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Efficacy and safety of eslicarbazepine acetate as adjunctive therapy for refractory focal-onset seizures in children: A double-blind, randomized, placebo-controlled, parallel-group, multicenter, phase-III clinical trial

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ABSTRACT

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

Methods: Children (2–18 years old) with FOS, receiving 1–2 antiepileptic drugs, were randomized to ESL or placebo. Treatment was started at 10 mg/kg/day, up-titrated up to 20–30 mg/kg/day, and maintained for 12 weeks, followed by one-year open-label follow-up. Primary efficacy endpoints were relative reduction in standardized seizure frequency (SSF) and proportion of responders (≥50% SSF reduction) from baseline. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Results: The intention-to-treat (ITT) set included 134 patients randomized to ESL and 129 to placebo; 89.6% and 91.5%, respectively, completed the trial. An unbalanced number of seizures at baseline were observed between groups. Least square (LS) mean relative change in SSF from baseline was higher in the ESL group (−18.1%) than in placebo (−8.6%). Proportion of responders between ESL and placebo groups was not statistically different. A post hoc analysis showed greater relative reduction in SSF in patients above 6 years old treated with ESL 20 or 30 mg/kg/day compared with placebo; this was significant in patients above 6 years old treated with ESL 30 mg/kg/day (LS mean difference: 31.9%; $p = 0.0478$). The observed safety profile in children was consistent with that established in adult studies.

Conclusions: Adjunctive ESL treatment was well-tolerated, but this trial failed to demonstrate that ESL was more effective than placebo in the predefined efficacy endpoints; factors that may have contributed to this outcome, affecting particularly the young age group, include etiological heterogeneity, difficulty in recognizing simple partial seizures, high seizure frequency with risk of imbalance, and underestimation of the efficacious dose range.

1. Introduction

Eslicarbazepine acetate (ESL) is a once daily antiepileptic drug (AED) [1,2] 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 [3]. A phase-II trial evaluated the effects of adjunctive ESL treatment on cognitive function and efficacy in children aged 6–16 years with FOS. Antiseizure efficacy was evaluated via secondary endpoints, and ESL was superior to placebo in standardized seizure frequency (SSF), responder rate, and seizure freedom rate [4]. These positive outcomes supported a rationale for the confirmatory phase-III study designed to assess the efficacy and safety of ESL as adjunctive therapy in children and adolescents with refractory focal epilepsy. Eslicarbazepine acetate has also been

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approved by EMA as adjunctive therapy in children aged above 6 years old with FOS. More recently, ESL received FDA approval to treat partial-onset seizures in patients 4 years of age and older.

The present report provides details of this phase-III, randomized, double-blind (DB), placebo-controlled study aimed to evaluate efficacy and tolerability of ESL as adjunctive therapy in pediatric patients with refractory FOS.

2. Patients and methods

This was a multicenter phase-III, randomized, DB, placebo-controlled, parallel study to evaluate the efficacy of ESL as adjunctive therapy in children and adolescents with refractory FOS (NCT00988156). The study was conducted in 20 countries from Europe and Asia (Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Ukraine, Austria, France, Germany, United Kingdom, Bosnia and Herzegovina, Croatia, Italy, Portugal, Serbia, Spain, Malaysia, Philippines, and Taiwan). Children (2–18 years old) diagnosed as having epilepsy for ≥6 months prior to enrollment, with FOS (≥4 seizures in the month before enrollment), receiving 1–2 AEDs (except oxcarbazepine), were randomized (1:1) to ESL or placebo (stratified by age: stratum I, 2–6 years; stratum II, 7–11 years; stratum III, 12–18 years).

The study consisted of an 8-week observational baseline period, followed by a 6-week DB titration period (treatment started at 10 mg/kg/day and up-titrated to 20 mg/kg/day) and a 12-week DB maintenance period (if tolerability and response were acceptable, 20 mg/kg/day was maintained for 12 weeks; if tolerability was acceptable but the therapeutic response was unsatisfactory, the patient was up-titrated to 30 mg/kg/day and maintained for 12 weeks; if intolerable adverse events [AEs] occurred, the patient was down-titrated to the previous dose or discontinued). There was an up to 4-week DB tapering-off period where study treatment was down-titrated in 10 mg/kg/day steps and then an additional 4-week observational follow-up period (Fig. 1). Treatment was given as oral suspension (50 mg/mL) for the age group of 2–6 years or tablets (200 mg) for use in the ≥7 years of age. During the study, a recall of oral suspension had to be conducted because of stability issues. Ongoing patients (n = 41) were offered to switch to the tablet formulation if they could swallow tablets. Subjects affected by the oral suspension recall were included in a modified intention-to-treat (mITT) analysis.

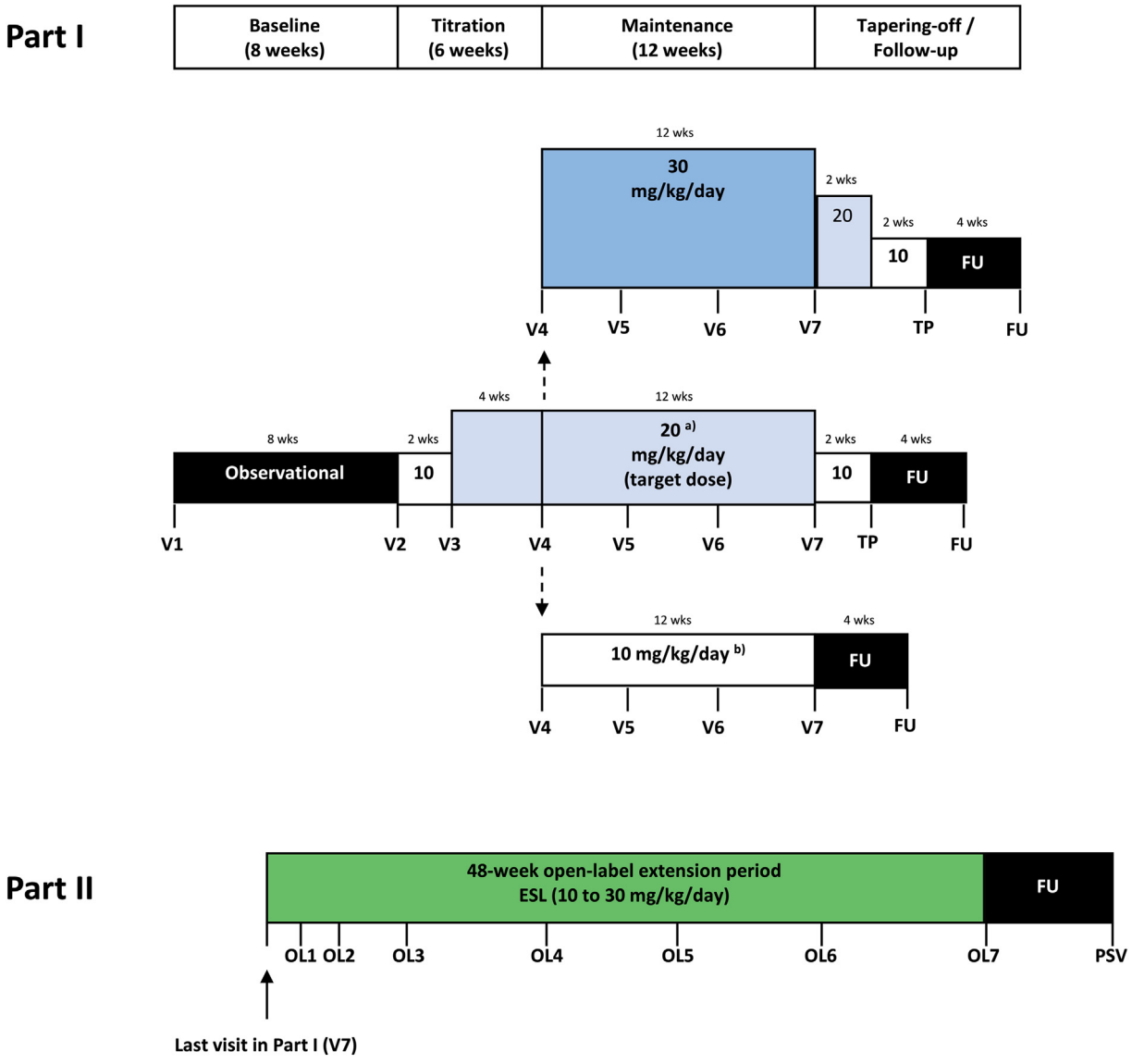

Fig. 1. Dose schedule and study design (Parts I and II). Abbreviations: FU = follow-up; PSV = poststudy visit; TP = tapering-off; V = Visit. (a) For those patients down-titrated from 30 mg/kg/day because of intolerable AEs. (b) For those patients down-titrated from 20 mg/kg/day because of intolerable AEs during the titration period. Note: Randomization occurred at V2. At the last double-blind visit in Part I (V7 or TP), patients had the option to enter a 48-week extension with open-label treatment with ESL, or to be discontinued and have a FU visit.

Part II consisted of a 48-week open-label (OL) extension period (Fig 1). All patients who entered this period initially received a dosage of 10 mg/kg/day ESL, but this dosage was titrated by the investigator according to clinical response, with a dosage range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg Once per day (QD)). Down-titration was allowed according to clinical response or in the case of intolerable AEs, as often as needed. As much as possible, concomitant AED therapy (1 or 2 AEDs) was kept stable throughout OL extension period under the direction of the patient's physician. Patients entering the 48-week OL extension attended the study clinic for six scheduled visits for ongoing safety monitoring and performance of study assessments. At the end of OL extension period, patients either entered a tapering-off/follow-up period or a further period of OL treatment with ESL (Part III). For patients who completed the OL extension period and did not enter the additional two-year OL extension, a poststudy visit (PSV) was performed approximately 4 weeks after study treatment was tapered off.

If a patient became adult during or after completion of the 48-week OL extension period (and wanted to continue receiving ESL) in those countries where ESL is available on the market (and reimbursed), the patient was switched to the commercially available product.

The primary efficacy endpoints were the responder rate, defined as the proportion of patients with at least 50% decrease in SSF from baseline and the relative reduction in standardized (/4-week) seizure frequency (SSF) in the ITT set. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs).

Blood and urine samples were obtained during the study for the purpose of monitoring laboratory safety parameters. A central laboratory was used for all clinical laboratory analyses. All laboratory values were classified as normal or abnormal according to the laboratory's normal ranges, and abnormal values had to be commented by the investigator on clinical relevance. Blood samples for the determination of concentrations of ESL and eslicarbazepine, the main circulating active metabolite, in plasma and concentrations of concomitant AEDs in serum were taken at visits 1, 3, 4, 7, and Part I follow up visit and at end of study visit (EDV), where applicable. Drug assays were performed according to previously validated methods.

The study was approved by the respective countries' Ethics Committees and Regulatory Authorities. Written informed consent was obtained from parent/legal representative, and written assent was obtained from the patient.

2.1. Pharmacokinetic analysis

Eslicarbazepine concentrations were considered to be at steady state as the ESL dosage regimen had remained unaltered for at least 1 week before each blood collection at each pharmacokinetic (PK) visit. As only a small number of samples were available from each subject, a simple PK screen had to be used for eslicarbazepine PK characterization, i.e., the model allows the estimation of the apparent clearance (CL/F) from the average concentration of eslicarbazepine at steady state, $C_{av\text{-}ss}$, based in a one compartmental model with first-order absorption:

$$CL/F = \text{Total daily dose}/(AUC_{\tau-ss})$$

where:

$AUC_{\tau\text{-}ss} = C_{av\text{-}ss} * \tau$

$C_{av\text{-}ss}$ - the average concentration at steady state.

$AUC_{\tau\text{-}ss}$ - the area under the plasma concentration versus the time curve from posological interval (τ) at steady state.

CL/F - the apparent clearance.

Subjects randomized before the investigational medicinal product (IMP) recall were removed from the PK population and therefore not considered for this PK analysis.

2.2. Statistical analysis

The statistical analysis for efficacy focused on the comparison between ESL and placebo, independent of the individual final ESL dose. The primary and secondary efficacy analyses were performed for the ITT set. Continuous variables were summarized using descriptive statistics (number of patients, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables were summarized using frequency counts (n) and percentages (%). The responder rate was analyzed by a Cochran–Mantel–Haenszel test with age group (2–6 years; 7–11 years; 12–18 years) as the stratification factor. Results are presented with responder rates, odds ratios, confidence intervals (CIs), and p-values. The relative reduction in SSF was compared between treatment groups using an analysis of covariance (ANCOVA) that modeled the relative change in SSF as a function of age group, baseline seizure frequency, and treatment. Results for SSF are presented with the least square (LS) mean relative change. Secondary efficacy variables were analyzed descriptively. All safety variables were analyzed descriptively. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. Safety variables were performed for the safety set. All statistical tests were 2-sided at an alpha level of 0.05. A post hoc analysis has been performed for all patients aged ≥7 years at time of study entry. These included selected baseline characteristics, efficacy, and safety summary tables. Primary efficacy endpoints were analyzed by ESL dosage (20 vs 30 mg/kg/day), excluding patients in age group 2–6 years, using a chi test for responder rate and ANCOVA for relative change in SSF. The responder rate during the combined titration and maintenance periods was also assessed.

Summary PK statistics are reported, as appropriate, using the geometric mean, arithmetic mean, standard error of the mean (SEM), SD, coefficient of variation (CV), median, minimum, and maximum.

3. Results

3.1. Analysis of populations

In this study, a total of 370 patients were enrolled and started the baseline period (Fig. 2). Of these, 66 discontinued the study either during or after the baseline period. Therefore, 304 patients were randomized. Of the 304 patients randomized, 41 patients belonged to stratum I before IMP recall; 20 of these patients were randomized to placebo and 21 to ESL. Six patients in each treatment group of this stratum I discontinued the study, resulting in 14 and 15 patients completing the study, respectively. The randomized population excluding stratum I before IMP recall consisted of 263 patients, constituting the safety set. Of these patients, 134 were randomized to ESL and 129 to placebo. During the study, 14 ESL patients and 11 placebo patients of the safety set discontinued the study, leading to 120 patients in the ESL group and 118 patients in the placebo group completing the DB period of the study (Fig. 2).

Demographic and baseline characteristics of the overall safety population are presented in Table 1. There were no relevant differences between treatment groups regarding demographics. In the safety set, the mean age was 9.9 years in the ESL group and 9.5 years in the placebo group. Slightly more patients belonged to the age groups of 7–11 years (38.1% of ESL patients, 41.1% of placebo patients) and 12–18 years (38.8% and 34.9%, respectively) than to the group of children aged 2–6 years (23.1% and 24.0%, respectively), owing to the exclusion of stratum I patients before IMP recall. In both treatment groups, there were slightly more female than male patients and at least 90% of patients were Caucasian. The majority of patients (59.70%) were from Eastern Europe.

There were no relevant differences between treatment groups regarding disease etiology and family history. In the safety set, the mean age at onset of epilepsy was 3.0 years in the ESL group and 2.9 years in the placebo group (Table 1). Mean durations of epilepsy in

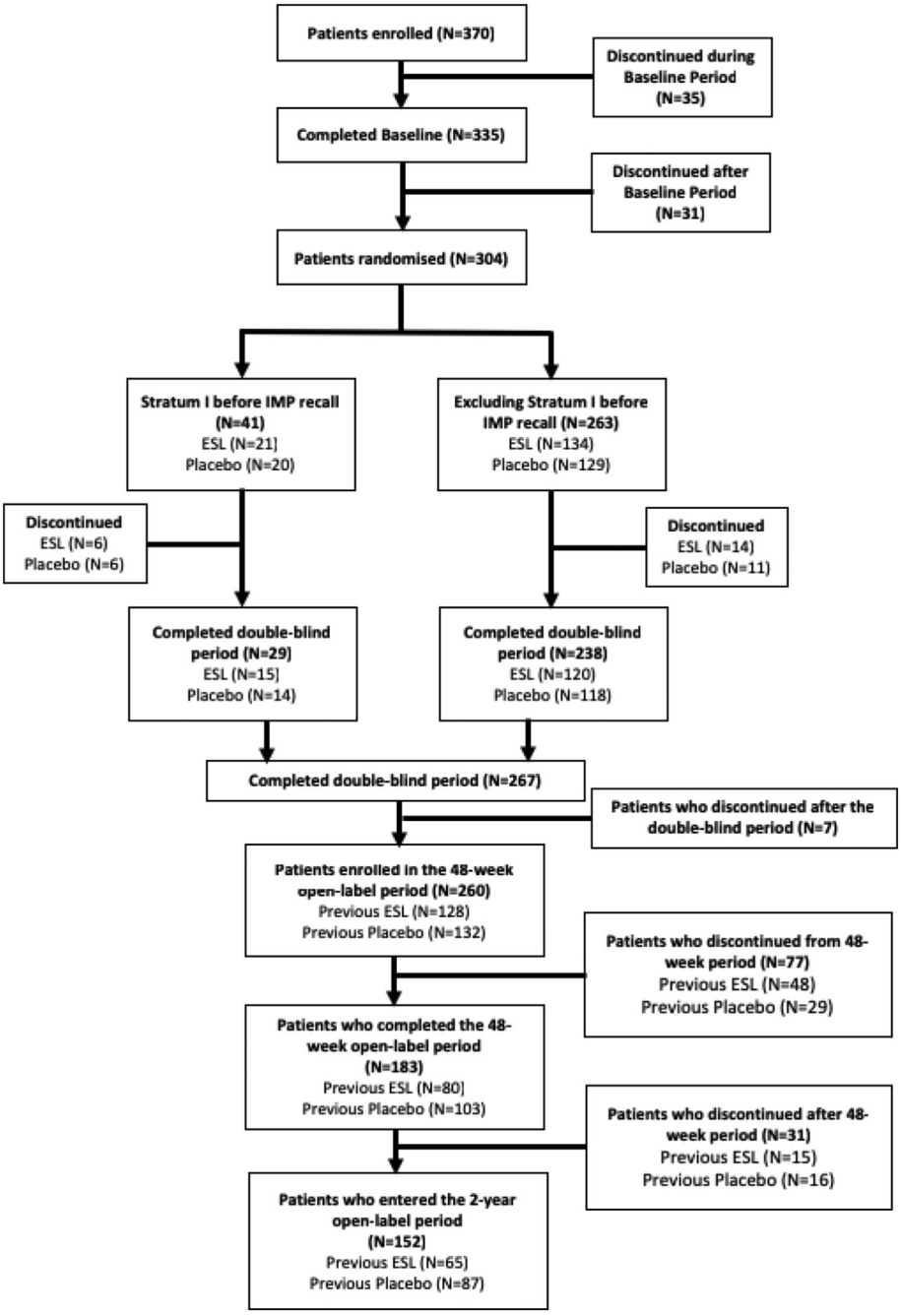

Fig. 2. Patient disposition. Abbreviations: ESL = eslicarbazepine acetate; IMP = investigational medicinal product. Notes: The total number of patients screened includes patients who failed at the screening visit (V1) or at randomization (V2). Patients could have more than one reason for discontinuation.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

the ESL group were 37.5 months in age group 1, 79.5 months in age group 2, and 106.7 months in age group 3; corresponding mean durations of epilepsy in the placebo group were 43.5, 75.3, and 105.8 months, respectively. The most frequently reported etiologies of the disease were congenital/hereditary (20.9% ESL, 20.2% placebo) and idiopathic (14.2% ESL, 16.3% placebo) (Table 1). The etiology was reported as unknown for 24.6% of ESL patients and for 30.2% of placebo patients. At least 90% of patients in either group had no disease history in their families.

The median standardized number of seizures during the baseline period was lower in the ESL group (11.5; range: 3.7, 605.8) than in the placebo group (17.0; range: 3.9, 1972.5) (Table 1). The majority of these seizures were simple partial seizures (aware FOS) reported by 65 (48.5%) ESL patients and 71 (55.0%) placebo patients. The median standardized simple partial seizure frequency was 8.0 in the ESL group and 14.0 in the placebo group. Respective frequencies for complex partial seizures (impaired awareness FOS) and partial evolving to secondarily generalized seizures (focal-onset evolving to bilateral tonic–clonic seizures) were slightly lower, without significant differences in median standardized frequencies between treatment groups (Table 1).

All patients took at least 1 concomitant AED during Part I (Table 2). There were no relevant differences between treatment groups in the use of concomitant AEDs during the study. At the end of the baseline period, the majority of patients took 2 concomitant AEDs (73.1% of ESL patients, 72.9% of placebo patients). The remaining patients either took 1 (15.7% and 19.4%, respectively) or 3 concomitant AEDs (11.2%

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

	Placebo (N = 129)	ESL (N = 134)
Age (years), (SD)	9.5 (3.9)	9.9 (4.2)
Age group, n(%)		
2–6 years	31 (24.0)	31 (23.1)
7–11 years	53 (41.1)	51 (38.1)
12–18 years	45 (34.9)	52 (38.8)
Gender, n (%)		
Male	62 (48.1)	64 (47.8)
Female	67 (51.9)	70 (52.2)
Ethnicity, n (%)		
Caucasian	117 (90.7)	123 (91.8)
African (black)	1 (0.8)	0
Asian	10 (7.8)	11 (8.2)
Other	1 (0.8)	0
Duration of epilepsy (months), mean (SD)		
Age group 2–6 years	43.5 (16.9)	37.5 (16.5)
Age group 7–11 years	75.3 (31.9)	79.5 (35.8)
Age group 12–18 years	105.8 (48.9)	106.7 (50.9)
Age at onset, mean (SD)	2.9 (3.4)	3.0 (3.4)
Min–max	0.0–14.0	0.0–14.0
Etiology, n (%)		
Congenital/hereditary disorders	26 (20.2)	28 (20.9)
Idiopathic	21 (16.3)	19 (14.2)
Infection disease	11 (8.5)	13 (9.7)
Cranial trauma/injuries	4 (3.1)	8 (6.0)
Cerebrovascular disease	4 (3.1)	8 (6.0)
Brain tumors	4 (3.1)	3 (2.2)
Systemic/toxic/metabolic disorders	1 (0.8)	1 (0.7)
Unknown	39 (30.2)	33 (24.6)
Other	21 (16.3)	28 (20.9)
Seizure frequency, median (min; max)[a]	17.0 (3.9, 1972.5)	11.5 (3.7, 605.8)
Seizure type, n (%)[b]		
Simple focal	71 (55.0)	65 (48.5)
Complex focal	78 (60.5)	84 (62.7)
Partial evolving to secondarily generalized	63 (48.8)	60 (44.8)
Unclassified	18 (14.0)	17 (12.7)
Other	10 (7.8)	11 (8.2)
Family history (yes), n (%)[b]	11 (8.5)	7 (5.2)

[a] Standardized seizure frequency per 28 days during the 8-week observational baseline period.
[b] During the 8 weeks prior to screening.

Table 2
Concomitant antiepileptic drugs during the study (safety set).

Double-blind (DB) period of the study	Placebo (N = 129)	ESL (N = 134)
Number of AEDs at baseline, n (%)		
1	25 (19.4)	21 (15.7)
2	94 (72.9)	98 (73.1)
3	10 (7.8)	15 (11.2)
AEDs continued onto DB period, n (%)		
Valproic acid[a]	62 (48.1)	67 (50.0)
Lamotrigine	40 (31.0)	37 (27.6)
Carbamazepine	31 (24.0)	35 (26.1)
Topiramate	32 (24.8)	32 (23.9)
Levetiracetam	31 (24.0)	30 (22.4)
Diazepam	11 (8.5)	15 (11.2)
Phenobarbital	7 (5.4)	7 (5.2)
Clobazam	9 (7.0)	5 (3.7)
Clonazepam	5 (3.9)	7 (5.2)

Open-label (OL) period of the study	Previous placebo (N = 115)	Previous ESL (N = 111)
Number of AEDs at start of OL period, n (%)		
1	20 (17.4)	18 (16.2)
2	85 (73.9)	81 (73.0)
3	9 (7.8)	12 (10.8)
4	1 (0.9)	0 (0.0)
AEDs used[b]		
Valproic acid	57 (49.6)	54 (48.6)
Lamotrigine	35 (30.4)	29 (26.1)
Carbamazepine	28 (24.3)	33 (29.7)
Topiramate	30 (26.1)	27 (24.3)
Levetiracetam	26 (22.6)	26 (23.4)
Diazepam	10 (8.7)	12 (10.8)
Clobazam	9 (7.8)	5 (4.5)
Phenobarbital	9 (7.8)	5 (4.5)
Switching to monotherapy	1 (0.9)	2 (1.8)

[a] Includes any concomitant medications coded to "valproate sodium", "valproic acid", and "valproate sodium; valproic acid".
[b] Reported in ≥5% of patients in total, sorted by frequency.

and 7.8%, respectively). The most common AED taken at the end of the baseline period was valproic acid (50.0% of ESL patients, 48.1% of placebo patients). Other common AEDs taken at the end of the baseline period and reported for ≥20% of patients were lamotrigine, carbamazepine, topiramate, and levetiracetam, with frequencies of patients taking these AEDs varying between 22.4% and 31.0% (Table 2).

Of the 267 patients who completed the preceding DB part of the study, 260 patients were enrolled into 48-week OL extension period and received OL treatment with ESL (Fig. 2). Of these, 128 patients had received ESL, and 132 patients had received placebo during the DB period. Of the 260 patients enrolled, 88 belonged to age stratum I (2–6 years), and 86 each were to age strata II (7–11 years) and III (12–17 years). The majority of patients (166 patients [73.5%]) took 2 concomitant AEDs during the OL extension period (Table 2). The most commonly reported concomitant AEDs (>20% of patients) were valproic acid, lamotrigine, carbamazepine, topiramate, and levetiracetam. Frequencies were balanced between groups by previous treatment. Three patients (1.3%) were switched to monotherapy during the OL extension period. Overall compliance during the 48-week OL extension period was good as shown by 217 patients (96.0%) of the safety set having taken at least 80% but not more than 120% of the study medication as prescribed per protocol.

3.2. Efficacy results

The ITT set that included all 134 treated ESL patients and all 129 treated placebo patients was used for all efficacy analyses. Selected analyses were also performed using the modified ITT (mITT) set, the stratum I before IMP recall set. As indicated above, a post hoc analysis has been performed for all patients aged ≥7 years at time of study entry (strata II and III). Patients in strata II and III received study drug orally as tablets while the younger patients of stratum I received study drug as oral suspension. Additional analyses defined after database lock and unblinding of the data were performed for the subgroup of patients included in stratum I (age 2–6 years; 31 ESL patients and 33 placebo patients) and those in strata II and III (age 7–18 years; 103 ESL patients and 96 placebo patients).

Forty-one patients (30.6%) in the ESL group compared with 40 patients (31.0%) in the placebo group were responders, defined as the proportion of patients with at least a 50% decrease in the SSF from the baseline period to the 12-week maintenance period, resulting in a nonsignificant odds ratio of 0.97 (Fig. 3A; Supplementary Table 1). The responder rate during the combined titration and maintenance periods was also assessed. Thirty-four patients (25.4%) in the ESL group compared with 29 patients (22.5%) in the placebo group were responders, resulting in a nonsignificant odds ratio of 1.15 (Supplementary Table 1). The responder rate in patients aged 2–6 years old receiving ESL (16.1%) was not different from those administered with placebo (33.3%), resulting in a nonsignificant odds ratio of 0.38 (95% CI: 0.12, 1.28; p = 0.1122) (Fig. 3A; Supplementary Table 1). In patients aged 7–18 years old, the responder rate was similar in the ESL (35.0%) and placebo (30.2%) treatment groups, resulting in a nonsignificant odds ratio of 1.24 (95% CI: 0.7, 2.2; p = 0.4759) (Fig. 3A; Supplementary Table 1). In the combined titration and maintenance periods in patients aged 7–18 years old, the responder rate was similar in both treatment groups (29.1% in ESL and 22.9% in placebo), resulting in an odds ratio of 1.38 (95% CI: 0.7, 2.6; p = 0.3191) (Supplementary Table 1). In patients aged 7–18 years old treated with 30 mg/kg/day during the

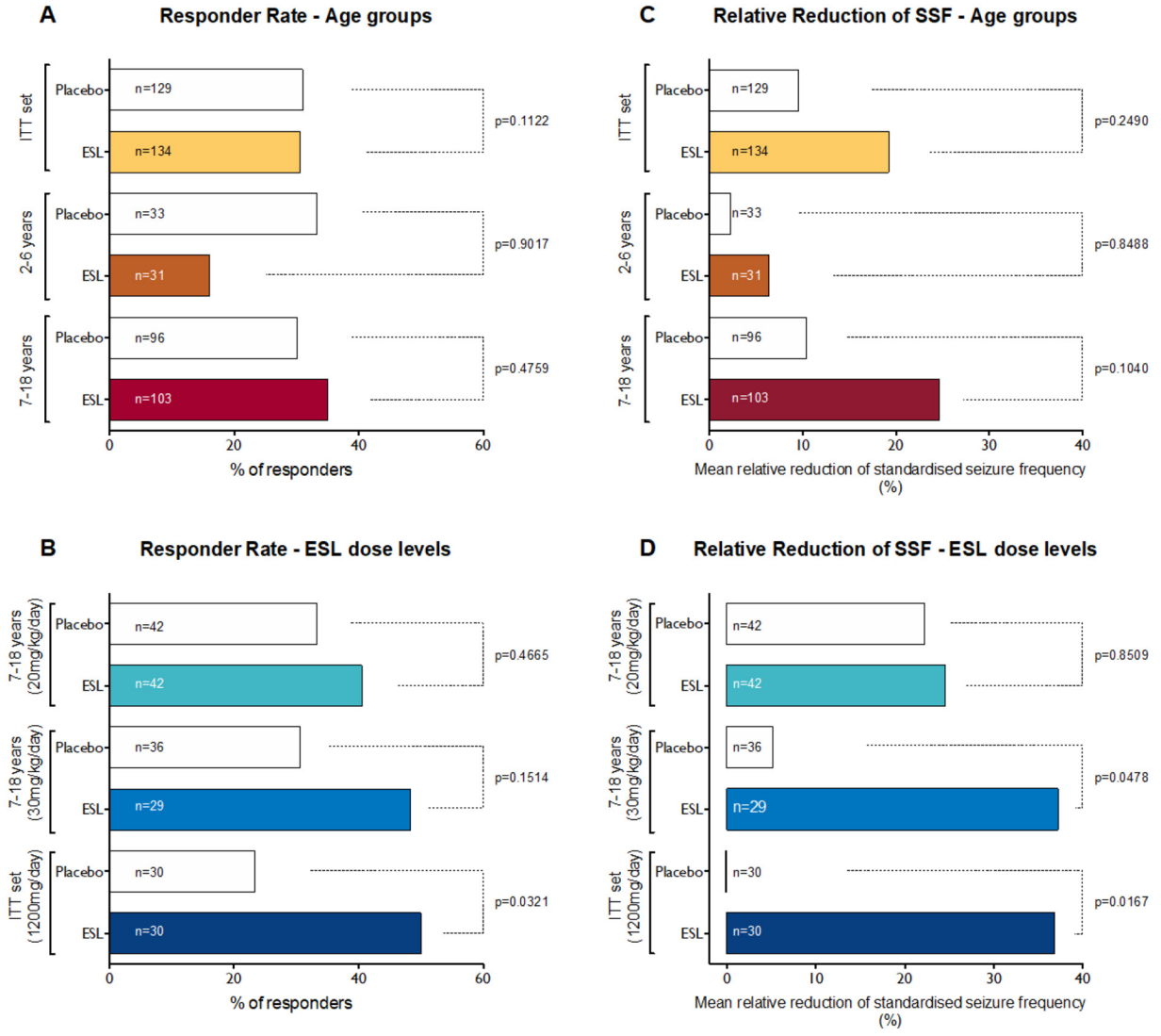

Fig. 3. Mean responder rate (A and B; i.e., percentage of patients with ≥50% reduction in seizure frequency per 4 weeks) and mean relative reduction in seizure frequency (C and D) over the 12-week maintenance period in the intention-to-treat (ITT) set and patients aged 2–6 years (stratum I) and patients aged 7–18 years (strata II and III) receiving placebo or eslicarbazepine acetate (ESL).

maintenance period, the responder rate was shown to be higher in the ESL group (48.3%) compared with placebo (30.6%) ($p = 0.1514$), in contrast to that in patients treated with 20 mg/kg/day during the maintenance period (Fig. 3B; Table 3). However, in patients treated with 1200 mg/day during the maintenance period (Fig. 3B), the responder rate was higher in the ESL group (50.0%) compared with the placebo group (23.3%) ($p = 0.0321$).

During the baseline period, the mean and median SSF was lower in the ESL group than in the placebo group (Supplementary Table 2). The mean SSF during the maintenance period was lower in both treatment groups compared with baseline, resulting in mean relative changes in SSF between periods of −19.2% in the ESL group and −9.6% in the placebo group (Fig. 3C). In the ITT set, the LS mean relative change in the standardized SSF from the baseline period to the 12-week maintenance period was higher in the ESL group (−18.1%) than in the placebo group (−8.6%); however, the LS mean difference of 9.5% was not statistically significant (Supplementary Table 2). The fixed effect for stratum group included in the model was statistically significant ($P = 0.0320$) (Supplementary Table 2). When based on the titration + maintenance period, LS mean relative reductions were lower in both treatment groups compared with the maintenance period: −16.4% in the ESL group and −4.7% in the placebo group. The LS mean difference of 11.7% was not statistically significant. The fixed effect for stratum group included in the model was statistically significant ($P = 0.0092$) (Supplementary Table 2). In patients aged 2–6 years old, the LS mean relative change in the SSF from the baseline period to the 12-week maintenance period was similar in the ESL group (−6.4%) and in the placebo group (−2.3%); in fact, the LS mean difference of 4.2% was not statistically significant ($P = 0.8488$) (Fig. 3C; Supplementary Table 2). In patients aged 7–18 years old, strata II and III, during the baseline period, the median SSF was slightly lower in the ESL group (10.6) compared with the placebo group (13.6) (Supplementary Table 2). The median SSF during the maintenance period was lower in both treatment groups compared with baseline, resulting in median relative changes in SSF between periods of −28.2% in the ESL group and −23.3% in the placebo group. The LS mean relative change in the SSF from the baseline period to the 12-week maintenance period was higher in the ESL group (−24.4%) than in the placebo group (−10.5%); however, the LS mean difference of 13.9% was not statistically significant ($P = 0.1040$) (Fig. 3C; Supplementary Table 2). The median standardized frequencies during the titration + maintenance period were similar to those in the maintenance period (Supplementary Table 2). When based on the titration + maintenance period, the LS mean difference between ESL and placebo was slightly larger than

Table 3
Number of responders and relative reduction in standardized seizure frequency (SSF) during maintenance and titration + maintenance in strata II and III (age 7–18 years) receiving placebo or ESL at 20 or 30 mg/kg/day.

	Placebo	ESL
(20 mg/kg/day)		
Responders	N = 42	N = 42
Number (%)	14 (33.3)	17 (40.5)
Chi test[a]		
Odds ratio vs placebo	0.72	
95% CI	[0.3; 1.8]	
p-Value	0.4665	
Relative reduction in SSF	N = 42	N = 42
LS mean relative reduction, % (SE)	−22.2 (8.8)	−24.5 (8.8)
95% CI	[−39.8; −4.6]	[−42.0; −7.1]
ESL vs placebo[b]		
LS mean, % (SE)	2.3 (12.4)	
95% CI	[−22.4; 27.1]	
p-Value (treatment)	0.8509	
(30 mg/kg/day)		
Responders	N = 36	N = 29
Number (%)	11 (30.6)	14 (48.3)
Chi test[a]		
Odds ratio vs placebo	2.11	
95% CI	[0.8; 5.8]	
p-Value	0.1514	
Relative reduction in SSF	N = 36	N = 29
LS mean relative reduction, % (SE)	−5.2 (10.8)	−37.2 (11.9)
95% CI	[−26.9; 16.4]	[−42.0; −7.1]
ESL vs placebo[b]		
LS mean, % (SE)	31.9 (15.8)	
95% CI	[0.3; 63.6]	
p-Value (treatment)	0.0478	

ESL = eslicarbazepine acetate; CMH = Cochran–Mantel–Haenszel; SSF = standardized seizure frequency; SD = standard deviation; CI = confidence interval; LS = least square; SE = standard error.
[a] Not stratified by age group.
[b] Analysis of covariance model with treatment as fixed effects and baseline seizure frequency as a covariate.

that based on the maintenance period, resulting in a statistically significant difference of 16.2 (P = 0.0359) (Supplementary Table 2). In patients aged 7–18 years old treated with 30 mg/kg/day during the maintenance period, the mean relative reduction SSF was significantly higher in the ESL group (-37.2%) compared with placebo (-5.2%) (p = 0.0478), compared with that in patients treated with 20 mg/kg/day during the maintenance period (Fig. 3D; Table 3). Again, in patients treated with 1200 mg/day during the maintenance period (Fig. 3D), the mean relative reduction in SSF was significantly higher in the ESL group (-36.8%) compared with placebo (-0.1%) (p = 0.0167).

The efficacy analysis during the OL period included all 225 patients (111 patients previously treated with ESL, 114 previously treated with placebo) who were treated and had at least 1 seizure frequency assessment during this period. The total responder rate during the OL extension period I was 46.7% (41.4% in the previous ESL group and 51.7% in the previous placebo group). Total responder rates steadily increased during the OL extension period, from 44.9% during weeks 1–4 to 57.5% during weeks >40. For each time interval, responder rates were higher in patients previously treated with placebo than in those previously treated with ESL (absolute between-group differences of ≥8.6%).

The total median SSF during the 48-week OL extension period was 6.1, resulting in a median relative change compared with the baseline period of −46.7%. The median relative change was larger in the previous placebo group (−51.4%) than in the previous ESL group (−40.4%). In line with the responder rate results, the total median SSF consistently decreased during the OL extension period, from 7.0 during weeks 1–4 to 4.0 during weeks >40. Corresponding median relative changes compared with the baseline period (prior Part I) varied between −60.5% and −44.4%. Changes were more pronounced in patients previously treated with placebo than in those previously treated with ESL; however, the baseline mean SSF was higher in previous placebo patients (16.0) than in previous ESL patients (11.5) (Fig. 4A).

In the OL period, all patients were categorized according to their percentage change from baseline in SSF, in four categories ranging from seizure-free (100% reduction) to exacerbation (≥25% increase) (Fig. 4B). The majority of patients showed >50% reduction in seizure frequency, overall and in each treatment group, as previously described. Within these responders, the majority showed a reduction of >50%, with comparable proportions between the two treatment groups (42% for previous DB placebo and 52% for previous DB ESL). Among patients with reduction >75%, the previous DB placebo group showed a lower rate relative to the previous DB ESL group.

3.3. Extent of exposure during the maintenance period

During the maintenance period, in age stratum I (after IMP recall), the median total daily dose was 23.9 mg/kg in the ESL group and 22.7 mg/kg in the placebo group overall, and 29.0 mg/kg and 27.7 mg/kg, respectively, during the maintenance period (Supplementary Table 3). In age stratum II, the median total daily dose was 18.6 mg/kg in the ESL group and 21.8 mg/kg in the placebo group overall, and 22.0 mg/kg and 26.4 mg/kg, respectively, during the maintenance period. In age stratum III, median total daily doses were 18.9 mg/kg and 17.8 mg/kg, respectively, overall, and 21.0 mg/kg and 20.0 mg/kg, respectively, during the maintenance period (Supplementary Table 3). All but 9 patients in each treatment group (3 of these patients had reached the maximum allowed daily dose of 1200 mg) were on a 20 mg/kg/day regimen at the end of the titration period (Supplementary Table 4). At the beginning of the maintenance period, about half of the patients in each group (59 [46.1%] ESL; 62 [50.0%] placebo) increased their dosage to 30 mg/kg/day, while the remaining patients mostly continued with the 20 mg/kg/day regimen. The distribution was similar at the end of the maintenance period in both treatment groups. During the maintenance period, 17 patients (13.3%) in the ESL group and 13 (10.5%) in the placebo group down-titrated their dose, while all other patients remained on a stable dose (Supplementary Table 4).

The proportion of patients who were up-titrated to 30 mg/kg/day at the beginning of the maintenance period was higher in stratum I of 2–6-year-old patients (71.4% ESL; 65.5% placebo) and stratum II of 7–11-year old patients (50.0% ESL; 60.0% placebo); consequently, this proportion was lower in stratum III including patients aged 12–18 years (28.8% ESL; 28.9% placebo). While these proportions in both treatment groups were lower at the end of the maintenance period in strata I and II, they had slightly increased in stratum III.

Overall compliance during the 48-week OL extension period was good as shown by 217 patients (96.0%) of the safety set having taken at least 80% but not more than 120% of the study medication as prescribed per protocol.

3.4. Safety results

The ESL treatment group during the DB part of the study reported higher incidence of all types of TEAEs: 112 patients (83.6%) in the ESL group and 94 (72.9%) in the placebo group experienced at least 1 TEAE (Supplementary Table 5). The safety set included 103 patients of stratum II (7–11 years) and 96 patients of stratum III (12–18 years). The AE reporting profile in the subgroup of combined strata II and III was similar to that in the overall safety set (Supplementary Table 5). The most frequently reported TEAEs were headache, nasopharyngitis, and somnolence (Table 4).

Fifty-six (41.8%) and thirty-two (24.8%) patients in ESL and placebo, respectively, had at least 1 TEAE possibly related to the treatment (Supplementary Table 6): somnolence, convulsion, and diplopia. In both treatment groups, TEAEs were mostly mild or moderate. Fifteen patients

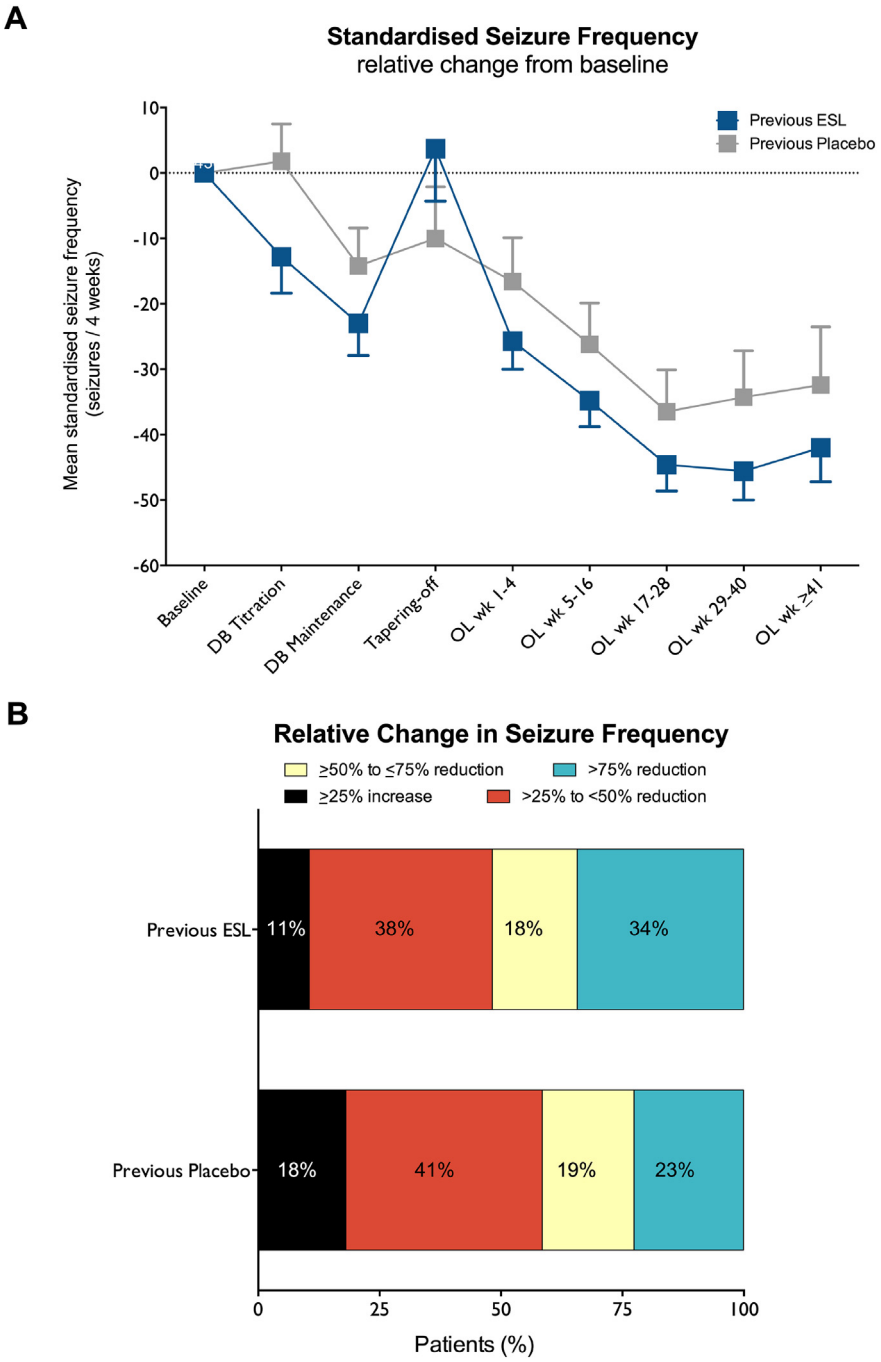

Fig. 4. Mean standardized seizure frequency per 4 weeks during the double-blind and 48-week open-label period (A) and standardized seizure reduction or exacerbation during the one-year open-label period (B).

(11.2%) and 11 patients (8.5%) in the ESL and placebo groups, respectively, experienced at least 1 TEAE of severe intensity during the study.

Thirty-two serious TEAEs were reported by 11.2% of patients in ESL and 7.0% of patients in placebo (Supplementary Table 7). The most frequent serious TEAEs were status epilepticus (2.2% in ESL), convulsion (1.5% in ESL and 1.6% in placebo), bronchopneumonia (1.5% in ESL), and device malfunction (ventriculoperitoneal shunt dysfunction) (1.5% in ESL). Pneumonia occurred in 1 patient (0.7%) in ESL and 3 patients (2.3%) in the placebo group. All other serious TEAEs were reported by only 1 patient in any treatment group. Five patients, 3 (2.2%) in ESL treatment group and 2 (1.6%) in the placebo group, had at least 1 serious TEAE considered as possibly related to the treatment.

Study treatment was discontinued because of a TEAE in 7 patients (5.2%) treated with ESL and in 3 patients (2.3%) in placebo (Supplementary Table 8). From these, the only TEAE reported more than once was convulsion in 1 patient (0.7%) in ESL and 3 patients (2.3%) in placebo.

Two patients died during the DB part of the study, 1 in each treatment group, because of Serious Adverse Event (SAE) considered to be unrelated or unlikely related to the study medication. A 6-year-old female had cluster seizures that occurred 55 days after start of treatment with ESL and led to death on the same day after reanimation failed; the cause of death was recorded as convulsion, brain edema, bronchopneumonia, and brain herniation. A 5-year-old female died from asphyxia that occurred 135 days after start of treatment with placebo. This severe SAE was considered unlikely related to the study medication by the

Table 4
Treatment-emergent adverse events reported by ≥3% of patients in any treatment group, by descending frequency in the ESL group (safety set).

	Double-blind part	
	Placebo (N = 129)	ESL (N = 134)
Patients with TEAEs	94 (72.9)	112 (83.6)
Headache	8 (6.2)	18 (13.4)
Nasopharyngitis	15 (11.6)	15 (11.2)
Somnolence	6 (4.7)	15 (11.2)
Convulsion	14 (10.9)	13 (9.7)
Pyrexia	7 (5.4)	10 (7.5)
Pharyngitis	9 (7.0)	9 (6.7)
Vomiting	8 (6.2)	8 (6.0)
Diplopia	2 (1.6)	8 (6.0)
Respiratory tract infection	7 (5.4)	7 (5.2)
Nausea	1 (0.8)	7 (5.2)
Decreased appetite	1 (0.8)	6 (4.5)
Upper respiratory tract infection	5 (3.9)	6 (4.5)
Vertigo	0	6 (4.5)
Viral infection	6 (4.7)	6 (4.5)
Agitation	1 (0.8)	5 (3.7)
Bronchitis	7 (5.4)	5 (3.7)
Dizziness	2 (1.6)	5 (3.7)
Fatigue	3 (2.3)	5 (3.7)
Viral upper respiratory tract infection	3 (2.3)	5 (3.7)
Weight increased	2 (1.6)	5 (3.7)
Abdominal pain upper	0	4 (3.0)
Influenza	1 (0.8)	4 (3.0)
Rhinitis	7 (5.4)	4 (3.0)
Abdominal pain	4 (3.1)	3 (2.2)
	Open-label part	
	Previous placebo (N = 129)	Previous ESL (N = 134)
Patients with TEAEs	94 (71.2)	97 (75.8)
Convulsion	20 (15.2)	19 (14.8)
Nasopharyngitis	17 (12.9)	16 (12.5)
Somnolence	16 (12.1)	8 (6.3)
Vomiting	11 (8.3)	13 (10.2)
Headache	13 (9.8)	10 (7.8)
Pyrexia	7 (5.3)	15 (11.7)
Respiratory tract infection	4 (3.0)	16 (12.5)
Pharyngitis	7 (5.3)	7 (5.5)
Diplopia	10 (7.6)	3 (2.3)
Gamma-glutamyltransferase increased	7 (5.3)	6 (4.7)
Viral infection	8 (6.1)	4 (3.1)
Bronchitis	7 (5.3)	4 (3.1)
Rhinitis	4 (3.0)	6 (4.7)
Upper respiratory tract infection	6 (4.5)	4 (3.1)
Gastroenteritis	4 (3.0)	5 (3.9)
Dizziness	6 (4.5)	1 (0.8)
Ear infection	5 (3.8)	2 (1.6)
Fatigue	3 (2.3)	4 (3.1)
Respiratory tract infection viral	3 (2.3)	4 (3.1)
Viral upper respiratory tract infection	3 (2.3)	4 (3.1)
Abdominal pain	2 (1.5)	4 (3.1)
Acute tonsillitis	3 (2.3)	3 (2.3)
Cough	2 (1.5)	4 (3.1)
Influenza	2 (1.5)	4 (3.1)
Pneumonia	3 (2.3)	3 (2.3)
Vertigo	3 (2.3)	3 (2.3)

ESL = eslicarbazepine acetate; N = number of patients in safety set; TEAE = treatment-emergent adverse event.
Note: Patients were counted only once in each preferred term category.

investigator. The patient was found dead at home after playing with a plastic bag that was found in the patient's mouth. No other events were reported for this patient. All 4 SAEs were severe in intensity and considered unrelated to study medication by the investigator.

No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index (BMI), head circumference, sexual maturation assessment, and ECG abbreviates electrocardiogram (ECG).

Changes from a normal laboratory value at baseline to an abnormally low or high value at endpoint occurred in fewer than 25% of patients per laboratory parameter and treatment group, and with similar frequency between treatment groups, except for the following parameters where a difference of ≥5% between treatment groups was observed: bicarbonate – 23 patients (18.5%) in the ESL group compared with 30 (24.4%) in the placebo group had a change to an abnormally low value at endpoint; calcium – 30 patients (23.1%) in the ESL group compared with 22 (17.5%) in the placebo group had a change to an abnormally low value at endpoint; and gamma-glutamyltransferase (GGT) – 28 patients (21.5%) in the ESL group compared with 3 (2.4%) in the placebo group had a change to an abnormally high value at endpoint. Of these patients, 1 patient in each treatment group also had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the upper limit of normal (ULN) (but <2 × ULN); free T4 – 31 patients (24.6%) in the ESL group compared with 3 (2.4%) in the placebo group had a change to an abnormally low value at endpoint. Of these patients, TSH was >ULN for 5 patients in the ESL group and none in the placebo group; total T4 – 18 patients (14.6%) in the ESL group compared with 5 (4.2%) in the placebo group had a change to an abnormally low value at endpoint. Of these patients, TSH was >ULN for 2 patients in the ESL group and none in the placebo group; TSH – 13 patients (10.3%) in the ESL group compared with 6 (4.9%) in the placebo group had a change to an abnormally high value at endpoint. In addition, 4 patients (3.0%) in the ESL group and 1 patient (0.8%) in the placebo group had a decrease from baseline in sodium levels of ≥10 mmol/L. Twelve patients (9.0%) in the ESL group and 3 patients (2.3%) in the placebo group had postbaseline sodium values ≤135 mmol/L (8 patients [6.0%] in the ESL group compared with 3 patients [2.3%] in the placebo group had a sodium value of >130–135 mmol/L).

The safety analysis during the OL part of the study included all 260 patients, 128 patients previously treated with ESL and 132 patients previously treated with placebo (Table 4); 191 patients (73.5%) experienced at least 1 TEAE during the OL extension period (Table 4). Eighty-six patients (33.1%) had at least 1 possibly related TEAE and 27 (10.4%) at least 1 serious TEAE, of whom 7 patients (2.7%) had at least 1 possibly related serious TEAE. Fourteen patients experienced TEAEs that led to treatment discontinuation. No cases of death were reported during the OL extension period (Supplementary Table 5). Frequencies for AE categories were generally similar between groups by previous treatment with the exception of the first 4 weeks of the OL extension period where more patients previously treated with placebo had TEAEs considered at least possibly related.

During the first 4 weeks of the OL extension period, most frequently reported TEAEs were as follows: somnolence (3.5%), respiratory tract infection (3.1%), nasopharyngitis (2.3%), and pyrexia (2.3%). Somnolence and diplopia were more frequent (>3% absolute difference) in previous placebo patients than in previous ESL patients, while respiratory tract infection was more frequent in previous ESL patients. After the first 4 weeks of the OL extension period, most frequently reported TEAEs were convulsion (13.8%), nasopharyngitis (10.4%), vomiting (7.7%), pyrexia (6.9%), somnolence (6.5%), respiratory tract infection (6.2%), and headache (5.4%). Vomiting, pyrexia, and respiratory tract infection were more frequent (>3% absolute difference) in previous ESL patients than in previous placebo patients.

Eighty-six patients (33.1%) had at least 1 TEAE that was considered at least possibly related to the IMP by the investigator (Supplementary Table 6). Most commonly reported possibly related TEAEs (≥5% of patients) were somnolence (8.5%) and convulsion (5.8%). More patients previously treated with placebo than those previously treated with ESL experienced somnolence considered at least possibly related to the IMP.

Twenty-six patients (6.3% previous ESL and 13.6% previous placebo patients) had at least 1 TEAE during the first 4 weeks of the OL extension period that was considered at least possibly related to ESL by the

investigator. The only such TEAEs reported by >2 patients were somnolence (9 patients [2 previous ESL; 7 previous placebo]), diplopia (5 patients [all previous placebo]), and ataxia (3 patients [1 previous ESL; 2 previous placebo]). After the first 4 weeks of the OL extension period, 73 patients (28.1%) (37 previous ESL and 36 previous placebo patients) had at least 1 TEAE considered at least possibly related. The only such TEAEs reported by >3 patients were somnolence (14 patients [5 previous ESL and 9 previous placebo]), convulsion (13 patients [8 and 5, respectively]), increased GGT (8 patients [4 each]), diplopia (8 patients [3 and 5, respectively]), vomiting (5 patients [3 and 2, respectively]), and fatigue (4 patients [2 each]).

A total of 27 patients (10.4%) had at least 1 serious TEAE during the 48-week OL extension period (Supplementary Table 7). The only serious TEAEs reported by more than 1 patient were convulsion (2.3%), pneumonia (1.5%), epilepsy, increased GGT, status epilepticus, varicella, and vomiting (0.8% each). Four patients (1.5%) (1 previous ESL and 3 previous placebo patients) had a total of 7 serious TEAEs during the first 4 weeks of the OL extension period. These events were diplopia, varicella, joint dislocation, ataxia, convulsion, dysarthria, and nystagmus. Twenty-four patients (9.2%) (10 previous ESL and 14 previous placebo patients) had at least 1 serious TEAE after the first 4 weeks of the OL extension period. The only such SAEs reported by ≥2 patients were convulsion (5 patients), pneumonia (4 patients), vomiting, increased GGT, epilepsy, and status epilepticus (2 events each). Seven patients had at least 1 serious TEAE that was considered at least possibly related to the IMP. These events were increased GGT (2 patients), diplopia, gastroduodenitis, acute pancreatitis, AST increased, ataxia, convulsion, dysarthria, hypotonia, nystagmus, and partial seizures with secondary generalization (1 patient each).

During the 48-week OL extension period, study treatment was discontinued because of a TEAE for 14 patients (5.4%), 7 patients in each group by previous treatment (Supplementary Table 8). The only TEAEs leading to treatment discontinuation reported more than once were convulsion (7 patients [2.7%]), abnormal behavior, and hypotonia (2 patients [0.8%] each).

None of the patients died during the 48-week OL extension period of the study.

Changes from a normal laboratory value at baseline (OL) to an abnormal value at endpoint occurred in fewer than 30.1% of patients per laboratory parameter. The frequency of changes from normal values to abnormally low or high values was similar between the previous ESL group and the previous placebo group, except for the following parameters where a difference of ≥5% between these groups was observed: bicarbonate – 25 patients (22.7%) in the previous ESL group compared with 19 (14.4%) in the previous placebo group had a change to an abnormally low value at endpoint; calcium – 25 patients (22.3%) in the previous ESL group compared with 20 (15.2%) in the previous placebo group had a change to an abnormally low value at endpoint; glucose – 13 patients (11.5%) in the previous ESL group compared with 4 (3.1%) in the previous placebo group had a change to an abnormally low value at endpoint; and free T4 – 38 patients (32.8%) in the previous ESL group compared with 33 (25.4%) in the previous placebo group had a change to an abnormally low value at endpoint. Of these patients, TSH was >ULN for 3 patients in the previous ESL group and 2 patients in the previous placebo group. In addition, 1 patient (0.9%) in the previous ESL group and 5 patients (4.3%) in the previous placebo group had a decrease from baseline in sodium levels of ≥10 mmol/L. Seven patients (6.3%) in the previous ESL group and 10 patients (8.7%) in the previous placebo group had postbaseline sodium values ≤135 mmol/L (5 patients [4.5%] in the previous ESL group compared with 10 patients [8.7%] in the previous placebo group had a sodium value of >130–135 mmol/L). For any laboratory parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of the following: GGT that was clinically significant for 13 patients (5.8%), 6 patients (5.4%) in the previous ESL group and 7 patients (6.1%) in the previous placebo group; and free T4 that was clinically significant for 5 patients (2.2%), all of whom were in the previous ESL group (4.3%).

3.5. Pharmacokinetics

A total of 339 steady-state plasma concentrations from 118 subjects collected at V3, V4, and V7 were used for PK analysis, statistical, and comparison purposes. From these, 70, 127, and 142 plasma concentrations were from subjects in group 2–6, 7–11, and 12–18 years, respectively. Patients randomized before the IMP recall were not considered for the PK analysis. The intervals between the last dose time and sampling time were distributed mostly within 12–24 h. In addition, subjects with <12 h between the last dose time and sampling at any visit were not considered for the analysis. Subjects with >24 h between the last dose time and sampling at V3 and V4 were considered for the analysis as ESL was administered once daily. Subjects with >24 h between the last dose time and sampling at V7 were few (5 cases in the 2–6 age group and 1 case in the 7–11 age group) and thus considered for the analysis. Plasma concentrations per age group and ESL dosage are depicted in Fig. 5A–C and found to be dose-dependent increase for each age group. Within each ESL dosage older (7–11 and 12–18 years of age), children presented slightly higher exposure to eslicarbazepine than younger (2–6 years of age) children.

Because of the sparse sampling time, the apparent plasma clearance was calculated taking into account the concentrations between 12- and 24-h postdose. This decision was supported by the following reasons: (1) more than 95% of the available concentrations were taken after 12-h postdose; and (2) using this approach, it could be assumed the concept of "average concentration" (although it is an approximation, this rationale is quite used in therapeutic drug monitoring). As shown in Fig. 5D–F, within each ESL dosage, younger (2–6 years of age) subjects presented a faster clearance than older (7–11 and 12–18 years of age) subjects. Furthermore, increasing doses of ESL denotes a decrease (a negative-dose relationship) in plasma clearance in the younger (2–6 years of age) age group.

3.6. Pharmacokinetic/pharmacodynamic relationships

To further assess the apparent trend between age, ESL dose, and efficacy, additional analyses based on relationships between age, exposure to eslicarbazepine, and SSF were performed. A significant ($P = 0.0007$) relationship between exposure to eslicarbazepine and relative reduction in SSF (slope = −0.001353; CI: −0.002130; −0.000577) during the maintenance period was found (Supplementary Fig. 1A), indicating a clear dependency between higher exposure to eslicarbazepine and the greater relative reduction in SSF. In addition, using a relationship analysis between age, including stratification, and SSF at end of maintenance period showed there is a clear dependency between age and SSF for stratum I (2–6 years) (Supplementary Fig. 1B; Supplementary Table 9).

4. Discussion

In this confirmatory multinational phase-III study in children and adolescents with refractory partial epilepsy, ESL did not show superior efficacy over placebo. Although the reasons for failure of this study cannot be definitively explained, factors affecting the 2–6 year age group such as etiological heterogeneity, difficulty in recognizing simple partial seizures, high seizure frequency with risk of imbalance, and inaccurate counting increasing variability, and therefore the risk of apparent response in placebo arm children [5] and underestimation of the efficacious dose range, are likely to have played a role. In fact, within each ESL dosage, no marked age-dependent differences in exposure to eslicarbazepine became apparent, but older (7–11 and 12–18 years of age) children presented slightly higher exposure to eslicarbazepine than younger (2–6 years of age) children. This fits well the observation

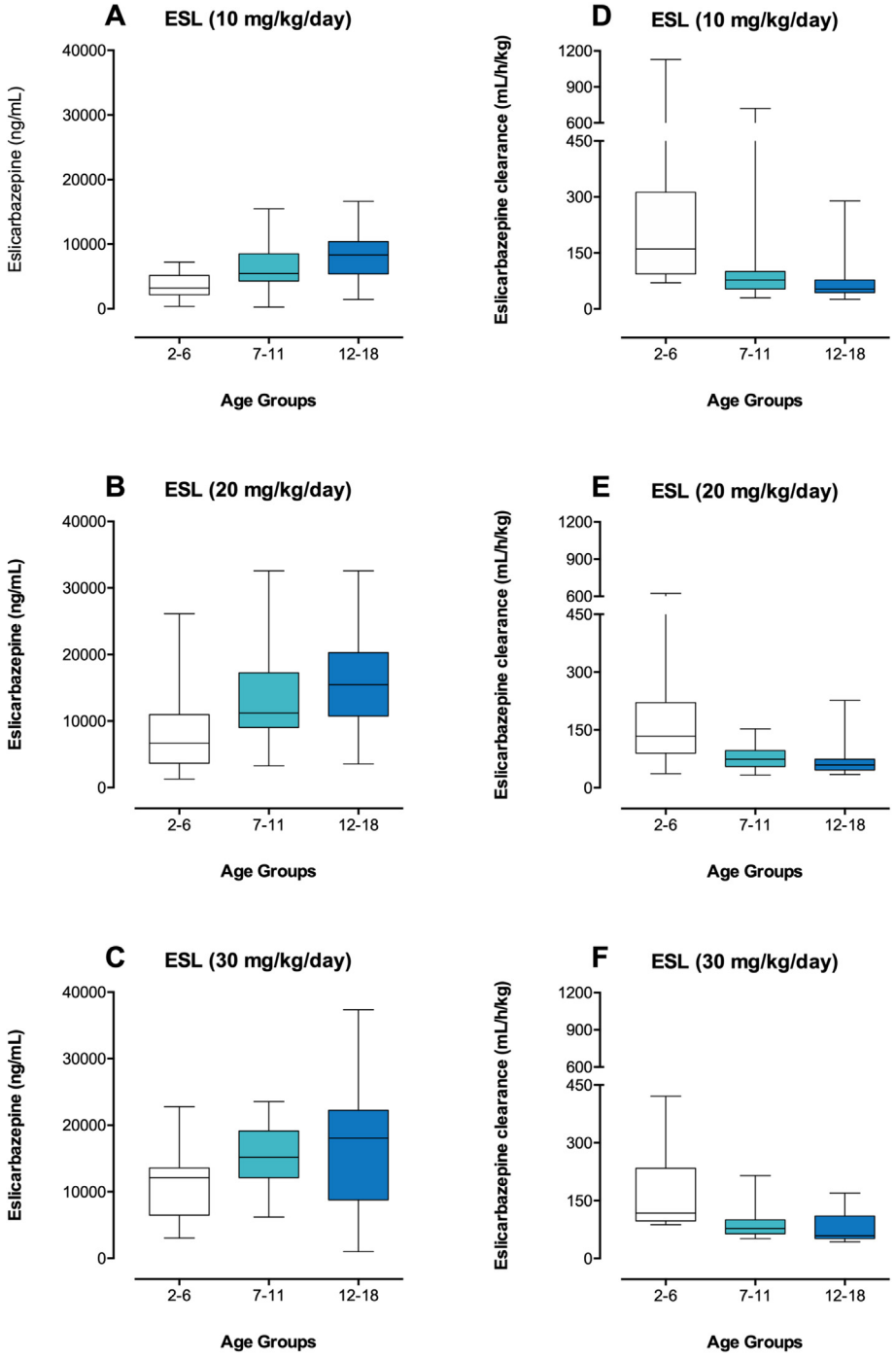

Fig. 5. Eslicarbazepine plasma concentrations (A–C) and eslicarbazepine plasma clearance (D–F) per age group for each ESL dosage. Box and whisker plots show median (central line), upper and lower quartiles (box), and range excluding outliers (whiskers), ESL = eslicarbazepine acetate.

that in eslicarbazepine plasma clearance, and within each ESL dosage, younger (2–6 years of age) subjects presented a faster clearance than older (7–11 and 12–18 years of age) subjects [6].

The choice of the ESL dose in the pivotal confirmatory phase 3 study reported here was based on the findings from the phase 4 add-on trials in the adult population [7–10], whereby the effective dosages were 800 and 1200 mg/day, when 1200 mg/day corresponds to an average of 20 mg/kg/day, assuming a body weight of 60 kg. However, PK studies in children with FOS had shown a faster clearance of the active ESL metabolite eslicarbazepine in younger children [6]. Based on these findings, the target dosage was set at 20 mg/kg/day with the possibility to increase the dosage to 30 mg/kg/day in case of unsatisfactory therapeutic response up to a maximum daily dose of 1200 mg. Previously, ESL in a phase-II, randomized, DB, placebo-controlled study in children (6–16 years old) with FOS and up-titrated up to 30 mg/kg/day (target dosage) was effective in reducing seizure frequency and was well-tolerated [4].

A total of 39% of patients were up-titrated to the maximum possible dosage (30 mg/kg/day for ESL). Of these, 34.0% in the ESL and 33.3% in the placebo group were responders. In stratum I, more patients in the placebo group (40.0%) than in the ESL group (11.0%) were responders at a dosage of 30 mg/kg/day. When excluding

stratum I patients from the analysis, 48.3% of patients in the ESL and 30.6% in the placebo group were responders. With regard to relative reduction in seizure frequency during the maintenance phase, patients receiving the 30 mg/kg/day dosage had a LS mean reduction of −30.3% compared with −8.3% in the corresponding placebo group. The LS mean difference was 22.1 ($p = 0.0644$). When excluding stratum I, the difference became statistically significant (LS mean difference: 31.9, $p = 0.0478$). Knowing that younger children may have a very high number of seizures [11], it can be assumed that stratum I affected the ESL group by introducing a high variability in response. Additionally, it should be underscored that younger children (2–6 years of age) had a lower exposure to eslicarbazepine in association with a higher eslicarbazepine plasma clearance and these factors might also have played a role for the decreased efficacy in this age group.

Even if only children above 6 years (strata II and III) are considered, the observed treatment effects were substantially lower than in the ESL phase-II study in children (6–16 years old) with FOS [4]; the LS mean difference between ESL and placebo of the change in SSF during the maintenance period was 13.9% for strata II and III in the study reported here ($p = 0.1040$) and −20.99 ($p < 0.001$) in study by Jozwiak et al. [4]. This raises the question whether the difference in the efficacy outcomes of both studies could be due to differences in the administered doses. While the target dosage in study by Jozwiak et al. [4] was 30 mg/kg/day (83% of ESL patients were titrated to this dose), the target dosage in the study reported here was 20 mg/kg/day, and only 39% of patients were titrated to the maximum allowed dosage of 30 mg/kg/day or 1200 mg/day, whichever was less. Additional analyses showed that the 50% response rates and change in relative reduction of SSF were larger in children receiving 30 mg/kg/day dosage compared with 20 mg/kg/day or all dosages combined. However, analyses for the 20 mg/kg/day dosage showed a larger placebo effect, which is likely due to the fact that patients in the placebo arm at the 20 mg/kg/day dosage level who were not 'up-titrated' were likely those less susceptible to seizures compared with those who were up-titrated. The observed larger effect size in the placebo arm for the 20 mg/kg/day dosage level was thus not surprising and may explain to some extent the smaller effect size for ESL at this dosage level.

The placebo response and the response to active medication have a different impact on sample size. When working with continuous variables (e.g., seizure frequency per week or percent change from baseline in seizure frequency), the sample size is dependent only on the treatment effect judged clinically relevant and the common SD. When working with percentages of improved subjects (e.g., responder rate), the treatment effect size and sample size are dependent on the magnitude of the placebo response [12]. This is clearly consistent with the present study, where the responder rates are very similar between placebo and active treatment. Moreover, stratum II does not present a lack of effect. There is a higher percent of responders at 30 mg/kg/day (44%) than at 20 + 30 mg/kg/day (37%), which is consistent with the stratum III results (54.5% versus 50.0%, respectively). In fact, the relative reduction in SSF may be more sensitive than responder rate as an efficacy measure, since it is affected by any change in seizure frequency during treatment, regardless of magnitude or whether seizure frequency worsened or improved [13]. In fact, the responder rate disregards any clinical benefit of seizure reduction below the established 50% level [13]. Thus, overall, it is not considered that the stratum II age group shows a lack of effect relative to the other strata. Stratum II patients show a reduction in seizure frequency with ESL compared with placebo as well as a greater response rate. Though higher levels of seizure frequency reduction associate with greater improvements in health-related quality of life [14], as has been demonstrated for ESL in adult adjunctive therapy [15], in any population of pediatric patients, as recruited in the study reported here, even a small reduction in seizure frequency may be of some benefit [16].

The results from the one-year OL extension showed a prolonged seizure frequency reduction for patients already receiving ESL during the DB part. The previous DB placebo group experienced a decrease in SSF during the OL period, gradually becoming numerically similar to the previous DB ESL group. Median postbaseline standardized seizure frequencies during the 48-week OL period were lower in the previous DB ESL group compared with the placebo group at most time points.

During the DB part of the study, the most common TEAEs with an incidence of >3% of patients in the ESL group were headache, nasopharyngitis, and somnolence. The incidences for nasopharyngitis and convulsion were similar between the placebo and ESL groups. Skin manifestations (including rash, rash pruritic, and allergic dermatitis), commonly observed with other AEDs of this class of drugs, were reported by less patients in the ESL groups. No AEs of hyponatremia were reported. Laboratory measure of sodium <135 was more common on ESL than placebo. The prevalence of SAEs was low overall.

As was seen in the DB part, the TEAEs reported during the 48-week OL period that were more frequent in the previous ESL group were convulsion, nasopharyngitis, and somnolence but these were infrequent overall. Somnolence and diplopia were more frequent in patients receiving previous placebo compared with those receiving previous ESL. The incidences for vomiting and headache were similar between the previous DB placebo and ESL groups. 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 incidence of AEs leading to discontinuation during DB and OL parts of this study. The AEs were qualitatively similar to those observed with ESL in adult clinical trials [17].

In conclusion, this multinational phase-III study in children and adolescents with refractory partial seizures, ESL as adjunctive therapy did not show superior efficacy over placebo, as thoroughly discussed above. The known safety profile of ESL was confirmed, without any new findings of real concern.

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Declaration of competing interest

F.K. reports receiving consulting fees from BIAL - Portela & C[a], S.A, Eisai, and Shire. S.A. and A.F. report receiving consulting fees from BIAL - Portela & C[a], S.A.

J.M., H.G., J.F.R., and P.S.S. 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. FK was the chief investigator for the UK and wrote a major part the first draft of the manuscript; SA, JM, HG, and AF made substantial contributions to the writing and 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.2020.106962.

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