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Effects of adjunctive eslicarbazepine acetate on neurocognitive functioning in children with refractory focal-onset seizures

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ABSTRACT

Purpose: This was a phase-II, randomized, double-blind (DB), placebo-controlled study aimed to evaluate neurocognitive effects of eslicarbazepine acetate (ESL) as adjunctive therapy in pediatric patients with refractory focal-onset seizures (FOS).

Methods: Children (6–16 years old) with FOS were randomized (2:1) to ESL or placebo. Treatment started at 10 mg/kg/day, was up-titrated up to 30 mg/kg/day (target dose), and maintained for 8 weeks, followed by one-year open-label follow-up. The primary endpoint was change from baseline to the end of maintenance period in the composite Power of Attention assessed with the Cognitive Drug Research (CDR) system. Behavioral and emotional functioning and quality of life (QOL), secondary endpoints, were assessed with Child Health Questionnaire-Parent Form 50 (CHQ-PF50), Child Behavior Checklist (CBCL), and Raven's Standard Progressive Matrices (SPM). Efficacy was evaluated through changes in standardized seizure frequency (SF), responder rate, and proportion of seizure-free patients. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Results: One hundred and twenty-three patients were randomized. A noninferiority analysis failed to reject the null hypothesis that the change from baseline in the Power of Attention score in the ESL group was at least 121 ms inferior to the placebo group for all age groups. The CDR scores showed no differences between placebo and ESL in Power of Attention (1868.0 vs 1759.5), Continuity of Attention (1.136 vs −1.786), Quality of Working Memory (−0.023 vs −0.024), and Speed of Memory (−263.4 vs −249.6). Nonsignificant differences between placebo and ESL were seen for CHQ-PF50, CBCL scores, and Raven's SPM. Episodic Memory Index showed significant negative effect on ESL. Efficacy results favored the ESL group (SF least square [LS] means 1.98 vs 4.29). The TEAEs had a similar incidence between treatment groups (41.0% vs 47.5%).

Conclusions: Overall ESL did not produce statistically significant effects on neurocognitive and behavioral functioning in patients with epilepsy aged 6 to 16 years. Additionally, ESL was effective in reducing seizure frequency and was well-tolerated.

1. Introduction

Worldwide, epilepsy is estimated to affect over 50 million people [1], with children and adolescents being disproportionally impacted by this neurological condition [2–4]. Antiepileptic drugs (AEDs) can be used to successfully treat up to 70% of the affected children and adults [1]. Despite combination therapy, a large proportion of patients continue to have seizures, and among children, 25% remain refractory to treatment [5]. Adverse effects (AEs) caused by antiepileptic drugs are major contributors for treatment failure [6], leading to low treatment adherence [7,8] or discontinuation [8,9]. Epilepsy is often accompanied by impairment of cognitive functions [10], and in children, it is linked to attention, internalization, and thought difficulties that lead to poor psychosocial outcomes in adulthood [11]. The underlying causes of these problems are often challenging to precisely identify, but factors such as the etiology, developmental problems of the disease, and adverse effects of antiepileptic treatment may all play a role [12,13]. The most common cognitive effects associated with chronic use of

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AEDs include impaired mental and psychomotor development, vigilance, and attention [14]. Even though many pediatric studies reporting cognitive effects of AEDs have been reviewed as inconclusive [15], the therapeutic benefits of AEDs may largely outweigh the negative cognitive effects. This is of particular concern in children given the potential to negatively impact learning, social behavior, and school performance [15]. The risk of cognitive effects also highlights the need for appropriately designed prospective studies, based on thorough and well validated tools, to evaluate the effects of AEDs on cognitive function in children and to enable better comparisons across studies [16].

Eslicarbazepine acetate (ESL) is a once-daily antiepileptic drug (AED) [17,18] that has been approved by the European Medicines Agency (EMA), Food and Drug Administration (FDA), and Health Canada as adjunctive therapy in adults with focal-onset seizures (FOS), with or without secondary generalization. Later, both EMA- and FDA-approved ESL for monotherapy in the same population of patients; ESL has also been approved by EMA as adjunctive therapy in children aged above 6 years old with FOS. More recently, ESL received FDA approval for expanded indication to treat FOS in children and adolescents 4 years of age and older.

The current study was aimed at evaluating the effect of adjunctive therapy with ESL on cognitive function in children and adolescents aged 6 to 16 years old with refractory FOS. Efficacy and safety of ESL treatment in this age group are also addressed.

2. Patients and methods

This was a multicenter phase II, randomized, double-blind (DB), placebo-controlled, parallel study to evaluate the cognitive effects of ESL as adjunctive therapy in children with refractory FOS (NCT01527513). The study was conducted in 4 countries (Italy [18 patients], Poland [18 patients], Russia [47 patients], and Ukraine [40 patients]). Children (6–16 years old), diagnosed with epilepsy for ≥12 months prior to enrolment, with at least 2 epileptic FOS (≥4 in the month before enrolment), receiving 1–2 AEDs (except oxcarbazepine), and intelligence quotient (IQ) ≥70, were randomized (2:1) to ESL or placebo.

Part I consisted of an observational baseline period of 4 weeks, followed by a double-blind period of 12 weeks, comprising a 4-week up-titration period from 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks (to a maximum of 1200 mg/day). This was followed by an 8-week double-blind maintenance period at 30 mg/kg/day (or to a maximum of 1200 mg/day) if no intolerable AEs occurred at 20 mg/kg/day; if intolerable AEs occurred, the patient was down-titrated to the previous dose or discontinued. Patients down-titrated to 10 mg/kg/day during titration period received this dose for the 8-week maintenance period. There was a tapering-off period of up to 4 weeks where study treatment was tapered off in 10 mg/kg/day steps, and then, there was an additional 4-week observational follow-up period (Fig. 1). Treatment was given in 200-mg divisible tablets. The individual calculated dose was rounded to the nearest 100 mg. Study treatments were provided as 200-mg tablets, and doses were rounded to the nearest 100 mg (half tablet).

Part II consisted of a one-year, open-label, uncontrolled period which started after completion of the last 2 weeks, 10 mg/kg/day down-titration step in Part I (Fig. 1). All patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg once daily (QD)). Doses were rounded to the nearest 100-mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored). Down-titration was allowed according to clinical response or in case of intolerable AEs, as often as needed. As much as possible, concomitant AED therapy (1 or 2 AEDs) was kept stable throughout Part II under the direction of the patient's physician. Patients entering the one-year open-label extension attended the study clinic for six scheduled visits during Part II for ongoing safety monitoring and performance of study assessments. At the end of Part II, patients either entered a tapering-off/follow-up period or a further period of open-label treatment with ESL (Part III). For patients who completed Part II and did not enter the additional two-year open-label extension, a poststudy visit (PSV) was performed approximately 4 weeks after study treatment was tapered off.

The Cognitive Drug Research (CDR) test battery [19,20] was used to assess changes in cognitive function. The test is designed to cover attention (focused and vigilant), working and episodic memory, and information processing/psychomotor speed, and has been validated in pediatric patients receiving AEDs [20]. An Episodic Memory Index (SI) was created, taking the Word Recognition Sensitivity Index (DRECSI) for children aged 9 to 16 years and the Picture Recognition Sensitivity Index (DPICSI) for children aged 6 to 8 years. Global cognitive skills were evaluated using the Raven's Standard Progressive Matrices (SPM) test [21–24] for children which consists in a series of short, non-verbal reasoning problems, based on visual spatial tasks that are used to assess intelligence in persons from age 6 to adulthood, independently of their cultural level. The test is composed of a total of 60 items presented in 5 sets (A–E), with 12 items per set. Social competence was assessed using the CBCL 6–18, which assesses child life function, and provides 2 major summary scores as follows: competence and problem behaviors. It is a parent-rated questionnaire for children aged 6–18 years old. In this study, only the competence score was evaluated as a measure of the child's social behavior and competence. Abnormal competence scores have been previously reported for children with epilepsy [25]. The quality of life (QOL) was evaluated using the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), a parent-rated questionnaire to assess the child's health, well-being, and the impact of illness on life function that was designed and normalized for children 5–18 years old. The CHQ-PF50 provides two weighted and standardized summary scores for physical and psychosocial health (CHQ summary scores). The physical health summary score measures the child's general health, pain, and limitations in physical and social activities due to health. The psychosocial health summary score measures the child's self-esteem, mental health, and the impact of the illness on physical and social activities. Efficacy was evaluated by relative reduction in standardized seizure frequency (SSF; seizure frequency per 4 weeks), proportion of responders (≥50% SSF reduction), and proportion of seizure-free patients (100% seizure reduction) from baseline. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Sample size was calculated for a noninferiority study comparing the Power of Attention following treatment with ESL as add-on therapy with the Power of Attention in patients on placebo. Assuming a SD of 202.3 for the Power of Attention score, a noninferiority limit of 121 ms, and a one-tailed test at the 0.025 significance level, a total of 102 patients in the Cognitive per-protocol (PP) population would provide 80% power to reject the null hypothesis that the mean increase from baseline Power of Attention was at least 121 ms smaller in the placebo group than in the ESL group versus the alternative hypothesis that any advantage in the placebo group was less than in the inferiority limit [20]. Allowing for premature discontinuations and/or major protocol violations (and hence exclusion from the Cognitive PP population), a total of 117 patients were to be randomized (39 patients in the placebo group and 78 patients in the ESL group).

The study was approved by an ethics committee. Written informed consent was obtained from parent/legal representative and written assent was obtained from the patient.

2.1. Statistical analysis

The primary endpoint was change from baseline to the end of maintenance period in the composite Power of Attention (sum of the reaction time measures from the attentional tasks) measured with the CDR to assess information processing speed and attention/psychomotor

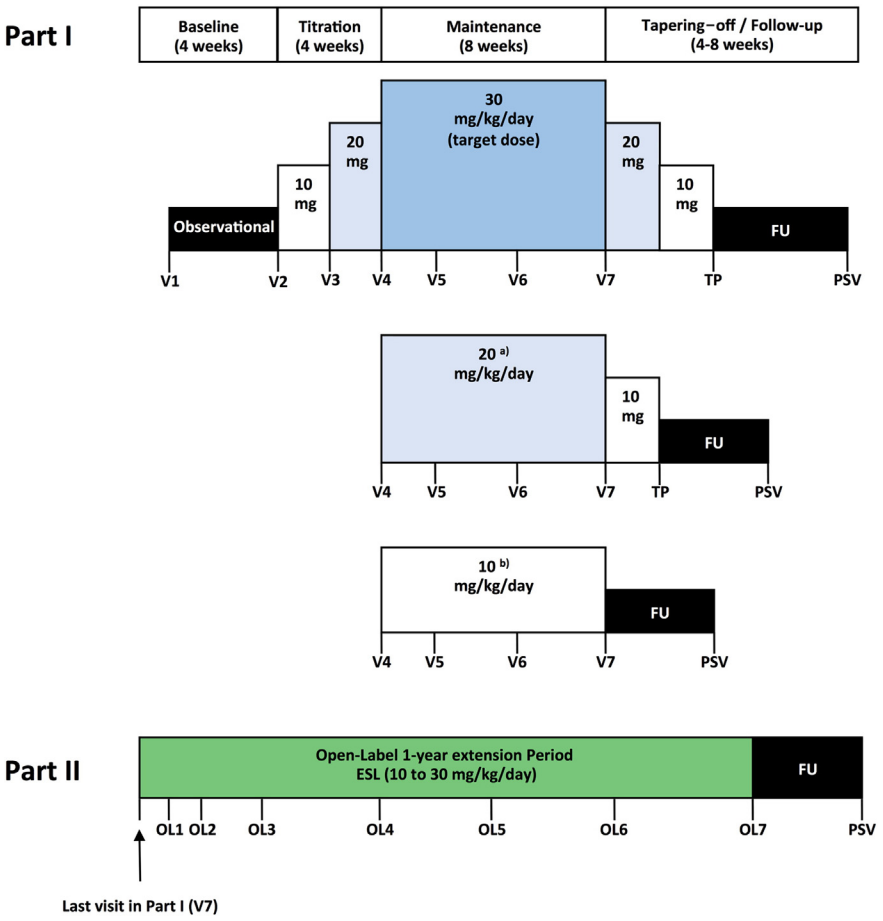

Fig. 1. Dose schedule and study design (Part I and II). Part I consisted of an observational baseline period of 4 weeks, followed by a double-blind period of 12 weeks, comprising a 4-week up-titration period from 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks (to a maximum of 1200 mg/day). Part II consisted of one-year, open-label, uncontrolled period which started after completion of the last 2 weeks, 10 mg/kg/day down-titration step in Part I all patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). Abbreviations: FU = follow-up; PSV = poststudy visit; TP = tapering-off; V = Visit. For those patients down-titrated from 30 mg/kg/day due to intolerable AEs (a) For those patients down-titrated from 20 mg/kg/day due to intolerable AEs during the titration period (b). Note: Randomization occurred at V2. At the last double-blind visit in Part I (V7 or TP), patients had the option to enter a one-year extension with open-label treatment with ESL, or to be discontinued and have a FU visit.

speed. Analysis of covariance (ANCOVA) was used for analyzing the effects of treatment in composite Power of Attention with treatment and country as fixed effects and baseline Power of Attention score, sex, and age as covariates. If treatment-by-sex or treatment-by-country interaction was statistically significant at the 10% level ($P \leq 0.10$), then a subgroup analysis (descriptive statistics and ANCOVA analyses) of the primary cognitive variable by sex and/or by country was to be performed. The least square means (LSMs) for the change from baseline in each treatment group obtained from the main ANCOVA model were presented together with their standard errors of the mean (SEM) and 95% confidence intervals (CIs). The differences between the LSM for the ESL versus placebo comparison were also presented together with the associated 95% CI and *P* value. Noninferiority of ESL versus placebo was assessed by comparing the 95% CI's upper bound of the difference of LSMs between treatment groups (ESL–placebo) with 121 ms. If the side of the confidence interval indicating impairment was greater than 121 ms, the null hypothesis was rejected. Other neurocognitive endpoints included as secondary endpoints were change from baseline to the end of maintenance period in the following CDR test battery: 1 — continuity of attention (aggregate of the accuracy measures from the attentional tasks); 2 — quality of working memory (combination of spatial and numeric working memory sensitivity indices); 3 — quality of episodic secondary memory (children ≥9 years only), 4 — word recognition (children ≥9 years only, defined using the sensitivity index); 5 — picture recognition (children <9 years only, defined using the sensitivity index); 6 — speed of memory (sum of the speed measures from the two working memory tasks (spatial and numeric); 7 — the word recognition task for children ≥9 years). Global cognitive skills, social competence, and quality-of-life endpoints included change from baseline to the end of maintenance period in number of correct answers on the Raven's SPM test, competence summary score from the Child Behavior Checklist (CBCL) 6–18, and physical and psychosocial functioning summary score from the Child Health Questionnaire (CHQ)-Parent Form 50 (PF50). Secondary analysis of change from baseline in the other scores of the CDR system, CHQ-PF50 and CBCL are presented for the PP population, with the respective baseline scores as covariates. The least square (LS) means for the change from baseline in each treatment group were computed together with their 95% CIs. Differences in LS means for the comparison between ESL and placebo are also presented together with their 95% CI and *P* value. For Raven's SPM, since the assumption of normality was not confirmed, a van Elteren (Cochran–Mantel–Haenszel test with modified ridit scores) nonparametric test was used. Efficacy results are presented for the intent-to-treat (ITT) population. Safety variables were analyzed descriptively and performed for the safety set. If data were missing or incomplete, it was allocated to the previous available visit. Adverse effects were coded using the Medical Dictionary for Regulatory Activities

(MedDRA). Demographic and baseline characteristics were analyzed descriptively for the overall safety population. Statistical programming and analyses were performed using SAS Versions 9.1.3 or 9.2.

3. Results

3.1. Analysis of populations

In this study, 123 pediatric patients were randomized 2:1 to ESL (83) or placebo (40) and stratified by the following age groups: 6–11 years (36 ESL, 18 placebo) and 12–16 years (47 ESL, 22 placebo). Of these, 7 ESL patients prematurely discontinued during titration period, and 116 patients entered the double-blind maintenance period (76 ESL, 40 placebo). Of the 123 randomized patients, 91.1% completed the part I of study (75 ESL, 37 placebo). All patients that completed Part I continued to the open-label extension. Of the 112 patients, 95 patients (84.8%) completed the open-label extension period (33 patients, 89.2% with previous double-blind placebo; 62 patients, 82.7% with previous double-blind ESL). Of the 95 patients (84.8%) who completed the one-year open-label extension period, 42 entered the two-year open-label extension period (Fig. 2; Supplementary Table 1).

Demographic and baseline characteristics of the overall safety population are presented in Table 1. Treatment groups were balanced for age, sex, and race. The mean age was 11.7 years, with a similar distribution between age groups, and with a higher percentage of males in both treatment groups (ESL, 56.6%; placebo, 65.0%). Body measurements and average IQ scores were similar between treatment groups. The most common concomitant AEDs were valproic acid (ESL 42.2%, placebo 57.5%), carbamazepine (ESL 31.3%, placebo 30.0%), and topiramate (ESL 24.1%, placebo 22.5%). Seizure frequency, standardized per 28 days during the observational baseline period, was similar in both groups, with median of 5.0 for ESL and 5.19 for placebo. Complex FOS was the

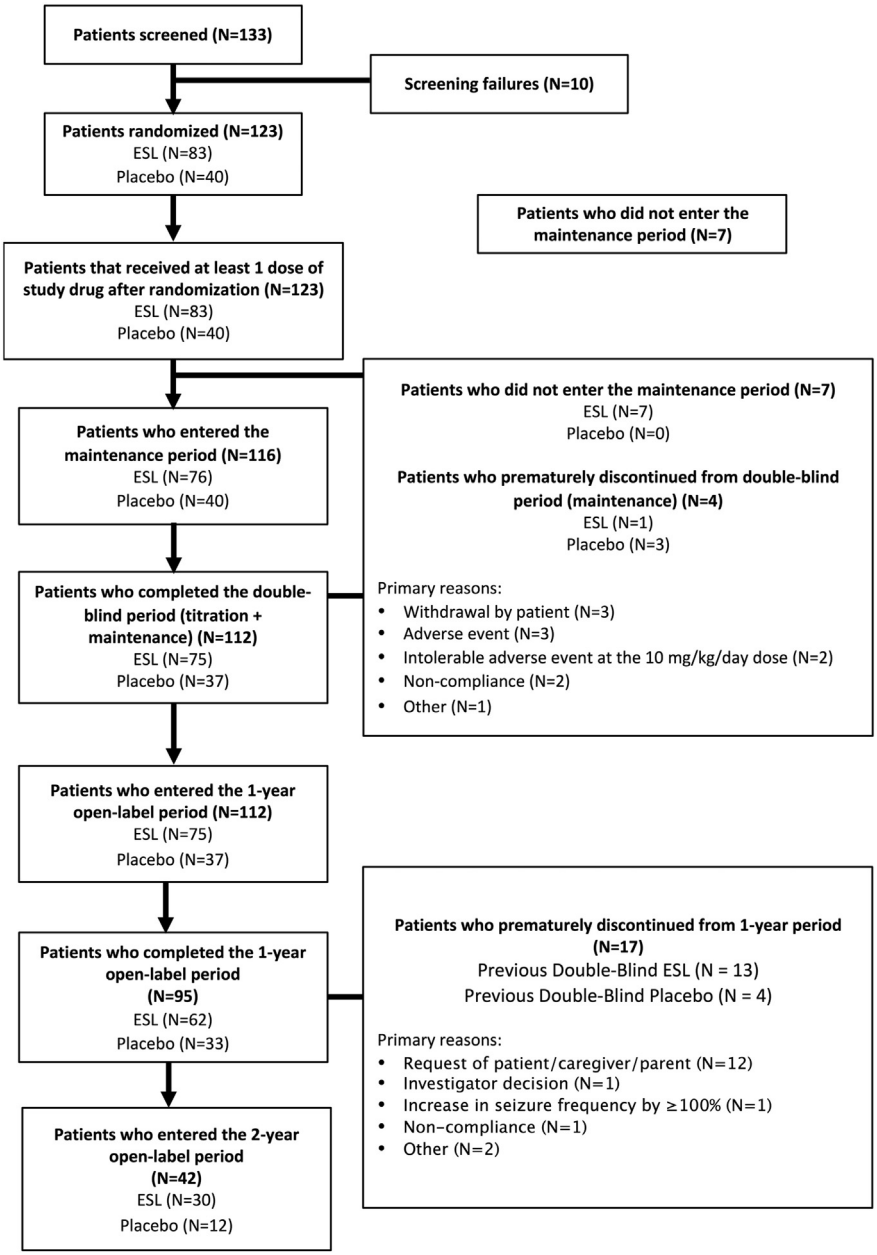

Fig. 2. Patient disposition. Abbreviations: DB = double-blind; ESL = eslicarbazepine acetate; OL = open-label; V = visit. Notes: The total number of patients screened includes patients who failed at the screening visit (V1) or at randomization (V2). Patients could have more than one reason for discontinuation. Reasons for premature discontinuation from the DB period include patients who discontinued from either the titration or maintenance periods.

Table 1
Patient's characteristics at baseline (safety set).

	Placebo (N = 40)	ESL (N = 83)	Total (N = 123)
Age (years), (SD)	11.6 (2.8)	11.8 (3.1)	11.7 (3.0)
Age group, n(%)			
6–11 years	18 (45.0)	36 (43.4)	54 (43.9)
12–16 years	22 (55.0)	47 (56.6)	69 (56.1)
Gender, n (%)			
Male	26 (65.0)	47 (56.6)	73 (59.3)
Female	14 (35.0)	36 (43.4)	50 (40.7)
Ethnicity, n (%)			
Caucasian	39 (97.5)	83 (100.0)	122 (99.2)
Other	1 (2.5)	0 (0.0)	1 (0.8)
Body measurements, mean (SD)			
Height (cm)	151.1 (17.4)	150.5 (17.4)	150.7 (17.3)
Weight (kg)	48.7 (18.4)	47.7 (18.8)	48.0 (18.6)
BMI (kg/m^2)	20.80 (5.3)	20.24 (4.6)	20.43 (4.9)
Head circumference (cm)	53.6 (3.2)	54.0 (2.8)	53.9 (2.9)
IQ, mean (SD)	89.1 (12.8)	87.9 (16.1)	88.3 (15.1)
min–max	70–141	70–154	70–154
Number of AEDs at baseline, n (%)			
1	19 (47.5)	44 (53.0)	63 (51.2)
2	18 (45.0)	37 (44.6)	55 (44.7)
AEDs continued onto DB period, n (%)			
Valproic acid	23 (57.5)	35 (42.2)	58 (47.2)
Carbamazepine	12 (30.0)	26 (31.3)	38 (30.9)
Topiramate	9 (22.5)	20 (24.1)	29 (23.6)
Lamotrigine	4 (10.0)	14 (16.9)	18 (14.6)
Levetiracetam	3 (7.5)	12 (14.5)	15 (12.2)
Valproate sodium	1 (2.5)	4 (4.8)	5 (4.1)
Vigabatrin	1 (2.5)	2 (2.4)	3 (2.4)
Zonisamide	2 (5.0)	1 (1.2)	3 (2.4)
Acetazolamide	0	1 (1.2)	1 (0.8)
Ethosuximide	0	1 (1.2)	1 (0.8)
Lacosamide	1 (2.5)	0	1 (0.8)
Phenytoin	0	1 (1.2)	1 (0.8)
Primidone	1 (2.5)	0	1 (0.8)
Seizure frequency, median (min; max)[a]	5.19 (1.6; 288.0)	5.00 (1.1; 152.4)	–
Seizure type, n (%)[b]			
Simple focal	11 (27.5)	21 (25.3)	32 (26.0)
Complex focal	32 (80.0)	54 (65.1)	86 (69.9)
Partial evolving to secondarily generalized	11 (27.5)	29 (34.9)	40 (32.5)

[a] Standardized seizure frequency per 28 days during the 4-week observational baseline period.
[b] During the 4 weeks prior to screening. Patients may have had more than one type of seizure.

most frequently reported seizure type (ESL 65.1%, placebo 80.0%). Overall, ≥50% of patients were taking at least one concomitant AED at any time point during the open-label period, with a higher proportion of patients in the previous double-blind ESL group than in the placebo group. No patients took ≥2 concomitant AEDs during the open-label period.

Exposure during the double-blind period is defined as the duration of study drug treatment during the titration period + maintenance period, which was scheduled to be 12 weeks (4-week titration and 8-week maintenance, total 84 days). The majority of patients started the maintenance period at 30 mg/kg/day (92.5% placebo; 83.1% ESL); however, between the 2 treatment groups the proportion of patients was lower in the ESL group. This difference corresponds to the higher proportion of patients in the ESL group who had an unscheduled dose reduction during the titration period (2.5% placebo; 6.0% ESL). In the ESL group, all of the unscheduled dose reductions during the titration period were due to adverse reactions. The proportion of patients who had an unscheduled dose reduction during the maintenance period was low and similar between the treatment groups (10.0% placebo; 9.6% ESL). During the one-year open-label period, the median values of the dose of study drug were 14.82 mg/kg/day for Weeks 1 to 4; 29.58 mg/kg/day for Weeks 5 to 16; and 30.00 mg/kg/day for Weeks 17 to 28, Weeks 29 to 40, and Weeks ≥41. The exposure was similar between patients who received placebo or ESL during the previous double-blind period. Very few patients were on monotherapy with ESL for some time in the course of the open-label period as follows: 6 patients, 3 from previous double-blind placebo (8.1%) and 3 from previous double-blind ESL (4.0%).

3.2. Analysis of neurocognitive performance

Summary results from the neurocognitive CDR system are presented in Table 2. At the end of the double-blind period, the mean change from baseline in composite Power of Attention was 95.6 for placebo and 62.4 for ESL. The difference in LS mean between placebo and ESL was 33.2 ms for the overall age group, 25.4 ms for the age group 6–11 years old, and 20.1 ms for the age group 12–16 years old. As shown in Fig. 3, there were essentially no differences between ESL and placebo (LS_{mean} 95% CI was +33 ms (−138, 204); $P > 0.5$) in what concerns Power of Attention. However, noninferiority failed to reject the null hypothesis because the 95% CI lower bound was below the noninferiority margin. Patients entered a one-year open-label follow-up after the end of the double-blind period. Over the year, the patients showed a mean improvement in Power of Attention of 182 ms (235 ms for the 6 to 11 year old patients and 144 ms for the 12 to 16 year old patients). A cross-sectional analysis on year-by-year change in Power of Attention in a large sample of healthy individuals aged 6 to 17 years was performed. From 6 to 16 years of age, the average yearly maturational improvement in healthy children was 70 ms. Thus, in the present study, the maturational development during the one-year open-label follow-up clearly showed no evidence of falling behind what would be expected for healthy children.

The score for Continuity of Attention also displayed no significant differences between placebo and ESL for the overall age group, the age group 6–11 years old, and the age group 12–16 years old (Table 2). The mean change from baseline was 1.1 for placebo and −1.8 for ESL for a difference in LS mean of 2.9 (95% CI: −1.2; 7.0). A similar outcome for the comparison between placebo and ESL was observed for the Quality of Working Memory (LS mean − 0.023 in placebo vs −0.024 in ESL; $P = 0.991$) and Speed of Memory (LS mean difference − 13.8; $P = 0.959$). In the Episodic Memory Index, there was a significant negative effect on subjects treated with ESL increasing with time. At the end of double-blind period, for the overall age groups, the LS mean for ESL and placebo were −0.13 and 0.02 ($P = 0.003$), respectively; for 6–11 age group, the LS mean for ESL was 0.17 and for 0.05 placebo ($P = 0.027$); age group 12–16 had LS means of −0.10 for ESL and 0.02 for placebo ($P = 0.048$). The mean score at the end of open-label follow-up represents small decreases which were of irrelevant effect sizes (all <0.01).

Results for the Physical Health and Psychosocial Health CHQ-PF50 summary scores are presented in Supplementary Table 2. At the end of the double-blind period, the LS mean change from baseline was 2.5 for placebo and 3.2 for ESL, with a LS mean difference of 0.7 (95% CI: −3.1; 4.4; $P = 0.73$) for the Physical Health summary score, for the overall age groups. The difference between treatment groups varied by age group with a LS mean difference of −1.49 points in the 6–11 age group ($P = 0.44$), and of 4.84 points ($P = 0.10$) in 12–16 age group, favoring ESL. For the Psychosocial Health summary score, the LS mean change from baseline was 2.5 for placebo and 3.2 for ESL, with a LS mean difference of 0.7 (95% CI: −2.5; 4.0; $P = 0.66$), for the overall age groups. Results were similar by age subgroup with statistically nonsignificant differences. The mean score at open-label baseline was 43.6 (11.1). Ninety (83%) of these patients had CHQ Physical Health Summary Score at week 52 or at early discontinuation from the open-label phase. The mean score at the end of open-label follow-up

Table 2
LS mean (SEM) changes in scores of the CDR test system at the end of the double-blind period by age group and overall following placebo or eslicarbazepine acetate (ESL).

	Placebo	ESL	Difference in LS means (95% CI)	*P* value[a]
Power of Attention				
Overall age group	95.63 (70.57)	62.43 (55.49)	33.20 (−137.59, 203.99)	0.700
6–11 years	78.61 (151.22)	53.24 (119.09)	25.37 (−356.36, 407.11)	0.893
12–16 years	69.36 (66.90)	49.23 (51.11)	20.12 (−146.57, 186.83)	0.809
Continuity of Attention				
Overall age group	1.136 (1.671)	−1.786 (1.314)	2.921 (−1.154, 6.997)	0.158
6–11 years	4.885 (3.483)	−1.655 (2.719)	6.541 (−2.241, 15.324)	0.139
12–16 years	−0.742 (1.741)	−0.847 (1.336)	0.1056 (−4.241, 4.453)	0.961
Quality of Working Memory				
Overall age group	−0.023 (0.056)	−0.024 (0.044)	0.0008 (−0.1372, 0.1388)	0.991
6–11 years	−0.036 (0.112)	−0.029 (0.087)	−0.0072 (−0.2909, 0.2763)	0.958
12–16 years	−0.007 (0.057)	0.011 (0.043)	−0.0186 (−0.1612, 0.1240)	0.794
Episodic Memory Index				
Overall age group	0.0268 (0.040)	−0.1270 (0.0322)	0.1537 (0.0529, 0.2546)	0.003*
6–11 years	0.0499 (0.0737)	−0.1672 (0.0577)	0.2171 (0.0260, 0.4083)	0.027*
12–16 years	0.0219 (0.0474)	−0.0984 (0.0364)	0.1203 (0.0013, 0.2393)	0.048*
Speed of Memory				
Overall age group	−263.4 (219.5)	−249.6 (172.0)	−13.8 (−545.7, 518.1)	0.959
6–11 years	−614.8 (491.6)	−281.8 (383.2)	−333.0 (−1575.1909.1)	0.588
12–16 years	−22.5 (175.5)	−210.3 (134.6)	187.8 (−250.4, 625.9)	0.393

CI: Confidence interval; EDB: end of double-blind; ITT: intent-to-treat; LS: least squares; PP: per-protocol; SE: standard error; SD: standard deviation.
Overall population (placebo, n = 36; ESL, n = 66); 6–11 years population (placebo, n = 16; ESL, n = 24); 12–16 years population (placebo, n = 20; ESL, n = 42).
[a] ANCOVA model analysis of change from baseline at EDB considering treatment as fixed variable and age group, sex and country as covariates.
* Significantly different from placebo.

(i.e., week 52 or at early discontinuation) was 44.5 (10.7), suggesting little change (−0.1(10.5)) over this period in patients from both treatment groups. Among patients originally randomized to ESL, scores improved, on average, only by 1.1 (10.2) points between randomization (double-blind baseline) and the end of the open-label phase.

In the mean CBCL, scores at baseline were similar between the study arms (33.2 points for placebo and 30.8 for ESL), and at the end of double-blind period, the LS mean difference between treatment groups was −0.23 (95%CI: −2.5; 2.1; $P = 0.84$). At baseline, there were also no statistically significant differences between placebo and ESL in both age groups (Supplementary Table 3). In part II, data were available from 97 patients as follows: 32 patients from the original placebo group and 65 from the original ESL group. The mean score at open-label baseline was 32.6 (8.4). Over three quarters (N = 76) of these patients had a CBCL score of 33.5 at week 52 or early discontinuation, suggesting little change over this period, and was similar between the initial treatment groups, when considered separately.

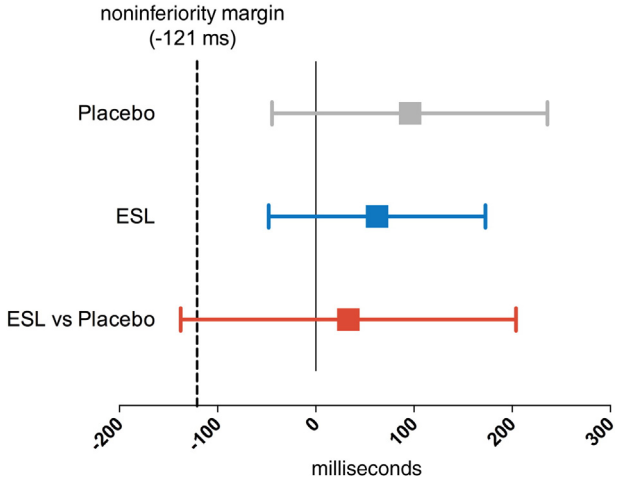

Fig. 3. Mean (95%CI) difference between placebo and ESL in the Power of Attention.

Results to Raven's SPM are presented in number of correct answers to the 60-item questionnaire (Supplementary Table 4). The median number of correct answers at baseline was 39 for placebo and 37.5 for the ESL group. At the end of double-blind period, median number of correct answers was 40.5 for placebo and 41.0 for ESL. Since the assumption of normality was not confirmed for the ANCOVA analyses, differences between groups were assessed using the nonparametric van Elteren test. The difference in the median change between treatment groups was 1.5 ($P = 0.82$). There were also no statistically significant differences between placebo and ESL in both age groups (Supplementary Table 4). Open-label data for the analyses of the Raven's SPM were available for 111 patients, 37 from the original placebo group and 74 from the original ESL group. At open-label baseline, the median number of correct responses was 41.0, and was unchanged at the end of this phase of the study. Patients originally randomized to placebo started the open-label phase with a median score of 42.0, compared with 40.5 for those in the ESL group. By week 52 (or at early discontinuation), the median number of correct answers dropped slightly to 40.0, whereas the ESL group improved to a median of 43.0.

3.3. Efficacy results

Fig. 4A depicts the results of the standardized seizure frequency during the maintenance period and titration + maintenance period for the ITT population. The least square means for standardized seizure frequency during the maintenance period alone (1.98 vs 4.29) and during the titration + maintenance period (2.58 vs 4.63) were significantly lower in the ESL group than in placebo group (Fig. 4A). In the ITT population, the median relative change in standardized seizure frequency from baseline during the maintenance period was −31.6% in the placebo group and −51.7% in the ESL group (Fig. 4B). Considering the titration + maintenance period, similar results were observed where the median relative change from baseline was −21.9% in the placebo group and −47.9% in the ESL group. The differences between the treatment groups with respect to relative change from baseline in standardized seizure frequency during the maintenance period alone and during the titration + maintenance period are statistically significant based on the nonparametric analyses ($P < 0.001$ each). The results of these

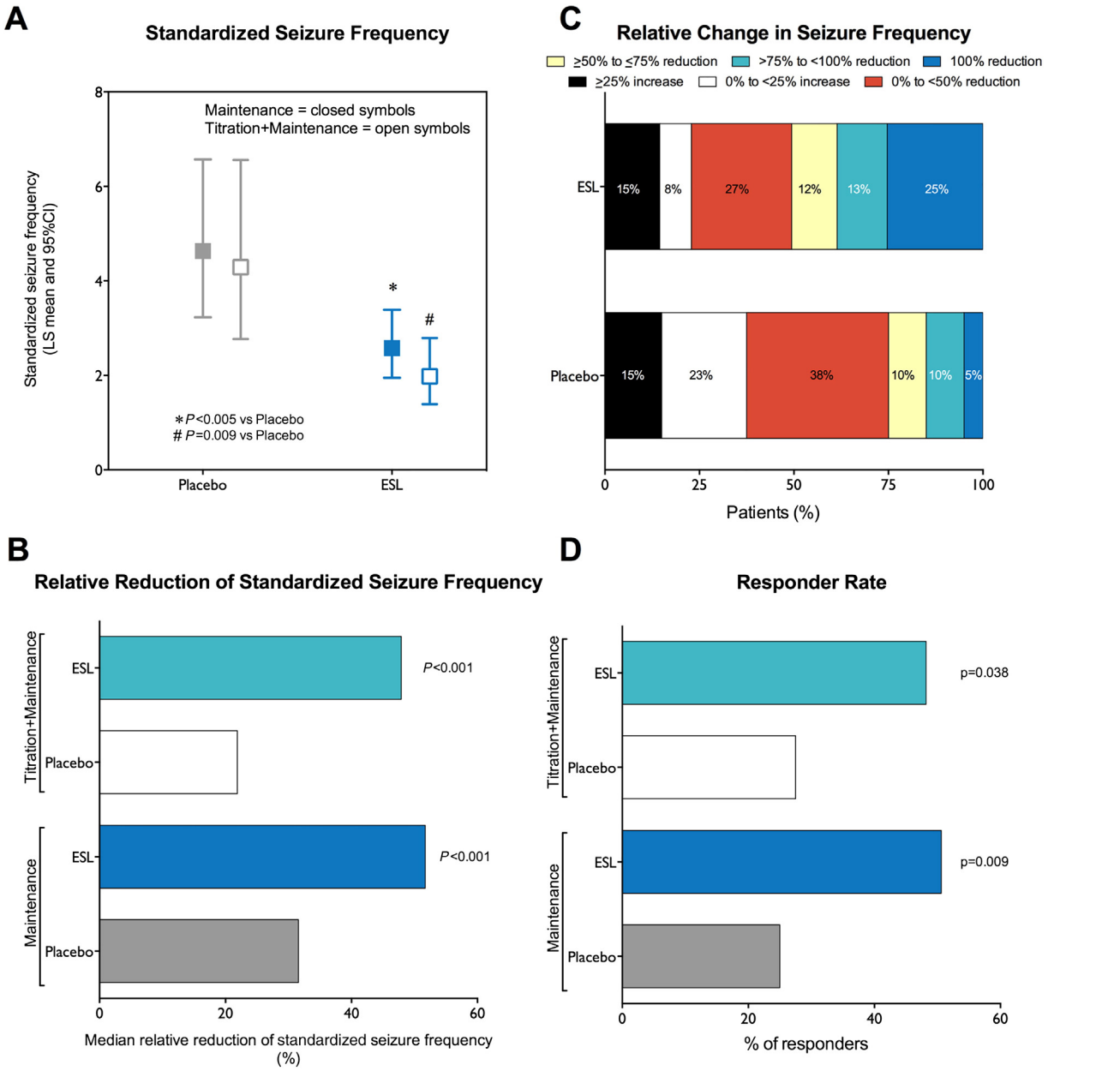

Fig. 4. Mean and 95%CI seizure frequency per 4 weeks (A), mean relative reduction in seizure frequency (B), mean relative change in seizure frequency (C) over the 8-week maintenance and mean responder rate (i.e., percentage of patients with ≥50% reduction in seizure frequency) (D).

analyses in each of the 2 age groups (6 to 11 years and 12 to 16 years) were similar to the overall results. Results for the efficacy PP population, with median relative changes were from baseline of −30.7% and −54.1% during the maintenance period alone and −20.9% and −48.2% during the titration + maintenance period for the placebo and ESL groups, respectively. Again, differences from placebo and ESL are statistically significant based on the nonparametric analyses ($P < 0.001$ each). Results for the ITT population for patients who completed the tapering-off period are shown in Supplementary Table 5. The results in this subset of patients indicate that there was no rebound effect in seizure frequency. The results of these analyses in each of the 2 age groups (6 to 11 years and 12 to 16 years) were similar to the overall results (Supplementary Table 5).

All patients were categorized according to their percentage change from baseline in standardized seizure frequency, in six categories ranging from seizure-free (100% reduction) to exacerbation (≥25% increase), as depicted in Fig. 4C. Two patients (5.0%) in the placebo group and 18 (21.7%) in the ESL group, who completed the entire maintenance period, achieved 100% reduction of seizures. When the analysis was limited to patients who had completed at least 4 weeks of treatment, the figures remained the same. The difference between the treatment groups with respect to the proportion of seizure-free patients during the maintenance period was statistically significant ($P = 0.024$). A minority of patients in both treatment groups showed exacerbation during the maintenance period, as evidenced by an increase of ≥25% from baseline in standardized seizure frequency. The rates were similar between the treatment groups (15.0% placebo and 14.5% ESL). The rates of reduction were similar between the placebo group and the ESL group for the range of >75% to <100% reduction and ≥50% to ≤75% reduction. For the range of 0% to <50% reduction, the trend reversed, with the rate higher in the placebo group than in the ESL group. The difference between the treatment groups with respect to the overall distribution of percentage change from baseline in standardized seizure frequency during the maintenance period was statistically significant ($P = 0.047$).

For the overall age groups, the percentage of responders during the maintenance period was of 50.6% for ESL and 25.0% for placebo ($P = 0.009$) (Fig. 4D). During the titration + maintenance period, the percentage of responders was 27.5% in the placebo group and 48.2% in ESL group ($P = 0.038$). The overall seizure-free rate for patients that completed the maintenance period was higher for ESL (25.3%) than placebo (5.0%) (Fig. 4C). During the maintenance period, the percentages of responders for children aged 6 to 11 years were 27.8% (placebo) and 55.6% (ESL) and for adolescents aged 12 to 16 years were 22.7% (placebo) and 46.8% (ESL). Supplementary Table 5 summarizes the relative change from baseline in standardized seizure frequency by study period, including the titration, maintenance, titration + maintenance, and tapering-off periods for the modified efficacy ITT population by age group and overall.

Analysis of covariance was performed on the relative change from baseline in standardized seizure frequency and the standardized seizure frequency during the maintenance period and included the baseline standardized seizure frequency as a covariate in the model, as well as age group (stratification variable) and sex as baseline covariates. The treatment-by-age group and treatment-by-sex interactions were investigated in separate ANCOVA models. In addition, other baseline covariates (e.g., age at onset of epilepsy, number of AEDs ongoing at baseline) and treatment-by-covariate interactions were also investigated in the primary cognitive analyses. There were no statistically significant treatment-by-age group (n = 104; $P = 0.927$), treatment-by-sex (n = 104, $P = 0.962$), or treatment-by-country (n = 104; $P = 0.801$) interactions in the analysis of standardized seizure frequency during the maintenance period.

During the open-label period, the previous double-blind placebo group experienced a decrease in standardized seizure frequency gradually becoming similar to the previous double-blind ESL group. Fig. 5A depicts the mean standardized seizure frequency during the double-blind and the one-year open-label period (Weeks 1 to 4, Weeks 5 to 16, Weeks 17 to 28, Weeks 29 to 40, and Weeks ≥41). Median postbaseline standardized seizure frequencies were lower in the previous double-blind ESL group compared with the placebo group at most timepoints. The median relative change from baseline during the one-year open-label period was −59.57% in the previous double-blind placebo group and −65.47% in the previous double-blind ESL group. During the open-label period, the percentage of responders increased over time in both treatment groups, with consistently higher percentages of responders who received previous double-blind ESL compared with patients who received previous double-blind placebo, respectively, as follows: Weeks 1 to 4 (56.0% vs. 51.4%), Weeks 5 to 16 (64.4% vs. 55.6%), Weeks 17 to 28 (67.6% vs. 54.5%), Weeks 29 to 40 (74.2% vs. 62.5%), Weeks ≥41 (75.4% vs. 65.6%). Overall, the percentage of responders for children aged 6 to 11 years was 63.0% (previous double-blind placebo, 50.0%; previous double-blind ESL, 70.0%), and 60.6% for adolescents aged 12 to 16 years (previous double-blind placebo, 57.1%; previous double-blind ESL, 62.2%), which shows a comparable effect in the 2 age groups.

In the open-label period, all patients were categorized according to their percentage change from baseline in standardized seizure frequency, in six categories ranging from seizure-free (100% reduction) to exacerbation (≥25% increase) (Fig. 5B). The majority of patients showed >50% reduction in seizure frequency, overall and in each treatment group, as previously described. Within these responders, the majority (32.1%) showed a reduction of >75% to <100%, with comparable proportions between the two treatment groups (29.7% for previous double-blind placebo and 33.3% for previous double-blind ESL). Among the patients with reduction <50%, the previous double-blind placebo group showed that the rate was higher for placebo.

3.4. Safety results

Safety results for this study have shown that TEAEs had a similar incidence between ESL and placebo (41.0% vs 47.5%) in the double-blind part; a brief summary of AEs overall and by age group is presented in Supplementary Table 6. The TEAEs with an incidence of >3% of patients, in either treatment group, in descending order by ESL group, by preferred term are presented in Table 3. The most commonly reported TEAEs with an incidence of >3% of patients, in either treatment group, were headache (9.6% in ESL vs 15.0% in placebo), somnolence (6.0% in ESL vs 5.0% in placebo), and vomiting (6.0% in ESL vs 2.5% in placebo). Most TEAEs were of mild or moderate intensity for both treatment groups. Severe TEAEs occurred in no more than 1 patient in either treatment group. A total of 5 patients reported at least one serious TEAE, with 2 patients (5.0%) in the placebo group and 3 patients (3.6%) in the ESL group. One patient (1.2%) in the ESL group experienced severe status epilepticus, which was considered serious, possibly related to study drug, and led to discontinuation of study treatment. The prevalence of serious TEAEs was generally low (2 patients in placebo and 3 in ESL), and no deaths occurred during the study. Five patients (6.0%) had TEAEs that led to premature discontinuation, all of which occurred in the ESL group. In the open-label part TEAEs that were more frequent in the previous double-blind ESL group than in the placebo group were respiratory tract infection, including viral (5.4% placebo; 9.4% ESL) and nasopharyngitis (0 placebo; 4.0% ESL), but these were infrequent overall. The proportion of patients who reported headache was higher in patients who received previous double-blind placebo (8.1%)

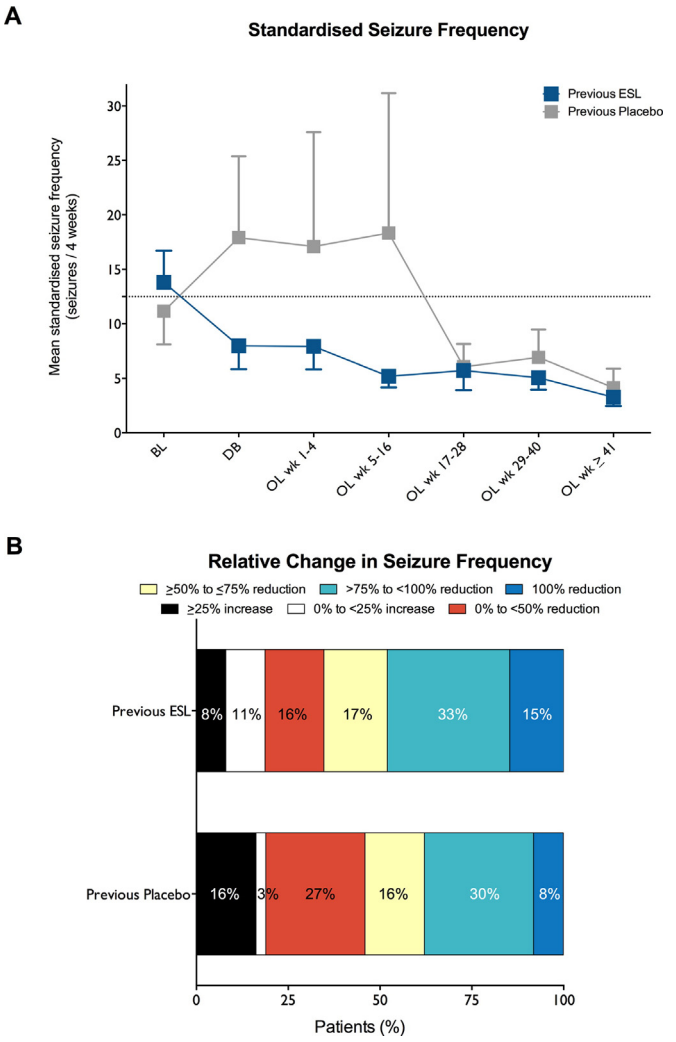

Fig. 5. Mean (and SD) standardized seizure frequency per 4 weeks during the double-blind and one-year open-label period (A) and standardized seizure reduction or exacerbation during the one-year open-label period (B).

Table 3
Treatment-emergent adverse events with an incidence >3% of patients in by preferred term (safety population).

	Double-blind part	
	Placebo (N = 40)	ESL (N = 83)
Patients with any TEAE	19 (47.5)	34 (41.0)
Headache	6 (15.0)	8 (9.6)
Somnolence	2 (5.0)	5 (6)
Vomiting	1 (2.5)	5 (6)
Dermatitis allergic	0	4 (4.8)
Respiratory tract infection	2 (5)	4 (4.8)
Diplopia	0	3 (3.6)
Dizziness	1 (2.5)	3 (3.6)
Respiratory tract infection viral	0	3 (3.6)
Nausea	2 (5.0)	2 (2.4)
Pyrexia	2 (5.0)	1 (1.2)
	Open-label part	
	Previous placebo (N = 37)	Previous ESL (N = 75)
Patients with any TEAE	17 (45.9)	28 (37.3)
Respiratory Tract Infection Viral	1 (2.7)	5 (6.7)
Headache	3 (8.1)	3 (4.0)
Vomiting	1 (2.7)	3 (4.0)
Pyrexia	1 (2.7)	3 (4.0)
Nasopharyngitis	0	3 (4.0)
Convulsion	2 (5.4)	2 (2.7)
Influenza	3 (8.1)	0
Head injury	2 (5.4)	0
Dizziness	2 (5.4)	0
Urticaria	2 (5.4)	0

Abbreviations: ESL = eslicarbazepine acetate; TEAE = treatment-emergent adverse event.
Percentages are calculated based on the number of patients in the Safety population. Adverse events are classed as treatment-emergent if they started on or after the date of first dose of study treatment. Adverse events with partial or missing start dates are classified as treatment-emergent, unless the nonmissing components of the start date confirm otherwise. A patient with more than one TEAE with the same preferred term is counted once for that term.

compared with those who received previous double-blind ESL (4.0%); however, there were only 3 patients in each treatment group.

4. Discussion

Treatment of epilepsy with AEDs may impact negatively upon cognitive function, but studies performed in children and adolescents have been insufficient or inconclusive [15,16,26]. Recent studies based on appropriate and thorough testing methods have been able to identify changes in specific measures of neurocognitive or behavioral functioning in pediatric patients with epilepsy in monotherapy or adjunctive therapy with AEDs [20,27–29]. The present study, designed to evaluate the effect of ESL when given as add-on therapy on cognitive function of ESL compared with placebo, in children and adolescents with refractory FOS over a 12-week double-blind period, is the first to evaluate the effects of ESL on neurocognitive and behavioral functioning, using standardized and validated tools (CDR system, CHQ-PF50, CBCL, and Raven's SPM).

Overall, the findings reported here show that in a 12-week study period, adjunctive ESL in children and adolescents with FOS mostly causes nonstatistically significant effects on neurocognitive and behavioral functioning. The primary noninferiority analysis failed to reject the null hypothesis that the change from baseline in the Power of Attention score in the ESL group was at least 121 ms inferior to the placebo group for all age groups. However, the primary outcome variable in this study, Power of Attention, a measure of focused attention, and speed of information processing, failed to show a negative effect of ESL; the study was adequately powered to detect such an effect (see below). This 121-ms margin was based on a clinical trial in 12- to 17-year-old adolescents comparing Power of Attention in newly diagnosed children with epilepsy with a healthy age-matched normative sample [20]. In the present study, patients were undergoing treatment with AEDs, and younger patients (6 to 11 years) were also included. These factors may have contributed to inferior scores, as indeed seen in the baseline scores of the study, but also possibly to greater variability. Therefore, this margin should have included not only the expected difference but also the variability associated with it, as done in a similar trial where a healthy normative sample was used as reference [30]. In this regard, it is of clear relevance that the difference between the two conditions at the end of the double-blind period was in favor of ESL (see Table 2). Data from a previous study comparing the effects of two study treatments (carbamazepine [CBZ] and remacemide) in the 12- to 17-year-old patients from the study have just been published [29]; it was identified that after 8 weeks of dosing, a significant difference of 107 ms on Power of Attention was detected ($P = 0.0059$) between remacemide (n = 30) and CBZ (n = 34). At 48 weeks this difference had increased to 127 ms ($P = 0.0055$), with 22 patients in the CBZ arm and 24 patients in the remacemide arm. In the present study, at the end of the double-blind period when the comparisons were performed, 36 patients were on placebo and 66 on ESL. This suggests that the present study was adequately powered to detect a difference between placebo and ESL had one existed. The patients then entered a one-year open-label follow-up after the end of the double-blind period. Over the year, the patients showed a mean improvement in Power of Attention of 182 ms (235 ms for the 6- to 11-year-old patients and 144 for the 12- to 16-year-old patients). A cross-sectional year-by-year change in Power of Attention in a large sample of healthy individuals aged 6 to 17 years (Data on file, the CDR system) indicates that from 6 to 16 years of age the average yearly maturational improvement in healthy children was 70 ms. Thus, in the present study, the maturational development during the one-year open-label follow-up clearly showed no evidence of falling behind what would be expected for healthy children.

The other secondary cognitive domains of the CDR system were also not significantly different between placebo and ESL, with the exception for the Episodic Memory Index, a measure of delayed recognition of previously presented information, which had a statistically reliable negative effect in the ESL group. However, ESL did have a statistically reliable negative effect on the Episodic Memory Index, a measure of delayed recognition of previously presented information. However, the two groups had notably different prestudy scores on this measure; the ESL group being initially superior to placebo, and the effect may instead have represented “regression to the mean”. In a recent study, adjunctive perampanel was found to have a negative effect on both Continuity of Attention and Speed of Memory but a possible benefit for the Quality of Working Memory [28].

In measures of QOL or emotional and behavioral functioning, no differences were found between ESL and placebo, as demonstrated by the similar scores obtained in the CBCL, CHQ-PF50, and Raven's SPM. In contrast, adjunctive levetiracetam negatively impacted specific aspects of behavioral and emotional functioning in children, particularly the CBCL scores for Aggressive Behavior [27], although neurocognitive effects of levetiracetam were no different from placebo using other testing methods [30]. Although an indirect comparison with other studies suggests that ESL appears to cause less neurocognitive and behavioral effects than other adjunctive treatments in pediatric patients, head-to-head studies would be useful to make comparative assessments between ESL and other AEDs.

In line with previous studies in adults [31–36], ESL in a pediatric population was demonstrated with a good efficacy in reducing overall seizure frequency, leading to a significantly higher proportion of treatment responders and of seizure-free patients, compared to placebo. The main secondary efficacy endpoint, standardized seizure frequency over the maintenance period in the ITT population, showed statistically significant improvement over placebo in the ESL group ($P < 0.001$). The

results in the PP population were consistent with those in the ITT population. The results from the analyses of the other efficacy endpoints in the ITT population, including the proportion of responders during the maintenance period, percent change from baseline in standardized seizure frequency, and standardized seizure frequency, are consistent with the conclusions on the analysis of the main secondary efficacy endpoint. On the other hand, the better control of seizures by ESL may be associated with the observed overall improvement of neurocognitive performance. There were no statistically significant treatment-by-age group, treatment-by-sex, or treatment-by-country interactions in the analysis of standardized seizure frequency during the maintenance period thus indicating that the treatment effect was consistent in each age group, sex, and country. The results from the one-year open-label extension showed a prolonged seizure frequency reduction for patients already receiving ESL during the double-blind part. The previous double-blind placebo group experienced a decrease in standardized seizure frequency during the open-label period, gradually becoming numerically similar to the previous double-blind ESL group. Median postbaseline standardized seizure frequencies during the one-year open-label period were lower in the previous double-blind ESL group compared with the placebo group at most time points. The previous double-blind placebo group experienced a decrease in standardized seizure frequency during the open-label period, gradually becoming similar to the previous double-blind ESL group. These results indicate reductions in standardized seizure frequency during the open-label period compared with baseline, with a greater treatment effect observed in the ESL group.

During the double-blind part of the study, the most common TEAEs with an incidence of >3% of patients in the ESL group were vomiting, diplopia, and somnolence, but these were few overall. Headache was more frequent in patients receiving placebo compared with those receiving ESL. The incidences for dizziness and somnolence were similar between the placebo and ESL groups. Events of rash (including rash, rash pruritic, and allergic dermatitis), commonly observed with other AEDs of this class of drugs, were reported by a few patients in the ESL groups. No events of hyponatremia were reported. The prevalence of Serious adverse events (SAEs) was low overall.

As was seen in the double-blind part, the TEAEs reported during the one-year open-label period that were more frequent in the previous ESL group were vomiting, allergic dermatitis, and diplopia, but these were infrequent overall. Headache was more frequent in patients receiving previous placebo compared with those receiving previous ESL. The incidences for dizziness and somnolence were similar between the previous double-blind placebo and ESL groups. Skin events were reported by a few patients; all 4 events occurred in patients who received previous double-blind placebo, and none of the events were considered related to study drug. No events of hyponatremia were reported. The prevalence of SAEs was low overall. Tolerability of ESL was suggested by high study completion rates and low incidences of AEs leading to discontinuation during double-blind and open-label parts of this study. The AE profile was consistent with previous data on ESL in adults [32].

Strengths of this study include the well-matched study populations – and their baseline scores – and testing with a very comprehensive neuropsychological battery. Even though well validated, the CBCL and the CHQ-PF50 are administered to the child's parents or legal guardians, and rely on their ability to recall and interpret the child's behavior, potentially leading to bias. Though the relatively short-time duration of the double-blind assessment described here could be seen as a limitation of this study, especially in what concerns the efficacy result conclusions, the efficacy results from the one-year open-label long-term extension to thistprins study supported the results from the double-blind phase in those patients who elected to remain on treatment. Furthermore, in the open-label extension, maturational development on cognition at least matched, if not exceeded, the expected rate of development seen in an age-matched cohort from the CDR system database. One potential limitation was the use of the last observation carried forward in the open-label part. However, the by-visit analysis does suggest this is not a limitation.

In conclusion, ESL overall did not produce statistically significant effects on neurocognitive and behavioral functioning in patients with epilepsy aged 6 to 16 years. Additionally, ESL was effective in reducing seizure frequency and was well-tolerated.

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Conflicts of interest

The author SJ reports receiving consulting fees from BIAL - Portela & C[a], S.A. and Eisai; PV reports receiving consulting fees from BIAL - Portela & C[a], S.A.

The authors JM, HG, JFR, and PSS are employed by BIAL - Portela & C[a], S.A.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Contributors

All authors participated in the design of the study. PSS and JFR participated in study implementation and data analysis. All authors were involved in data interpretation, and together discussed the initial ideas presented in the introduction and discussion of this Article; SJ was the principal coordinating investigator and wrote the first draft of the manuscript, PV, JM, and HG made substantial contributions to the revising of the manuscript, and JFR and PSS provided critical review. All authors approved the final submitted manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.01.029.

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