

Long-term therapeutic effect of eslicarbazepine acetate in children: An open-label extension of a cognition study in children aged 6–16 years

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ABSTRACT

Objective: In Europe, eslicarbazepine acetate (ESL) is approved as adjunctive therapy for the treatment of focal seizures (FS) in children aged >6 years. In the US, ESL is approved as both monotherapy and adjunctive therapy for the treatment of FS in patients aged ≥4 years. In a phase II study of children aged 6–16 years with FS, ESL had no significant effects on attention or behavioral functioning and decreased seizure frequency during double-blind therapy and a 1-year open-label extension (OLE). This report presents data from an additional 2-year OLE of the phase II study.

Methods: Previous recipients of ESL or placebo were treated with open-label ESL (10–30 mg/kg/day, adjusted for clinical response and/or adverse events [AEs]). Safety was assessed by incidence of treatment-emergent AEs (TEAEs). Efficacy endpoints were treatment retention time and change from baseline in Clinical Global Impression-Severity (CGI-S) scale scores.

Results: Forty-two patients entered and 31 (73.8%) completed the 2-year OLE. Median treatment retention time was 735 (95% confidence interval 728–741) days. Seven patients (17% of total, 23% of completed) experienced ≥1 TEAE during the 2-year OLE, mostly of mild or moderate intensity. The incidence of serious TEAEs was low ($n = 2$; 5% of total, 6% of completed) and none were related to ESL. One child was withdrawn because of splenomegaly that was considered possibly related to ESL. The only change from baseline in CGI-S was a 0.5-point reduction in the severity of illness score. All findings were consistent across patient subgroups based on previous double-blind treatment (placebo or ESL) and patient age (6–11 or 12–16 years).

Conclusions: The majority of patients remained on ESL during the 2-year OLE, and treatment efficacy was maintained. Adverse events were consistent with the known safety profile of ESL, and no new safety signals were identified.

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Abbreviations: AE, adverse event; ASM, antiseizure medication; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; ESL, eslicarbazepine acetate; FS, focal seizures; OLE, open-label extension; SD, standard deviation; TEAE, treatment-emergent adverse event; VGSC, voltage-gated sodium channel.

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1. Introduction

Eslicarbazepine acetate (ESL) is a central nervous system (CNS)-active compound that belongs to the dibenz[b,f]azepine family of antiseizure medications (ASMs), [1]. ESL is a single enantiomer agent with voltage-gated sodium channel (VGSC) blocker activity [1–3]. There is also evidence that ESL enhances the slow inactivation of VGSCs, which may dampen neuronal excitability [4]. In this respect, ESL differs from carbamazepine or oxcarbazepine, which act primarily on fast channel inactivation [5]. After oral administration, ESL undergoes hydrolytic first-pass metabolism and is rapidly converted to its active component, eslicarbazepine [6,7].

Eslicarbazepine acetate is approved in the European Union as monotherapy for the treatment of focal (formerly known as partial-onset) seizures (FS), with or without secondary generalization, in adults with newly diagnosed epilepsy, and as adjunctive therapy in adults, adolescents and children aged >6 years with focal seizures (FS), with or without secondary generalization [8]. In the US, ESL is approved both as monotherapy and adjunctive therapy for the treatment of FS in patients aged ≥4 years [9].

Research into the effect of ASMs on cognitive function in children and adolescents is an important part of the clinical development of any new ASM for use in these patient populations [10]. A phase II, multicenter, randomized, double-blind, placebo-controlled trial was designed to investigate the effects of adjunctive therapy with ESL on neurocognitive and behavioral functioning in children and adolescents with FS [11]. Overall, ESL had no significant effects on attention and behavioral function in the double-blind phase of the study (Part I) or during a 1-year open-label extension (OLE; Part II). In addition, ESL effectively reduced seizure frequency and was well tolerated [11]. Patients who completed Part II of the trial were eligible to take part in an additional, 2-year, OLE phase (Part III). The objectives of Part III were to evaluate the safety, tolerability, and sustainability of the therapeutic effect of ESL during long-term use in children with FS.

2. Methods

2.1. Study design

The objective of this report was to present data from the second OLE (Part III) of a multinational, multicenter phase II, randomized, double-blind, placebo-controlled, parallel study investigating the neurocognitive effects of adjunctive therapy with ESL in children with refractory FS (NCT01527513). The study protocol was approved by the relevant ethics committees at the study centers. Written informed consent was obtained from the parent or legal representative of each patient, and all provided written assent. All trial procedures were conducted in accordance with the principles laid down in the Declaration of Helsinki and adhered to Good Clinical Practice requirements.

Part I of the study included the 12-week double-blind treatment phase, and Part II consisted of a one-year, uncontrolled OLE; full details of the study design have been reported previously (Fig. 1) [11]. At the end of Part II, patients entered either a tapering off period or received an additional two years of open-label treatment with ESL.

2.2. Patients

Patients enrolled in the study (Part I) were aged 6–16 years, had an intelligence quotient (IQ) of ≥70, and had been diagnosed with epilepsy at least 12 months before Part I initiation. All had experienced at least two epileptic FS (at least four in the month before enrolment) and were receiving 1–2 ASMs (except oxcarbazepine)

[11]. Eligible patients for Part III had to complete Part II and be willing to enter this part of the study, based on previous seizure control and tolerability during the course of the study to date. Exclusion criteria for the overall trial have been described previously [11]; there were no additional exclusion criteria for Part III of the study.

2.3. Treatment

Patients continued on the same ESL dosage used in Part II (10–30 mg/kg/day; maximum 1200 mg once daily). Eslicarbazepine acetate was provided as 200-mg tablets. Doses were rounded to the nearest 100-mg unit. Half tablets could be used for dosage adjustment, if necessary. The dosage was titrated up or down based on clinical response or the occurrence of adverse events (AEs). At the end of the 2-year OLE, the ESL dosage was tapered in 10 mg/kg/day steps every 2 weeks. There was no tapering-off period for patients who had reached 18 years of age during Part III and had switched to commercially available ESL. Concomitant ASM therapy with one or two agents was based on physician discretion and was kept as stable as possible during the study. The total duration of treatment in patients who completed all three parts of the study was 3.5 years.

3. Assessments

Study visits took place every four months during the 2-year OLE. In addition, there was one post-study visit (in case of study completion) or one early discontinuation visit. The following assessments were performed at each study visit: concomitant medication; type/dosage of ASMs; physical/neurological exam; Clinical Global Impression-Severity (CGI-S) scale [12]; height; head circumference; vital signs; body weight; treatment compliance (patient interview and tablet count); and urine pregnancy test (in girls of child-bearing age). Adverse events were assessed at each study visit. A 12-lead electrocardiogram (ECG) was performed at 8, 12, 20, and 24 months and at the post-study or discontinuation visit. The CGI-S scale was only used in Part III of the study. Clinicians rated the severity of a patient's illness at the time of assessment relative to the clinician's past experience with patients who have the same diagnosis [12]. Ratings were made using a 7-point scale from 1 (healthy, not ill at all) to 7 (among the most extremely ill patients) [12].

3.1. Outcomes

For this analysis, safety was determined by evaluation of treatment-emergent AEs (TEAEs), vital signs, body weight, height, head circumference, 12-lead ECG recordings, and physical and neurological examinations. Adverse events were rated as treatment-related if either the sponsor or the investigator considered the relationship to study drug to be possible, probable or definite. Efficacy endpoints were treatment retention time (defined as actual time on treatment), and change in the CGI-S score from the end of Part II (defined as the baseline for Part III) to the end of treatment.

3.2. Statistical analysis

For the efficacy analysis of Part III, the modified intent-to-treat population included all patients who entered this part of the study, received at least one dose of study treatment, and had at least one post-baseline CGI-S assessment. The safety population included all patients who entered Part III and received at least one dose of study medication.

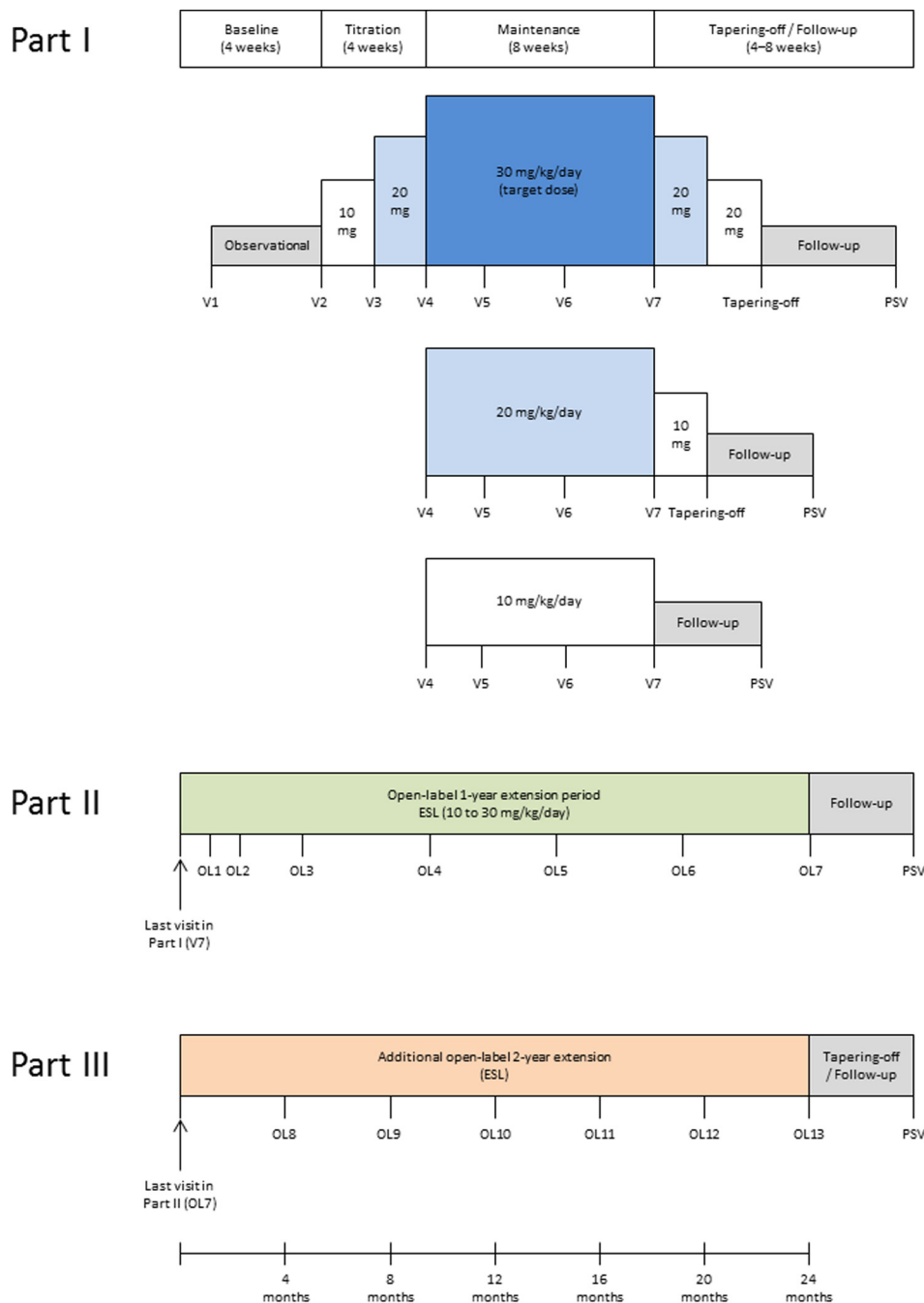


Fig. 1. Study design. ESL, eslicarbazepine acetate; OL, open-label visit; PSV, post-study visit; V, visit.

No formal inferential statistical analysis was performed on Part III data. Categorical variables were summarized using frequencies (counts) and percentages; the denominator used for percentage calculation was the number of patients with non-missing data in each treatment group (unless otherwise stated). Continuous variables were summarized using descriptive statistics, including mean, standard deviation (SD), median, and range. Data were presented for the overall population, and in subgroups based on previous double-blind treatment (ESL or placebo).

Treatment retention time was calculated as actual time on treatment using Kaplan–Meier methods for the overall population, and in subgroups based on previous double-blind treatment and patient age (6–11 or 12–16 years). For patients who continued on ESL after the end of the study, data were censored at the last

contact date. If patients were lost to follow-up, they were censored at the time of last known contact.

4. Results

4.1. Study population

In Part I, 123 patients were randomized 2:1 to ESL ($n = 83$) or placebo ($n = 40$). Of these, 112 (91.1%) completed Part I and continued to the first OLE (Part II). A total of 95 (84.8%) patients completed Part II, 42 of whom entered Part III (Fig. 2 and Table 1).

There were no significant differences in characteristics between patients who had previously received double-blind treatment with placebo ($n = 12$) or ESL ($n = 30$). The most common concomitant

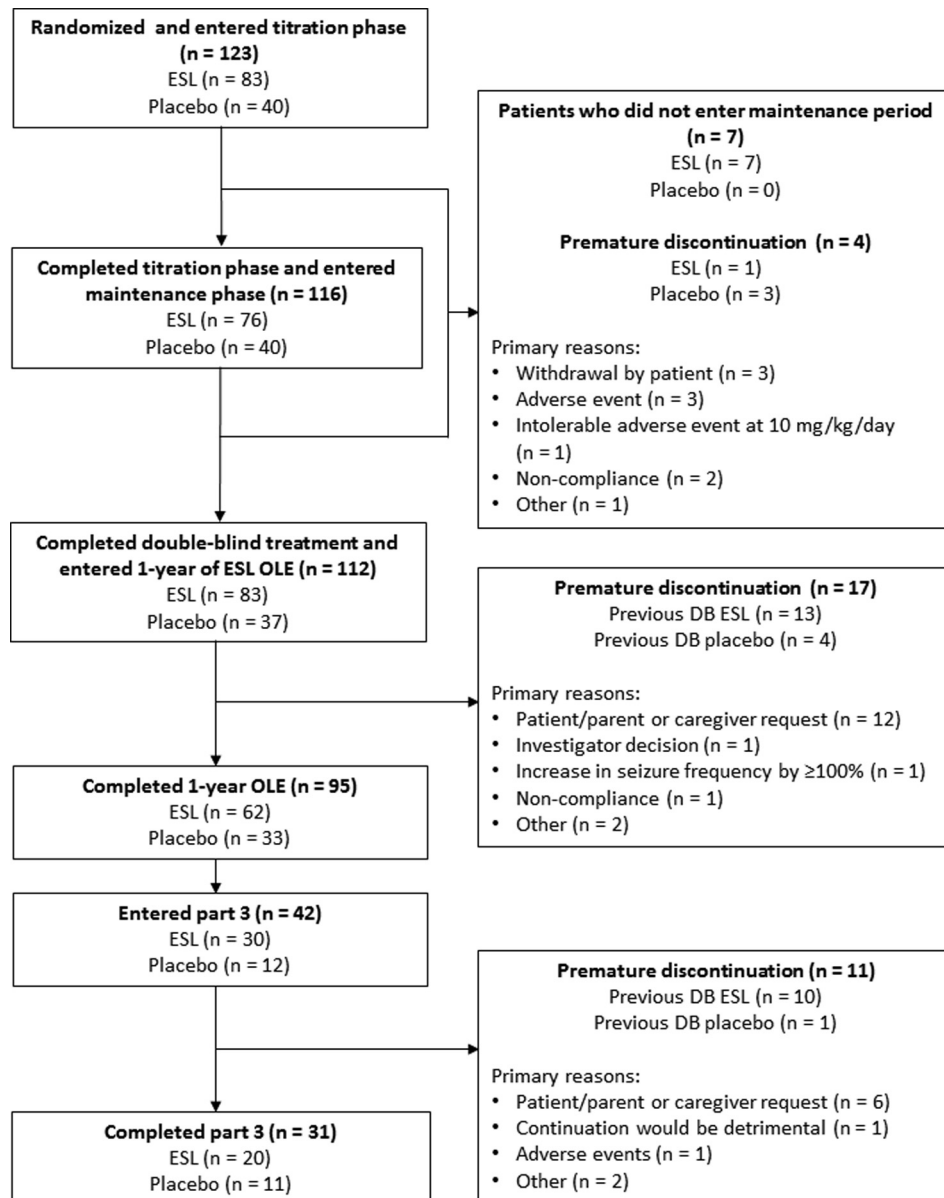


Fig. 2. Patient disposition. DB, double-blind; ESL, eslicarbazepine acetate.

ASMs were valproate (acid or salt), followed by carbamazepine, topiramate, lamotrigine, and levetiracetam (Table 1). Thirty-one (73.8%) patients completed Part III. Regarding the change of concomitant ASMs during Part III, one patient (who had been randomized to placebo in Part I) discontinued topiramate, keeping valproic acid as concomitant ASM. In the group that received ESL in Part I, two patients had a change of ASMs during Part III: one patient that started Part III with carbamazepine switched to topiramate and kept topiramate until the end of the study. Another patient who was using topiramate and carbamazepine since the start of Part III, discontinued topiramate. The remaining patients did not change ASMs during Part III. Two of the patients who discontinued ESL treatment were 6 years old, but the other eight patients who discontinued were aged 13–16 years. The most common reason

for patient discontinuation was patient/parent/caregiver request (n = 6; 60%). Only one patient discontinued due to an AE (splenomegaly, considered non-serious [see Section 3.4]).

4.2. Treatment exposure

Median exposure to study drug in the safety population was 729 (range 139–817) days. This value was comparable between patient groups based on previous double-blind treatment (median 738 [484–772] days for those who received double-blind placebo and 728 [130–817] days for those who received double-blind ESL). The median ESL dosage during Part III was 30.0 mg/kg/day in months 1–4 of the 2-year OLE, 25.9 mg/kg/day in months 5–8, 25.0 mg/kg/day in months 9–12, 26.0 mg/kg/day

Table 1
Patient demographics and characteristics of the safety population (Part III).

	Overall (<i>n</i> = 42)	Previous DB treatment	
		Placebo (<i>n</i> = 12)	ESL (<i>n</i> = 30)
Baseline demographics			
Male, <i>n</i> (%)	21 (50)	8 (66.7)	13 (43.3)
Age, years			
Mean (SD)	12.2 (3.08)	10.7 (3.14)	12.8 (2.90)
Median (range)	13.0 (6–16)	11.5 (6–14)	13.0 (6–16)
Body mass index, kg/m ²			
Mean (SD)	20.66 (5.09)	21.30 (6.44)	20.40 (4.54)
Median (range)	19.44 (14.2–33.3)	19.69 (14.2–33.3)	19.44 (14.3–30.9)
Epilepsy-related characteristics			
Age at onset of epilepsy, years			
Mean (SD)	6.3 (3.9)	4.7 (3.3)	7.0 (3.9)
Median (range)	6.5 (0–14)	4.5 (0–11)	7.5 (0–14)
Duration of epilepsy, years			
Mean (SD)	7.2 (3.5)	7.5 (3.8)	7.1 (3.5)
Median (range)	6.8 (3–15)	7.2 (3–15)	6.4 (3–15)
Concomitant ASMs			
Patients with ≥1 ASM, <i>n</i> (%)	39 (92.9)	10 (83.3)	29 (96.7)
Most frequently used agents (≥10% of patients), <i>n</i> (%)			
Valproic acid/valproate sodium	17 (40.5)	5 (41.7)	12 (40.0)
Carbamazepine	11 (26.2)	5 (41.7)	6 (20.0)
Topiramate	9 (21.4)	1 (8.3)	8 (26.7)
Levetiracetam	6 (14.3)	0	6 (20.0)
Lamotrigine	6 (14.3)	1 (8.3)	5 (16.7)

ASM, antiseizure medication; DB, double-blind; ESL, eslicarbazepine acetate; SD, standard deviation.

in months 13–20, and 22.0 mg/kg/day from month 21 onward, with no differences between patients previously treated with double-blind placebo or ESL. Overall, four patients (9.5%) received ESL monotherapy during Part III, two each from the groups who had received ESL and placebo during double-blind treatment.

4.3. Efficacy

Median treatment retention time was 735 (95% confidence interval [CI] 728–741) days, and was similar in previous placebo (739 days, 95% CI 716–760) and ESL (734 days, 95% CI 728–741) recipients (Fig. 3). Treatment retention time was also similar in subgroups based on patient age (738 days [95% CI 716–770] in those aged 6–11 years and 735 days [95% CI 728–755] in those

aged 12–16 years). The proportion of patients who remained on treatment was higher in the previous placebo (11/12; 91.7%) versus previous ESL group (20/29; 69.0%), and among patients aged 6–11 versus 12–16 years (85.7% vs 70.4%).

Overall efficacy was maintained during the 2-year OLE and there was no worsening of disease severity. At the final assessment, scores for all CGI-S scales were unchanged from baseline, with the exception of a slight reduction in the CGI-S severity of illness score (Table 2). Again, these results were consistent across patient subgroups based on previous double-blind treatment or age (Table 2).

4.4. Safety

A total of seven patients (16.7%) experienced at least one TEAE during the 2-year OLE; the only events reported more than once were cough and pyrexia (Table 3). Twelve events were of mild intensity and three were moderate; only two events were severe. One TEAE was considered to be possibly related to the study drug (moderate-severity splenomegaly in a 6-year-old male patient who had previously received placebo, had no previous history of hemoglobinopathy, and who experienced recurrent episodes of upper respiratory infections in the 9 months prior to being diagnosed with splenomegaly). This event resulted in treatment discontinuation (Table 3), and the patient made a full recovery within 1 month. Rates of TEAEs were similar in previous placebo or ESL recipients and by patient age group (Supplementary Table 1). No deaths occurred during the study. The rate of serious AEs was low (4.8%; Table 3). Only two patients developed a serious AE – one who had received placebo and one who had received ESL during the double-blind portion of the study. These events were a brain operation in one patient in the 6- to 11-year age group and complex FS in one patient in the 12- to 16-year age group. Neither of these events was considered to be treatment-related. In addition, no serious or possibly drug-related TEAEs of special interest (cutaneous, cardiovascular, or cerebrovascular) were reported.

5. Discussion

The effectiveness of ESL therapy was maintained during long-term therapy in children aged >6 years with FS. In addition, ESL was safe and well tolerated and no new safety signals were identified during up to 3.5 years of treatment. The findings obtained during this part of the phase II study are consistent with those from the double-blind (Part I) and first OLE phase of the trial (Part II), but provide clinically relevant data because conditions during

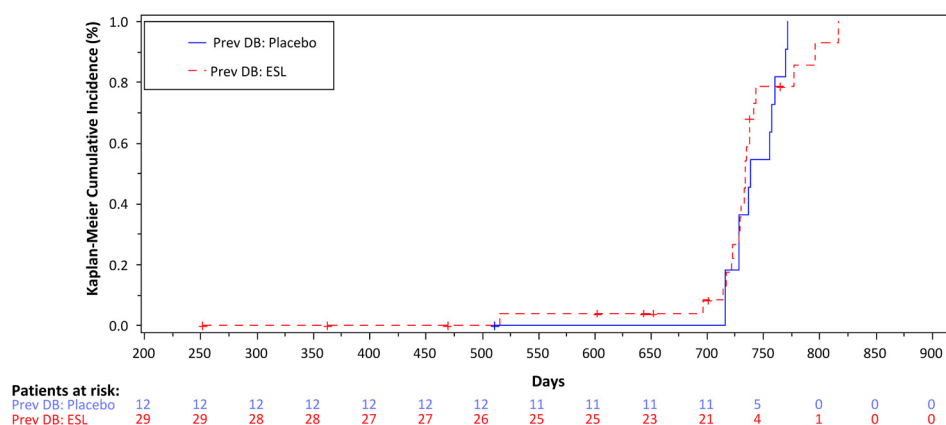


Fig. 3. Kaplan-Meier plot of time to last dose of eslicarbazepine acetate in the modified intent-to-treat population. DB, double-blind; ESL, eslicarbazepine acetate.

Table 2

Change in Clinical Global Impression-Severity scores in the modified intent-treat population, and in subgroups based on previous treatment and patient age.

Mean (SD) change from baseline to last assessment	Overall (n = 41)	Previous DB treatment		Patient age, years	
		Placebo (n = 12)	ESL (n = 29)	6–11 (n = 14)	12–16 (n = 27)
Severity of illness	−0.5 (0.85)	−0.3 (0.47)	−0.6 (0.95)	−0.6 (0.77)	−0.4 (0.89)
Global improvement	−0.1 (0.69)	−0.1 (0.54)	−0.1 (0.75)	−0.2 (0.55)	0.0 (0.76)
Therapeutic effect	0.0 (0.56)	−0.1 (0.30)	0.0 (0.64)	0.0 (0.41)	0.0 (0.76)
Side effect	0.0 (0.16)	−0.1 (0.32)	0.0 (0.0)	0.0 (0.0)	0.0 (0.20)

DB, double-blind; ESL, eslicarbazepine acetate; SD, standard deviation.

Table 3

Summary of treatment-emergent adverse events.

No. of patients (%)	ESL (n = 42)
Any TEAE	7 (16.7)
Possibly treatment-related TEAE	1 (2.4)
Serious TEAE	2 (4.8)
Possibly treatment-related serious TEAE	0
TEAE leading to discontinuation of study treatment	1 (2.4)
Most frequently reported TEAEs (≥1% of patients)	
Cough	2 (4.8)
Pyrexia	2 (4.8)
Brain operation	1 (2.4)
Complex focal seizures	1 (2.4)
QT prolongation on ECG	1 (2.4)
Foot fracture	1 (2.4)
Headache	1 (2.4)
Hypersensitivity	1 (2.4)
Laryngitis	1 (2.4)
Nasopharyngitis	1 (2.4)
Pharyngotonsillitis	1 (2.4)
Viral respiratory tract infection	1 (2.4)
Respiratory disorder	1 (2.4)
Splenomegaly	1 (2.4)

ECG, electrocardiogram; ESL, eslicarbazepine acetate; TEAE, treatment-emergent adverse event.

long-term open-label treatment are similar to those encountered in routine clinical practice.

Although the reasons that prevented patients who had completed Part II from entering Part III were not recorded, an analysis of the efficacy and safety of ESL in these patients during Part II ([Supplementary results](#)) suggests that, for most, neither lack of efficacy nor AEs were the likely reason. Several factors could have led to these patients deciding not to enter Part III (e.g., burden of continuing to participate in the trial including the need to make multiple visits and travel to study sites, and parent/caregiver/patient and/or investigator decision); however, due to the lack of information, these are only hypothetical.

The proportions of patients who remained on treatment in our study ranged from 69.0% in patients who previously received double-blind ESL to 91.7% in those previously treated with placebo. Interestingly, the proportion of patients who remained on treatment was higher in younger patients (age 6–11 years; 85.7%) versus older patients (age 6–16 years; 70.4%). Potential explanations for this include the fact that older adolescents might have begun to exert more independence as they got closer to adulthood (patient/parent/caregiver request was the most common reason for treatment discontinuation during the 2-year OLE), or patients may have had a general improvement in their disease with age. In addition, compliance with adolescents is often one of the biggest management problems encountered in clinical practice, and this could help us understand this difference. Nevertheless, the fact that such a high proportion of both children and adults are willing to continue open-label treatment with ESL suggests that they find therapy to be effective and acceptable. The fact that ESL dosage adjustments were permitted during open-label therapy (vs a

fixed-target dose in the double-blind phase) may have also contributed to good retention of patients on treatment. The ability to adjust the ESL dosage allowed physicians to maximize therapeutic efficacy and minimize unwanted AEs, something that appears to have been successfully achieved during Part III of the study, with a gradual decrease in average dose per kilogram likely to reflect ongoing efficacy despite increasing weight in these growing children. Only five from 42 patients entering Part III of the study (11.9%) had a dose increase during this part of the study.

Treatment-emergent AEs were uncommon during ESL therapy in this OLE. Cough and pyrexia (in two patients each) were the only events reported by more than one patient, and there was only one TEAE that was determined to be possibly related to ESL treatment (splenomegaly). Although occurring at lower rates, AEs in Part III were generally consistent with those reported in Parts I and II of this study [11], in clinical trials of ESL in adults [13–18] and in the Phase III randomized controlled trial in children [19]. Also consistent with previous studies, there were no changes in laboratory findings (including sodium levels or hematologic parameters) that indicated a safety concern during long-term ESL therapy, and there were no clinically relevant changes in vital signs, body weight, or ECG evaluation. Importantly, data from Part I, II, and III showed that ESL had no patient developed hyponatremia as seen in some adults receiving ESL [20]. In addition, we found no statistically significant detrimental effects on behavior or cognitive function, and its maturational improvement over time, in children with FS, and no AEs related to cognition or behavior [11].

According to the pooled analysis of the safety data from Part I of the present study and the previously mentioned Phase III randomized controlled trial [19], the overall incidence of TEAEs was similar in the ESL (67.8%) and the placebo groups (65.6%) [21]. However, in Part I of the present study, compared with the placebo group, serious AEs (9.9% vs 5.0%) and TEAEs leading to discontinuation (5.9% vs 2.5%) were more common in the ESL group. In the ESL group, the incidence of TEAEs was numerically higher in younger vs older patients and in patients with lower vs higher body weight; however, due to low patient numbers, these findings should be treated with caution. The incidence of serious AEs observed with ESL was higher in the Phase III trial (14.3%) than in the Part I of the present study (3.6%). The Phase III study did not restrict patient recruitment based on IQ, and eight of the 17 patients who had a serious AE during that study had evidence of intellectual and developmental disability (IDD). Based on this, the authors concluded that the presence of IDD could increase the susceptibility of patients to medication intolerance [21]. This further highlights the importance of the finding that ESL does not significantly affect neurocognitive function or behavior [11].

To our knowledge, this study is the first to provide real-world data on the long-term use of ESL in children with FS. However, a few limitations need to be taken into account when interpreting the results. The open-label nature of the extension period meant that there was no control group. Therefore, it is possible that confounding factors could have contributed to the findings obtained. In addition, patients who continued with long-term ESL therapy

were a self-selected group, meaning that sources of bias cannot be excluded. Finally, the total duration of long-term therapy varied between patients, but data were censored at last visit date.

6. Conclusions

Consistent with the positive findings from the double-blind (Part I) and 1-year OLE (Part II) treatment periods in this phase II study, ESL showed long-term effectiveness and safety in children with FS. This suggests that the therapeutic benefits of ESL are maintained during prolonged treatment periods. Therefore, ESL may be an appropriate therapeutic option for long-term adjunctive antiepileptic therapy in pediatric patients with FS.

Declaration of Competing Interest

Pierangelo Veggiotti has received speaker's fee from Eisai, Nutricia and Schär SPA.

Sergiusz Jóźwiak reports receiving consulting fees from BIAL - Portela & Ca, S.A.

Fenella Kirkham has received fees for her work in advisory boards for BIAL/Eisai with expenses paid to present data at meetings in Europe (Helsinki, London, Lyon and Athens).

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Author contributions

Both Pierangelo Veggiotti and Sergiusz Jóźwiak were the principal investigators for the BIA-2093-208 study. They enrolled patients and read and approved drafts of the manuscript.

Joana Moreira and Ana Pereira participated in study implementation and Joana Moreira, Ana Pereira, Fábio Ikedo and Helena Gama participated in data analysis. All authors were involved in data interpretation and together discussed the initial ideas presented in the introduction and discussion of this article. Fenella Kirkham, Helena Gama, Fabio Ikedo, Joana Moreira, and Ana Pereira made substantial contributions to the writing and revising of the manuscript. All authors approved the final submitted manuscript.

Appendix A. Supplementary data

Supplementary data (Results and Table 1) to this article can be found online at <https://doi.org/10.1016/j.yebeh.2021.108515>.

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