocognitive testing, antihistamines were administered within 48 h prior to neurocognitive testing, or alcohol was consumed within 48 h prior to neurocognitive testing.

The study was performed in accordance with the Declaration of Helsinki and in full compliance with the International Conference on Harmonisation and all applicable local Good Clinical Practices and regulations. All patients provided written informed consent.

2.2. Assessments

2.2.1. Cognitive, language, and motor assessments

Changes in cognition from Baseline were determined using the CDR system. Changes in language skills were assessed using the Controlled Oral Word Association Test (COWAT), and changes in motor skills were assessed using the Lafayette Grooved Pegboard Test (LGPT). Assessments were conducted at baseline; Weeks 9, 19, 30, 39, and 52; and end of treatment.

The CDR system comprises five domains: power of attention (a measure of focused attention and information processing), continuity of attention (a measure of sustained attention), quality of episodic memory (a measure of the ability to encode, store, and retrieve verbal and nonverbal episodic information), quality of working memory (a measure of the ability to hold numeric and spatial information in the working memory), and speed of memory (a measure of the time needed to retrieve information from episodic and working memory). Changes in the CDR system global cognition score and core domain scores were evaluated and converted into normalized T-scores. T-scores have a mean of 50 and a standard deviation (SD) of 10 and are based on the norms from healthy age-matched controls from the CDR system database. Improvements in cognition were reflected by increased T-scores whereas a decrease in score indicated worsening; a change in T-score of 8 units (0.8 SDs) over time was specified as reflecting a large effect size, according to Cohen's criteria [12].

The COWAT, a measure of language skills, consists of two parts, both measured over 1 min — a letter fluency test, where patients list as many words as they can starting with a given letter and a category fluency test, where patients list as many words relating to a given topic as they can. The number of correct items was summarized, with improvements reflected by increased scores.

The LGPT is a measure of manual dexterity skills. Time to complete the LGPT was reported for each hand, with improvements reflected by reductions in time.

2.2.2. Efficacy assessments

Patients, or their designated caregivers, recorded seizure counts and types daily in a seizure diary during Part A of the extension phase. Data were used to calculate the following efficacy variables: median percentage change in seizure frequency per 28 days from pre-perampanel baseline; 50% responder rate (proportion of patients with a ≥50% reduction in seizure frequency per 28 days compared with pre-perampanel baseline); and seizure freedom (proportion of patients with a 100% reduction in seizure frequency per 28 days compared with pre-perampanel baseline). Baseline seizure frequency data were computed from the pre-randomization phase of the prior double-blind phase plus 4 weeks prior for perampanel-treated patients and during the entire double-