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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-

blind phase including the pre-randomization phase for placebo-treated patients. Efficacy endpoints were summarized by 13-week intervals until Week 52.

2.2.3. Growth and development assessments

Prespecified growth and development assessments included height and weight, bone age, Tanner staging, and blood levels of thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1). All data were summarized descriptively. Height was measured at baseline; Weeks 10, 19, 33, 52, 78, and 104; and end of treatment. Weight was measured at baseline; Weeks 2, 4, 6, 10, 19, 33, 52, 78, and 104; and end of treatment. Bone age was assessed at baseline, Week 30, and end of treatment by hand X-ray using Greulich and Pyle Atlas X-ray standards (female age standards: 12/13/13.5/14/15/16/17/18 years; male age standards: 11/11.5/12.5/13/13.5/14/15/15.5/16/17/18 years; an age that falls between these standards may be selected when considered appropriate) [13]. Tanner staging [14] was used to assess sexual development at baseline; Weeks 8, 19, 30, 52, 78, and 104; and end of treatment; in the event that a patient reached Stage V in Tanner staging, no further assessments were made. Blood levels of TSH and IGF-1 were measured in blood samples taken at baseline, Weeks 8, 19, 30, 52, 78 (for TSH only), 104, and end of treatment.

2.2.4. Safety assessments

Safety was assessed by monitoring incidences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), as well as changes in hematology, blood chemistry, urine values, and vital signs. The TEAEs were also assessed as a function of time on perampanel therapy.

2.3. Statistical methods

Changes in cognitive assessments were measured using the Full Analysis Set for Cognition. This consisted of all randomized patients who received perampanel during the extension phase, had baseline cognition data, and had at least one postdose CDR system cognitive test battery assessment after Week 27. All cognition analyses were presented by modal perampanel dosage (defined as the perampanel dose taken for the longest duration during the double-blind phase plus extension phase; for placebo patients, only Part A extension data were used to define the modal dosage). A paired T-test was used to assess the statistical significance of changes in the CDR system global cognition and core domain T-scores. Analyses for individual domains of the CDR were not corrected for multiplicity.

The Full Analysis Set for Efficacy consisted of all patients who received perampanel during the extension phase, had baseline seizure frequency data, and at least one observation of seizure diary data during the extension phase. The Safety Analysis Set consisted of all enrolled patients who took at least one dose of perampanel in the extension phase and had a safety assessment after the first dose of perampanel in the extension phase. For perampanel, the extension phase analysis included data from the blinded and extension phases of the study. For placebo, the extension phase analysis only included data from the extension phase.

3. Results

3.1. Patients and treatment

A total of 114 patients completed the prior double-blind phase and continued into the extension phase (Fig. 1). Of these, 41 patients had

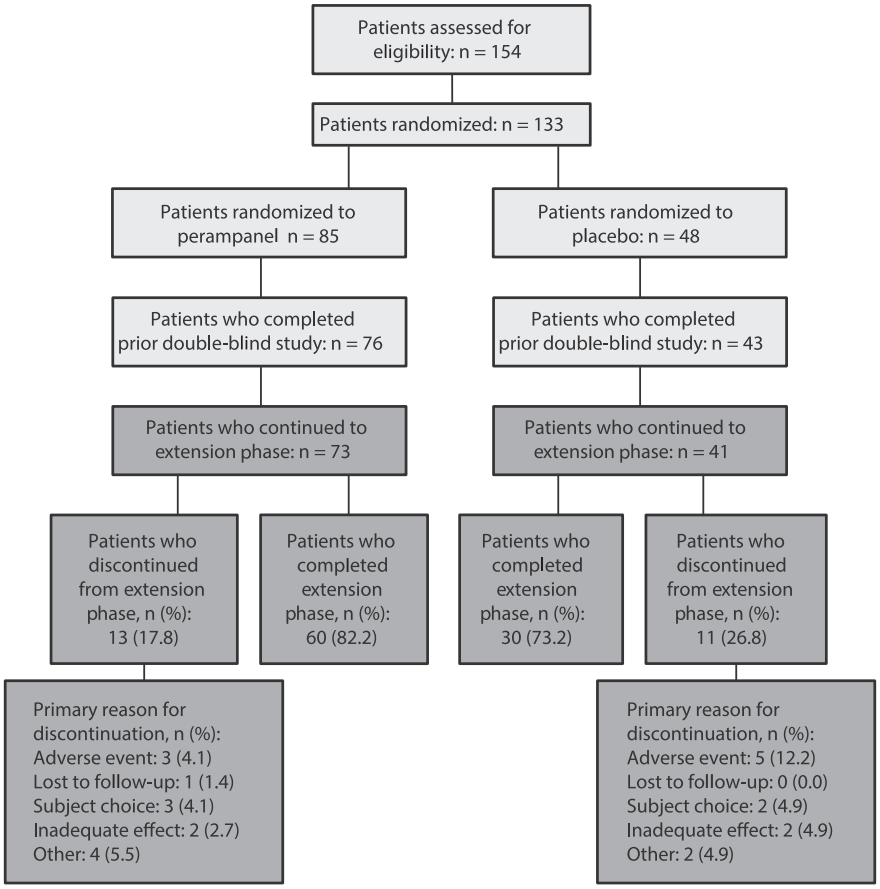

Fig. 1. Patient disposition for prior double-blind study [11] and extension phase.

Table 1
Demographics and baseline characteristics (Safety Analysis Set; n = 114).

	Modal perampanel dosage				
	2 mg/day (n = 1)	4 mg/day (n = 4)	6–8 mg/day (n = 39)	10–12 mg/day (n = 70)	Total (N = 114)
Mean age, years (SD)	12.0 (−)	13.8 (1.5)	14.3 (1.9)	14.3 (1.8)	14.3 (1.8)
Female, n (%)	0 (0.0)	1 (25.0)	17 (43.6)	29 (41.4)	47 (41.2)
Race, n (%)					
White	0 (0.0)	2 (50.0)	26 (66.7)	41 (58.6)	69 (60.5)
Asian	0 (0.0)	2 (50.0)	12 (30.8)	27 (38.6)	41 (36.0)
Other[a]	1 (100.0)	0 (0.0)	1 (2.6)	2 (2.8)	4 (3.5)
Seizure type, n (%)					
Simple partial seizure without motor signs	0 (0.0)	0 (0.0)	6 (15.4)	11 (15.7)	17 (14.9)
Simple partial seizure with motor signs	1 (100.0)	0 (0.0)	12 (30.8)	26 (37.1)	39 (34.2)
Complex partial seizures	0 (0.0)	3 (75.0)	30 (76.9)	49 (70.0)	82 (71.9)
Partial seizures with secondary generalization	1 (100.0)	2 (50.0)	16 (41.0)	37 (52.9)	56 (49.1)
Generalized seizures	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.9)
Unclassified epileptic seizures	0 (0.0)	1 (25.0)	0 (0.0)	1 (1.4)	2 (1.8)
Number of concomitant AEDs, n (%)					
1	0 (0.0)	1 (25.0)	17 (43.6)	27 (38.6)	45 (39.5)
2	0 (0.0)	1 (25.0)	17 (43.6)	31 (44.3)	49 (43.0)
3	1 (100.0)	2 (50.0)	5 (12.8)	12 (17.1)	20 (17.5)
Type of concomitant AEDs, n (%)					
Valproic acid	0 (0.0)	3 (75.0)	16 (41.0)	30 (42.9)	49 (43.0)
Levetiracetam	1 (100.0)	1 (25.0)	11 (28.2)	25 (35.7)	38 (33.3)
Lamotrigine	0 (0.0)	2 (50.0)	7 (17.9)	16 (22.9)	25 (21.9)
Oxcarbazepine	1 (100.0)	0 (0.0)	5 (12.8)	17 (24.3)	23 (20.2)
Carbamazepine	0 (0.0)	0 (0.0)	10 (25.6)	11 (15.7)	21 (18.4)
Topiramate	0 (0.0)	1 (25.0)	11 (28.2)	8 (11.4)	20 (17.5)
Lacosamide	1 (100.0)	1 (25.0)	3 (7.7)	7 (10.0)	12 (10.5)
Phenytoin	0 (0.0)	1 (25.0)	0 (0.0)	5 (7.1)	6 (5.3)
Zonisamide	0 (0.0)	0 (0.0)	2 (5.1)	2 (2.9)	4 (3.5)
Other[b]	0 (0.0)	0 (0.0)	1 (2.6)	4 (5.7)	5 (4.4)
Use of EIAEDs, n (%)					
Yes	1 (100.0)	1 (25.0)	15 (38.5)	34 (48.6)	51 (44.7)
No	0 (0.0)	3 (75.0)	24 (61.5)	36 (51.4)	63 (55.3)

AED, antiepileptic drug; EIAED, enzyme-inducing antiepileptic drug; SD, standard deviation.
[a] Includes Black and African-American.
[b] Includes one each of eslicarbazepine, acetazolamide, ethosuximide, rufinamide, and tiagabine.

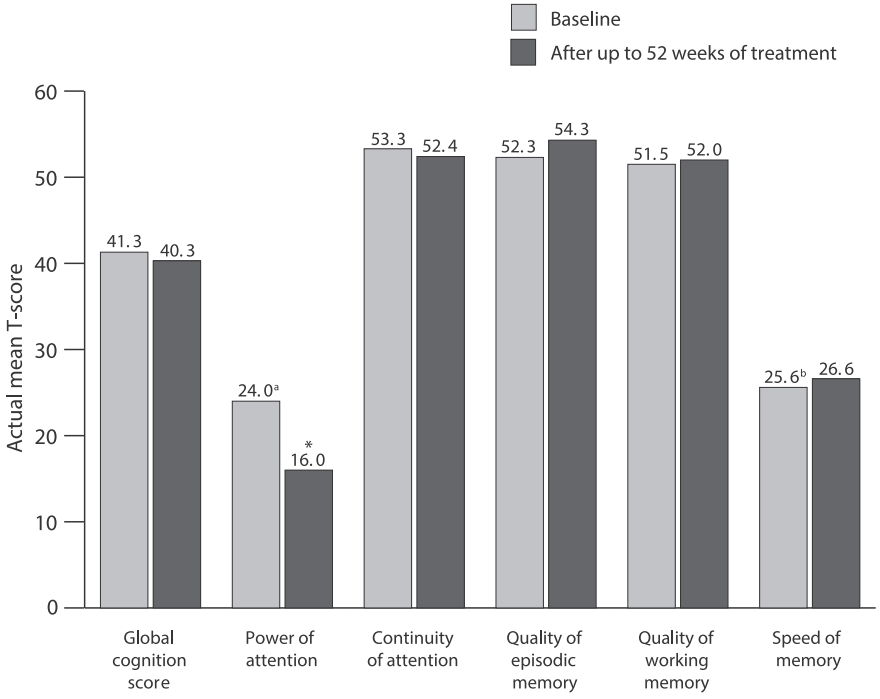

Fig. 2. CDR system global cognition T-score and five core domain T-scores[†] at baseline and end of treatment (Full Analysis Set for Cognition; n = 112). *$p < 0.05$ vs. baseline. [†]All cognitive measure scores were expressed as T-scores. T-scores are normalized standard scores and have a mean of 50 and an SD of 10. The T-scores are based on the norms from healthy age-matched controls from the CDR system database. A paired t-test was used to assess the statistical significance of changes in the CDR system global score and core domain T-scores. Analyses for individual domains of the CDR were not corrected for multiplicity. [a]For power of attention, it should be noted that patients had Baseline impairments of over two SDs on this measure of focused attention and information processing compared with healthy age-matched controls. [b]For speed of memory, it should be noted that patients had a large Baseline impairment in their ability to rapidly retrieve information held in either their working or episodic memory. CDR, Cognitive Drug Research; SD, standard deviation.

been previously randomized to placebo and 73 to perampanel. In total, 24 patients (21.1%) discontinued from the extension phase, with the most common reason for discontinuation being TEAEs (eight patients [7%]). At the time of discontinuation, 13 patients were receiving perampanel 10–12 mg/day, 10 were receiving perampanel 6–8 mg/day, and one was receiving perampanel 4 mg/day. The Full Analysis Set for Cognition consisted of 112 patients whereas the Full Analysis Set for Efficacy and the Safety Analysis Set both consisted of 114 patients.

Patient demographics and medical history were similar across groups of patients treated with different perampanel doses (Table 1). Overall, 39.5% of patients were receiving one concomitant AED, 43.0% two AEDs, and 17.5% three AEDs. The most commonly coadministered AEDs were valproic acid (43.0%), levetiracetam (33.3%), lamotrigine (21.9%), oxcarbazepine (20.2%), carbamazepine (18.4%), and topiramate (17.5%).

In total, 90 patients (78.9%) completed the extension phase and received up to a maximum of 108.9 weeks of treatment with perampanel. Mean (SD; range) duration of perampanel exposure was 61.3 weeks (27.7; 4.3–108.9) and mean (SD; range) daily dosage was 9.3 mg (2.0; 3–12).

3.2. Cognitive outcomes

3.2.1. CDR system scores

The mean CDR system global cognition T-score and five core domain T-scores at baseline and end of treatment are shown in Fig. 2. The mean (SD) change in global cognition T-score was −1.0 (9.9) from baseline to end of treatment; this change was not statistically significant ($p = 0.96$) and not considered to be clinically relevant.

There was a significant decline in mean (SD) power of attention score by 8.0 (25.8) ($p = 0.03$) from baseline to end of treatment; this change was considered to be clinically relevant, although patients had marked impairments in this domain at baseline compared with healthy age-matched controls. When patients were categorized according to whether they did (n = 81) or did not have worsening of power of attention (n = 31), the modal dosage of perampanel received was similar between the two groups (mean [SD] 9.8 [2.1] mg vs. 9.4 [3.1] mg, respectively) as was the maximum dosage (mean [SD] 10.5 [1.8] mg vs. 10.7 [1.7]). Baseline characteristics, including age and gender, were also broadly similar between the two groups, although a lower proportion of patients in the group who had worsening of power of attention were taking concomitant enzyme-inducing AEDs (EIAEDs), particularly oxcarbazepine or carbamazepine, and/or ≥2 AEDs compared with those who did not have worsening of power of attention (37.0% vs. 64.5% and 55.6% vs. 74.2%, respectively; Table S1).

Compared with baseline, there were no significant changes at end of treatment in continuity of attention ($p = 0.44$), quality of episodic memory ($p = 0.10$), quality of working memory ($p = 0.46$), or speed of memory ($p = 0.23$).

3.2.2. COWAT scores

For letter fluency, mean (SD) at baseline was 27.5 (12.3); at end of treatment, mean (SD) change in score was 2.2 (8.0). For category fluency, mean (SD) at baseline was 15.3 (4.8); at end of treatment, mean (SD) change in score was −0.3 (4.0).

3.2.3. LGPT score

For the dominant hand, mean (SD) time taken to complete the test at baseline was 82.1 (22.1) seconds; at end of treatment, mean (SD) change in time taken to complete the test increased by 0.5 (18.7) seconds. For the nondominant hand, mean (SD) time taken to complete the test at baseline was 100.7 (44.3) seconds; at end of treatment, mean (SD) change in time taken to complete the test decreased by 3.3 (22.5) seconds.

3.3. Efficacy outcomes

There was a continual increase in median percentage reduction in seizure frequency per 28 days, 50% responder rate, and seizure-freedom rate throughout the Extension Phase (Fig. 3); improved efficacy appeared related to longer perampanel exposure (≥39 weeks). For the 53 patients who were exposed to perampanel for ≥52 weeks and had data available, a median percentage reduction in seizure frequency of 74.1%, a 50% responder rate of 66.0%, and a seizure-freedom rate of 35.8% were achieved at Weeks 40–52.

A similar trend was also observed for patients with complex partial plus secondarily generalized seizures and for patients with secondarily generalized seizures (Fig. S1). Patients who had worsening of power of attention had greater reductions in seizure frequency per 28 days than those who did not have this worsening (Fig. S2).

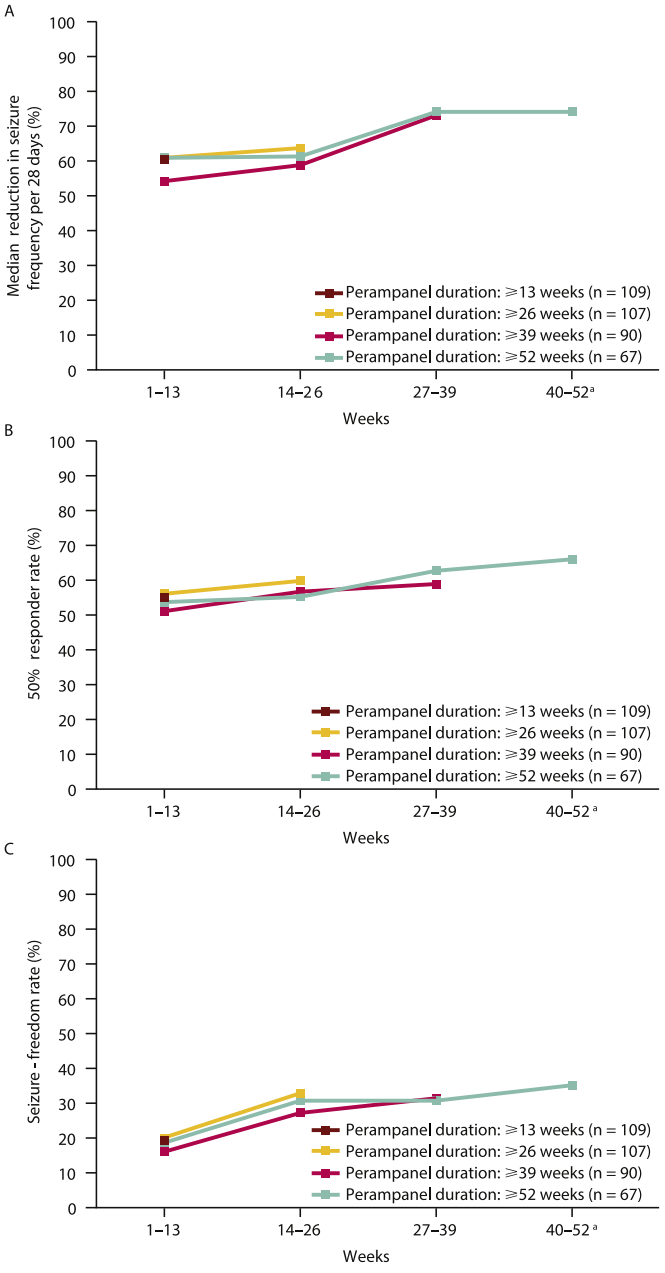

Fig. 3. (A) Median percentage reductions in seizure frequency per 28 days; (B) 50% responder rates; (C) seizure-freedom rates (Full Analysis Set for Efficacy; n = 114). [a]N = 53.

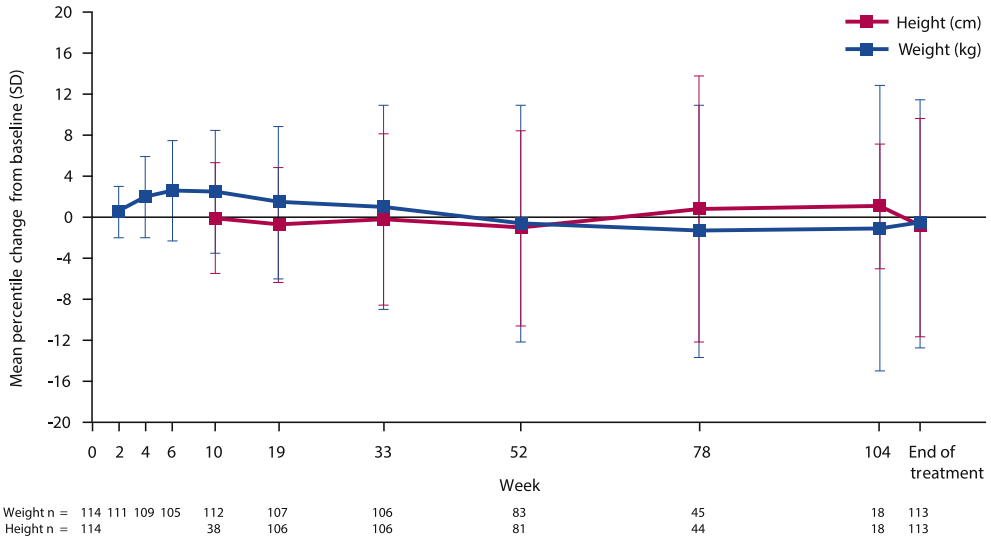

Fig. 4. Mean percentile change from baseline in weight and height by visit (Safety Analysis Set; n = 114). The sex- and age-specific percentiles are based on the 2000 Center for Disease Control Growth Charts for the United States. Only patients with nonmissing data at both baseline and end of treatment are included in the change from baseline summary statistics. End of treatment is defined as the last nonmissing value after date of first dosage up to 14 days after date of last dosage. For both height and weight parameters, data were recorded at all the visits during the maintenance period of the extension phase and at early termination. Weight data were recorded during the conversion period as well. SD, standard deviation.

3.4. Growth and development outcomes

There were no clinically relevant changes in mean weight or height percentiles from baseline to the end of treatment (Fig. 4). Most patients showed no change in Tanner stage from baseline to end of treatment (75/114 patients, 65.8%) or an advance of one Tanner Stage (33/114 [14 females and 19 males], 28.9%). Two female patients and one male patient advanced from Tanner Stage III to V and three male patients from Stage II to IV. For five of these six patients, the first recorded Tanner stage was low for their age, and the final recorded Tanner stage was within the expected range for their age.

There were no clinically relevant mean changes in thyroid hormones or IGF-1 levels at end of treatment vs. baseline: change of −7.1 (125.5) μg/L for IGF-1, −0.3 (0.8) μIU/mL for TSH, −0.1 (2.0) pmol/L for thyroxine, and −0.1 (0.7) pmol/L for free triiodothyronine.

3.5. Safety outcomes

Overall, 84.2% of patients experienced at least one TEAE and 70.2% of patients had at least one treatment-related TEAE across the double-blind and extension phases of the study (Table 2). There was no apparent relationship between the number of TEAEs experienced and modal perampanel dosage. The most common TEAEs were dizziness (n = 34; 29.8%) and somnolence (n = 22; 19.3%), and the most common TEAEs related to hostility/aggression were aggression (n = 13; 11.4%) and irritability (n = 7; 6.1%) (Table 2). The total proportion of patients experiencing TEAEs decreased from 73.8–74.6% at Weeks 1–13 to 26.7–26.9% at Weeks 40–52 (Table 3). The majority of the most common TEAEs (including dizziness, somnolence, aggression, fatigue, and headache) occurred during Weeks 1–13 and reduced in frequency at later time points.

Table 2
TEAE summary by modal perampanel dosage, including listing of TEAE types occurring in ≥5% of total patients (Safety Analysis Set; n = 114).

	Modal perampanel dosage				
AE, n (%)[a]	2 mg/day (n = 1)	4 mg/day (n = 4)	6–8 mg/day (n = 39)	10–12 mg/day (n = 70)	Total (N = 114)
All TEAEs	1 (100.0)	4 (100.0)	33 (84.6)	58 (82.9)	96 (84.2)
Dizziness	1 (100.0)	1 (25.0)	11 (28.2)	21 (30.0)	34 (29.8)
Somnolence	0 (0.0)	1 (25.0)	6 (15.4)	15 (21.4)	22 (19.3)
Aggression	0 (0.0)	2 (50.0)	6 (15.4)	5 (7.1)	13 (11.4)
Fatigue	1 (100.0)	1 (25.0)	3 (7.7)	8 (11.4)	13 (11.4)
Headache	0 (0.0)	1 (25.0)	3 (7.7)	9 (12.9)	13 (11.4)
Nasopharyngitis	0 (0.0)	0 (0.0)	6 (15.4)	7 (10.0)	13 (11.4)
Convulsions	0 (0.0)	0 (0.0)	2 (5.1)	10 (14.3)	12 (10.5)
Pyrexia	0 (0.0)	0 (0.0)	4 (10.3)	4 (5.7)	8 (7.0)
Weight increased	0 (0.0)	0 (0.0)	2 (5.1)	6 (8.6)	8 (7.0)
Irritability	0 (0.0)	0 (0.0)	2 (5.1)	5 (7.1)	7 (6.1)
Vertigo	0 (0.0)	0 (0.0)	4 (10.3)	2 (2.9)	6 (5.3)
Vomiting	0 (0.0)	0 (0.0)	2 (5.1)	4 (5.7)	6 (5.3)
Treatment-related TEAEs[b]	1 (100.0)	4 (100.0)	28 (71.8)	47 (67.1)	80 (70.2)
Severe TEAEs	0 (0.0)	0 (0.0)	3 (7.7)	6 (8.6)	9 (7.9)
SAEs	1 (100.0)	1 (25.0)	5 (12.8)	12 (17.1)	19 (16.7)
TEAEs leading to dosage adjustment	1 (100.0)	4 (100.0)	15 (38.5)	20 (28.6)	40 (35.1)
Discontinuation	0 (0.0)	1 (25.0)	3 (7.7)	3 (4.3)	7 (6.1)
Dosage increase	0 (0.0)	0 (0.0)	1 (2.6)	3 (4.3)	4 (3.5)
Dosage reduction	1 (100.0)	3 (75.0)	13 (33.3)	15 (21.4)	32 (28.1)
Dosage interruption	1 (100.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (1.8)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] A patient with more than one TEAE in a category was only counted once in that category.
[b] Considered by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.

Table 3
TEAEs occurring in ≥5% of total patients[a] by duration of perampanel exposure and treatment period (Safety Analysis Set; n = 114).

AE, n (%)[b]	Duration of perampanel exposure			
	≥13 weeks (n = 109)	≥26 weeks (n = 107)	≥39 weeks (n = 90)	≥52 weeks (n = 67)
All TEAEs				
Weeks 1–13	81 (74.3)	79 (73.8)	67 (74.4)	50 (74.6)
Weeks 14–26	48 (44.4)	47 (43.9)	39 (43.3)	30 (44.8)
Weeks 27–39	28 (26.2)	28 (26.2)	25 (27.8)	20 (29.9)
Weeks 40–52	23 (26.7)	23 (26.7)	23 (26.7)	18 (26.9)
Dizziness				
Weeks 1–13	30 (27.5)	29 (27.1)	25 (27.8)	19 (28.4)
Weeks 14–26	7 (6.5)	7 (6.5)	7 (7.8)	6 (9.0)
Weeks 27–39	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 40–52	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.5)
Somnolence				
Weeks 1–13	13 (11.9)	13 (12.1)	11 (12.2)	8 (11.9)
Weeks 14–26	5 (4.6)	5 (4.7)	5 (5.6)	3 (4.5)
Weeks 27–39	2 (1.9)	2 (1.9)	2 (2.2)	1 (1.5)
Weeks 40–52	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.5)
Aggression				
Weeks 1–13	8 (7.3)	7 (6.5)	6 (6.7)	6 (9.0)
Weeks 14–26	4 (3.7)	3 (2.8)	2 (2.2)	1 (1.5)
Weeks 27–39	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Weeks 40–52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue				
Weeks 1–13	7 (6.4)	7 (6.5)	7 (7.8)	6 (9.0)
Weeks 14–26	2 (1.9)	2 (1.9)	1 (1.1)	1 (1.5)
Weeks 27–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 40–52	1 (1.2)	1 (1.2)	1 (1.2)	0 (0.0)
Headache				
Weeks 1–13	9 (8.3)	8 (7.5)	8 (8.9)	4 (6.0)
Weeks 14–26	3 (2.8)	3 (2.8)	2 (2.2)	1 (1.5)
Weeks 27–39	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 40–52	2 (2.3)	2 (2.3)	2 (2.3)	2 (3.0)
Nasopharyngitis				
Weeks 1–13	5 (4.6)	5 (4.7)	4 (4.4)	4 (6.0)
Weeks 14–26	5 (4.6)	5 (4.7)	4 (4.4)	2 (3.0)
Weeks 27–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 40–52	5 (5.8)	5 (5.8)	5 (5.8)	5 (7.5)
Convulsions				
Weeks 1–13	4 (3.7)	3 (2.8)	3 (3.3)	3 (4.5)
Weeks 14–26	4 (3.7)	4 (3.7)	3 (3.3)	2 (3.0)
Weeks 27–39	3 (2.8)	3 (2.8)	3 (3.3)	3 (4.5)
Weeks 40–52	4 (4.7)	4 (4.7)	4 (4.7)	3 (4.5)
Pyrexia				
Weeks 1–13	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 14–26	4 (3.7)	4 (3.7)	3 (3.3)	2 (3.0)
Weeks 27–39	2 (1.9)	2 (1.9)	2 (2.2)	1 (1.5)
Weeks 40–52	2 (2.3)	2 (2.3)	2 (2.3)	1 (1.5)
Weight increased				
Weeks 1–13	6 (5.5)	6 (5.6)	6 (6.7)	3 (4.5)
Weeks 14–26	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 27–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 40–52	2 (2.3)	2 (2.3)	2 (2.3)	2 (3.0)
Irritability				
Weeks 1–13	5 (4.6)	5 (4.7)	4 (4.4)	2 (3.0)
Weeks 14–26	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 27–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 40–52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo				
Weeks 1–13	4 (3.7)	3 (2.8)	3 (3.3)	2 (3.0)
Weeks 14–26	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 27–39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weeks 40–52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting				
Weeks 1–13	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 14–26	1 (0.9)	1 (0.9)	1 (1.1)	0 (0.0)
Weeks 27–39	1 (0.9)	1 (0.9)	1 (1.1)	1 (1.5)
Weeks 40–52	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.5)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a] These TEAEs were experienced by ≥5% of patients in the total population, as shown in Table 2.
[b] A patient with more than one AE in a category was only counted once in that category.

A total of 23 SAEs occurred in 19 patients (Table 2). Of these, only two SAEs occurred in more than one patient (convulsion [n = 4] and aggression [n = 4]). One SAE (accidental overdose of moderate severity in a 12-year-old male) was considered probably related to perampanel; the study drug was interrupted, and the patient was reported to have recovered 6 days after the start of the event. A further 10 patients had a total of 11 SAEs that were considered possibly related to treatment with perampanel. The TEAEs resulted in the discontinuation of treatment in seven patients (6.1%), and the only TEAE that led to discontinuation in more than one patient was aggression (n = 3). No clinically important mean changes in laboratory values were observed.

4. Discussion

It is well recognized that AEDs may have a negative effect on cognition, particularly in children [1–5,8,15], and the cognitive abilities most likely affected include processing speed, sustained attention, dual processing, verbal learning, verbal fluency, and memory [2,15]. Our study is the first to investigate the long-term effects of perampanel on cognition in adolescent patients (aged ≥12 to <18 years) and a valuable addition to the limited data available for the effects of AEDs on cognition in children [16]. In the open-label extension phase of Study 235, long-term adjunctive treatment with perampanel at dosages up to 12 mg/day (mean [SD] daily dosage of 9.3 mg [2.0]) was associated with mild effects on cognition (up to 52 weeks) in adolescent patients (aged ≥12 to <18 years) with inadequately controlled partial seizures. In addition, seizure control was maintained over time (up to 52 weeks), and there were no clinically relevant effects on growth or any unexpected safety concerns (up to 104 weeks) associated with long-term adjunctive treatment with perampanel.

At baseline in our study, the overall mean performance for power of attention was 24.0, indicating that patients showed impairments of over two SDs on this measure of focused attention and information processing compared with healthy age-matched controls. Impairments in attention have previously been observed in patients with new-onset and/or untreated epilepsy, including children [17–19]. A previous study by Masur et al. found that many newly diagnosed children with childhood absence epilepsy had rates of attention deficits approximately four fold higher than in the general population, despite having average intellectual ability, suggesting that attention problems may be a comorbidity of childhood epilepsy [17]. For speed of memory, the overall mean performance at baseline was 25.6, indicating that our patients showed a large impairment in their ability to rapidly retrieve information held in either their working or episodic memory. No baseline deficits were observed for the three other CDR domain scores. At the end of treatment, perampanel showed no significant effect on continuity of attention, quality of episodic memory, quality of working memory, speed of memory, language skills, or manual dexterity skills. However, there was a significant decrease in power of attention ($p = 0.03$), indicating a decline in focused attention and information processing. As noted, power of attention was lower at baseline in this population than that of age-matched controls, and it remains to be seen whether this decrease has a clinically significant effect in school and everyday life. A lower proportion of patients who had a decline in power of attention were receiving EIAEDs or ≥2 AEDs compared with patients who did not have this decline. Patients receiving fewer AEDs are likely to have epilepsy that is less severe and a lower exposure to AEDs that could exacerbate cognitive impairment, which may reduce the likelihood of declines in power of attention in these patients.

Of the handful of studies published, which have investigated the effect of AEDs on cognition in children, the results have been mixed and inconclusive, often due to limitations in the design of the studies [20]. A double-blind, counter-balanced, crossover study found that children with epilepsy taking phenobarbital had significantly worsened cognitive performance compared with those taking valproic acid [21]. However, case studies of newly diagnosed childhood epilepsy found that

moderate doses of carbamazepine affected memory whereas there was no effect with valproic acid or phenytoin [22]. In an open-label, randomized study, carbamazepine, oxcarbazepine, and valproic acid were associated with no impairment of cognitive function in children and adolescents with newly diagnosed partial seizures [23]. Ethosuximide was reported to have a significantly smaller negative effect on attentional measures than valproic acid in a double-blind, randomized, controlled study in children (aged 2.5–13 years) with newly diagnosed childhood absence epilepsy [24]. In contrast, ethosuximide monotherapy was associated with impairments of intelligence, visuomotor, and attentional function, including activation/alertness in a retrospective, cross-sectional study involving children (aged 6–16 years) with epilepsy [25]. Zonisamide has also been associated with cognitive dysfunction in retrospective studies of children with epilepsy [26,27]. However, in an open-label extension of a Phase III, randomized, double-blind, placebo-controlled study involving children (aged 6–18 years) with partial epilepsy, zonisamide was associated with minimal changes from baseline in cognitive impairment when assessed using COWAT [28]. For adjunctive levetiracetam, neurocognitive effects were found to be similar in pediatric patients (aged 4–16 years) with partial seizures compared with placebo in a randomized, double-blind, placebo-controlled study [29], and this was maintained in the open-label extension, suggesting long-term stability of cognitive function [30].

In our study, seizure outcomes observed for patients exposed to perampanel for ≥52 weeks (median percentage reduction in seizure frequency of 74.1% and a 50% responder rate of 66.0% at Weeks 40–52) were consistent with those observed in the prior double-blind phase of Study 235 (58.0% and 59.0%, respectively [31]) and indicate that long-term seizure control can be maintained. The efficacy results are also consistent with those from the extension phase of the pivotal Phase III studies of adjunctive perampanel in patients ≥12 years old with partial seizures; a median percentage reduction in frequency of seizures of approximately 50% was achieved within 9 months of treatment and maintained for up to 2 years [32].

At end of treatment in the current study, there was a slight reduction in bone age vs. baseline values (by 2.0 months). As the Greulich and Pyle Atlas X-ray standards used when determining skeletal age for a hand X-ray are mostly 1 year apart [13] and the user is allowed to choose an age which falls between these standards where appropriate, it is reasonable to expect variance in Greulich and Pyle bone age results to be within 1 year. Therefore, the reduction in bone age of 2.0 months was not considered to be clinically relevant. Furthermore, these results were similar to those from a Phase III open-label extension study of adjunctive zonisamide in pediatric patients (aged 6–18 years), in which Tanner staging and skeletal development were as expected for the study population, with no significant differences observed between placebo and treatment populations in either Tanner stage or bone age as measured by hand X-ray [28]. Similarly, in a study involving pediatric patients (aged ≥2 years) treated with valproic acid, levetiracetam, or carbamazepine, bone mineral density was not significantly different from an age-matched control group [33].

The TEAE profile of perampanel observed during the extension phase of Study 235 was consistent with the double-blind phase as well as that reported in the pivotal Phase III studies of perampanel (Studies 304, 305, and 306) and their associated open-label extension (Study 307) [32,34–36]. Most TEAEs were mild to moderate, and the most frequently reported TEAEs included dizziness and somnolence.

Interpretation of study results from the extension phase of Study 235 should be countered against possible limitations due to the study design — open label, small number of patients, and lack of placebo or active control group. However, the results are consistent with those from the prior double-blind, randomized, placebo-controlled part of the study, which found no significant overall effects on cognition relative to placebo [11] and no short-term effect of perampanel on growth or development [37]. Further studies are needed to investigate the cognitive, growth, and development effects of perampanel compared with other AEDs.

5. Conclusions

At daily dosages of up to 12 mg for ≤52 weeks, adjunctive treatment with perampanel did not have significant effects on cognitive parameters, with the exception of power of attention, in adolescent patients (aged ≥12 to <18 years) with inadequately controlled partial seizures. These results were generally consistent with findings from the 19-week double-blind phase. Furthermore, perampanel was effective in improving and maintaining long-term seizure control and had no clinically meaningful effects on growth and development. The safety profile in this long-term extension study was consistent with prior clinical studies with perampanel [32,34–36].

Disclosures

Jesus E. Piña-Garza has served as an advisor and speaker for Eisai, Lundbeck, Sunovion, Supernus, and UCB Pharma.

Lieven Lagae has provided consultancy for and received honoraria from Zogenix, Livanova, Shire, UCB Pharma, Novartis, and Takeda.

Vicente Villanueva has participated in advisory boards and pharmaceutical industry-sponsored symposia for Bial, Cyberonics, Eisai, Esteve, GlaxoSmithKline, Medtronic, Merck Sharp & Dohme, Novartis, Pfizer, and UCB Pharma.

J. Ben Renfroe has served as a speaker and participated in advisory boards for LivaNova and Eisai.

Betsy Williams and Dinesh Kumar are employees of Eisai Inc.

Antonio Laurenza is a former employee of Eisai Inc.

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Submission declaration and verification

We confirm that the work described in this manuscript is consistent with the journal's position on ethical publication (https://www.elsevier.com/authors/journal-authors/policies-and-ethics). The work has not been published previously (other than in the form of an abstract), is not under consideration for publication elsewhere, is approved for publication by all authors, and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere in any language in the same form, including electronically, without the written consent of Epilepsy & Behavior.

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Author statement

All authors contributed to data interpretation, critically reviewed each draft of the manuscript, approved the final manuscript for submission, and accept accountability for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.03.029.

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