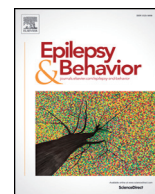




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Long-term safety and tolerability of adjunctive eslicarbazepine acetate in children with focal seizures



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ABSTRACT

Objective: The objective of this study was to evaluate long-term safety and tolerability outcomes in two open-label extension (OLE) studies of adjunctive eslicarbazepine acetate (ESL) in children with focal seizures.

Methods: Safety data from patients aged 4–17 years in OLEs of Studies 2093-208 and -305 were pooled and analyzed. Studies 208 and 305 were randomized, double-blind, placebo-controlled studies of adjunctive treatment with ESL in children with focal seizures refractory to treatment with 1–2 antiseizure drugs; patients could continue into uncontrolled OLEs (up to 5 years total duration). The OLEs evaluated the safety and tolerability of ESL (10–30 mg/kg/day; maximum 1200 mg/day).

Results: The 1-year OLE and post-1-year OLE safety populations comprised 337 and 177 ESL-treated patients, respectively. The overall incidence of treatment-emergent adverse events (TEAEs) with ESL was 64.1% during the 1-year OLE and 52.5% during the post-1-year OLE. Nasopharyngitis, partial seizures, vomiting, pyrexia, headache, somnolence, and respiratory tract infection were the most frequently reported TEAEs during the 1-year OLE. The overall incidence of serious adverse events (AEs) was 8.9% during the 1-year OLE and 10.2% during the post-1-year OLE. Partial seizures (1.2%) and pneumonia (1.2%) were the most frequently reported serious AEs during the 1-year OLE. The overall incidence of TEAEs leading to discontinuation was 4.2% during the 1-year OLE and 0.6% during the post-1-year OLE. Partial seizures (1.5%) was the most frequently reported TEAE leading to discontinuation during the 1-year OLE.

Conclusions: Overall, long-term treatment with ESL was generally well tolerated in pediatric patients aged 4–17 years with focal seizures. TEAEs were comparable to those observed in adults with no new events of concern.

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ASD, antiseizure drug; AST, aspartate aminotransferase; BECTS, benign epilepsy with centrotemporal spikes; DRESS, drug reaction with eosinophilia and systemic symptoms; ESL, eslicarbazepine acetate; FDA, Food and Drug Administration; IQ, intelligence quotient; LFT, liver function test; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; PEACE, Pediatric Epilepsy Academic Consortium for Extrapolation; SD, standard deviation; SUDEP, sudden unexpected death in epilepsy; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

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1. Introduction

The onset of seizures and subsequent diagnosis of epilepsy is common in childhood, with focal seizures usually more common than generalized seizures [1]. Indeed, the incidence of epilepsy is highest during the first year of life, and global prevalence of epilepsy peaks at ages 5–9 years, as well as later in life (at ages >80 years) [1,2]. Nonlesional focal epilepsies, such as benign epilepsy with centrotemporal spikes (BECTS) and occipital epilepsies (Gastaut and Panayiotopoulos types), typically begin during childhood [3]. Furthermore, number of years lived with disability and years of life lost due to disability peak during childhood/adolescence (years lived with disability: at 5–9 years; years of life lost due to disability: under the age of 5 years, and at ages 15–19 years) [2]. Children diagnosed

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as having epilepsy are usually treated with antiseizure drugs (ASDs) for at least 1–2 years if seizure freedom is achieved. Children with seizures intractable to an initial ASD are typically treated with alternative ASDs in a serial manner; maintenance ASD therapy is continued at least into late adolescence, even if seizure frequency improves. To ensure that children have access to suitable ASDs, it is important to examine short- and long-term safety and tolerability in pediatric patients.

Eslicarbazepine acetate (ESL) is a once-daily, oral ASD for focal (partial-onset) seizures. Previous analyses demonstrated that adjunctive ESL was generally well tolerated during placebo-controlled clinical trials in children (aged 4–17 years) with focal seizures and that the short-term safety profile of ESL was comparable between children and adults [4].

Here, we analyze 1-year and post-1-year safety and tolerability data pooled from two open-label extension (OLE) studies of adjunctive ESL in pediatric patients (aged 4–17 years) with focal seizures. We evaluate the demographic and clinical characteristics of children who continued to take ESL for one or more years during these OLE studies and safety and tolerability outcomes, including treatment-emergent adverse events (TEAEs) of special interest such as allergic reactions, hyponatremia, hypothyroidism, cytopenia, hepatic events, and seizure exacerbation.

2. Methods

2.1. Study design

Study 208 and Study 305 were designed, conducted, and monitored in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and relevant national and local laws. The study protocols were approved by the relevant independent ethics committees/institutional review boards, and written informed consent was provided for all patients.

2.2. Study BIA-2093-208

The controlled portion of Study 208 (NCT01527513) was a 12-week, phase II, randomized, double-blind, placebo-controlled study of once-daily, adjunctive ESL in children aged 6–16 years with focal seizures refractory to treatment with 1–2 ASDs. Eligibility criteria, site locations, and sample size determination, as well as neurocognitive and behavioral functioning, seizure frequency, and safety outcomes have been reported previously [5]. Patients were required to have been diagnosed with epilepsy ≥ 12 months prior to enrollment, to have had ≥ 2 focal seizures in the month prior to screening, and an intelligence quotient (IQ) ≥ 70 . Patients taking oxcarbazepine were excluded.

Patients were randomized 2:1 to receive an ESL target dosage of 30 mg/kg/day (maximum 1200 mg/day) or placebo. After the 12-week double-blind period, there was an option for patients to continue into a 1-year OLE and a subsequent 2-year OLE (Fig. 1a). Patients were required to complete the last 2 weeks of the tapering-off period in the controlled portion of the study before entering the OLE on ESL 10 mg/kg/day. The ESL dose was then titrated according to clinical response within a dosage range of 10–30 mg/kg/day (maximum 1200 mg/day). Patients continued to take their baseline ASDs.

2.3. Study BIA-2093-305

The controlled portion of Study 305 (NCT00988156) was an 18-week, phase III, randomized, double-blind, placebo-controlled study of once-daily, adjunctive ESL in children aged 2–18 years with focal seizures refractory to current treatment with 1–2 ASDs. Eligibility criteria, site locations, seizure frequency, and safety outcomes, as well as pharmacokinetic and pharmacodynamic data have been reported previously [6]. Patients were required to have had ≥ 4 focal seizures in the month prior to enrollment. Patients taking oxcarbazepine were excluded.

Patients were randomized 1:1 to receive an ESL target dosage of 20 mg/kg/day or placebo. Randomization was stratified by age (stratum I: 2–6 years; stratum II: 7–11 years; stratum III: 12–18 years). Children aged ≤ 6 years were treated with an oral suspension and those aged > 7 years with tablets (the protocol neither required nor prohibited the crushing of tablets). There was an option for patients to continue into a 1-year OLE, two subsequent 1-year OLEs, and a 2-year OLE (Fig. 1b). The ESL dose was titrated according to clinical response within a dosage range of 10–30 mg/kg/day (maximum 1200 mg/day). Patients continued to take their baseline ASDs.

2.4. Assessments and analysis

During the 1-year OLEs of Studies 208 and 305, patients attended 6–8 clinic visits for ongoing safety monitoring and study assessments; patients continued to attend clinic visits every 12–13 weeks.

Safety was evaluated based on the incidence of TEAEs, serious adverse events (AEs), and TEAEs leading to discontinuation, which were reported by investigators throughout the studies and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. Medically significant events related to allergic reactions, hyponatremia, hypothyroidism, cytopenia, hepatic events, or seizure exacerbation were also evaluated.

Based on analyses conducted by the US Food and Drug Administration (FDA), the University of Maryland, and the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE), the relationship between drug exposure and response (reduction in seizure frequency) is considered preserved between adult and pediatric subjects (aged ≥ 4 years) with focal seizures [7]. To gain FDA approval of an ASD for children with focal seizures based on extrapolation of efficacy, one of the FDA requirements is provision of long-term safety data in children aged ≥ 4 years [8]. Therefore, although Studies 208 and 305 recruited patients aged 2–18 years, OLE safety data from patients aged 4–17 years were pooled and analyzed to support the FDA approval of ESL for the treatment of focal seizures in children aged ≥ 4 years.

The pooled 1-year OLE safety population included all patients (including investigational medicinal product recall patients) who received at least one dose of ESL during the 1-year OLE period of Study 208 or 305 (Fig. 1). The post-1-year OLE safety population included all patients (including investigational medicinal product recall patients) who received at least one dose of ESL during the post-1-year OLE periods of Study 208 or 305 (Fig. 1). Investigational medicinal product recall patients included those in the 2–6-year age group in Study 305 who were taking the ESL oral suspension before it was withdrawn because of stability issues. These patients had the option to reenroll into the OLE of Study 305 using an updated oral suspension formulation; patients who chose to reenroll were included in the OLE safety evaluation.

3. Results

3.1. Patients

The 1-year OLE safety population comprised 337 patients, 112 from Study 208 and 225 from Study 305. The post-1-year OLE safety population comprised 177 patients, 42 from Study 208 and 135 from Study 305. Overall, 257/337 patients (76%) completed the 1-year OLE, and 61/177 patients (34%) completed the post-1-year OLE (Fig. 2). Primary reasons for discontinuation included withdrawal of consent and administrative (a large proportion of patients switched to continued treatment with ESL as part of a compassionate use program) (Fig. 2).

In the 1-year OLE safety population, median age was 11 years, and 53% of patients were male (Table 1). The majority of patients (96%) were Caucasian because most patients who continued into the OLE were from sites in Eastern Europe. The majority of patients (74%) were receiving two or more concomitant ASDs at baseline; the most frequently

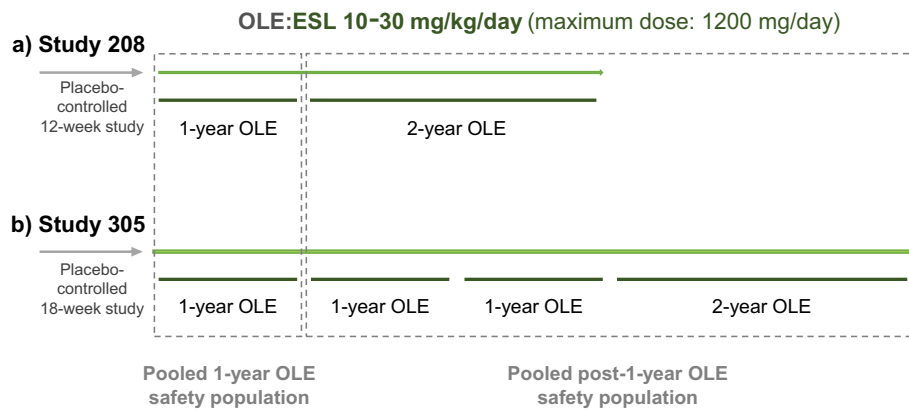


Fig. 1. OLE study designs and study populations (a) Study 208, (b) Study 305. ESL, eslicarbazepine acetate; OLE, open-label extension.

used concomitant ASDs were valproic acid (50%), carbamazepine (31%), lamotrigine (26%), topiramate (25%), and levetiracetam (18%) (Table 1).

During the 1-year OLE, patients were exposed to ESL for a mean duration of 314 (standard deviation [SD]: 92) days to a mean daily dosage of 822 (SD: 288) mg/day (Table 2). During the post-1-year OLE, patients were exposed to ESL for a mean duration of 653 (SD: 390) days to a mean daily dosage of 949 (SD: 274) mg/day (Table 2). Mean daily dose increased with increasing weight during both the 1-year and post-1-year OLEs (Table 2).

3.2. TEAEs and vital signs

The overall incidence of TEAEs with ESL was 64% during the 1-year OLE and 53% during the post-1-year OLE (Table 3). Most TEAEs were of

a mild (1-year OLE: 37.4%; post-1-year OLE: 32.4%) or moderate (47.1%; 44.8%) intensity. During the 1-year OLE, nasopharyngitis, partial seizures, vomiting, pyrexia, headache, somnolence, and respiratory tract infection were reported for >5% of patients. The most frequently reported TEAEs were similar during the post-1-year OLE; partial seizures, pyrexia, nasopharyngitis, headache, vomiting, rhinitis, bronchitis, diarrhea, upper respiratory tract infection, pharyngitis, and cough were reported for >5% of patients. Somnolence was reported more frequently during the 1-year OLE than during the post-1-year OLE (6.8% vs 1.1%); there was a <5% difference in incidence between all other TEAEs.

During the 1-year OLE, the overall incidence of TEAEs appeared to be higher in patients taking lower ESL dosages (<15 mg/kg/day: 74%; 15–25 mg/kg/day: 72%) compared with the highest dosages (≥25 mg/kg/day: 53%) (Table 3); there was no clear relationship between

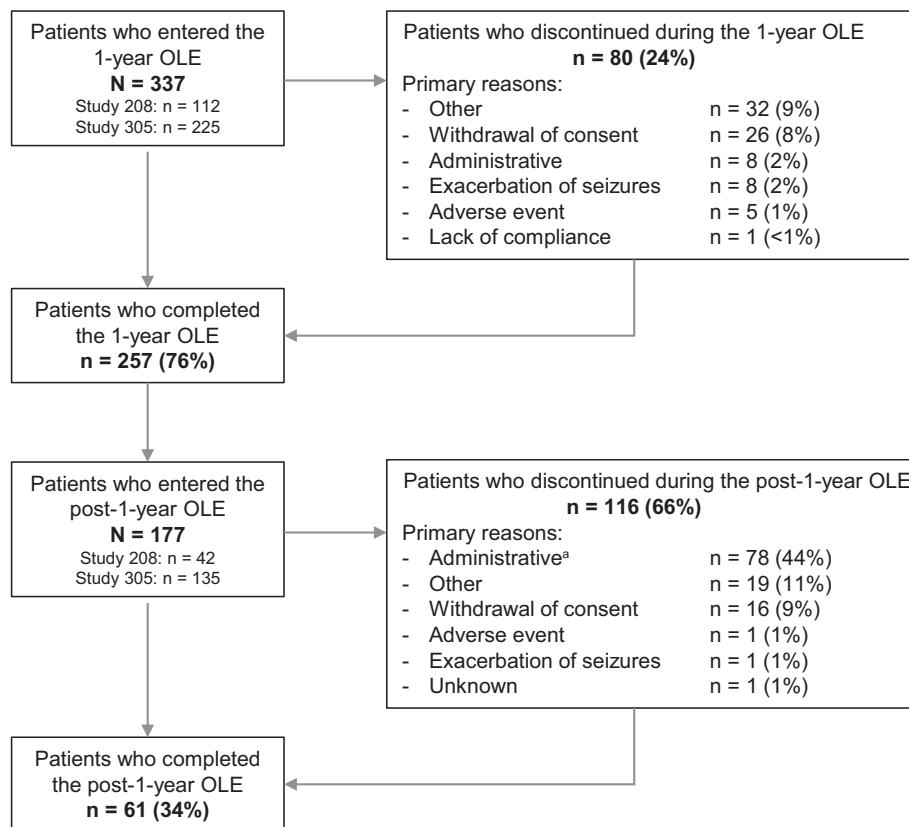


Fig. 2. Patient flowchart. ^aThere was the option for patients to switch to continued treatment with ESL as part of a compassionate use program. ESL, eslicarbazepine acetate; OLE, open-label extension.

Table 1
Patient baseline^a demographics and clinical characteristics.

	Study 208 n = 112	Study 305 n = 225	Total N = 337
Gender; n (%)			
Male	64 (57.1)	115 (51.1)	179 (53.1)
Race; n (%)			
Caucasian	111 (99.1)	213 (94.7)	324 (96.1)
Asian	0	10 (4.4)	10 (3.0)
Other	1 (0.9)	2 (0.9)	3 (0.9)
Age, years; median	12.0	10.0	11.0
Age subgroup; n (%)			
4–6 years	9 (8.0)	54 (24.0)	63 (18.7)
7–11 years	37 (33.0)	89 (39.6)	126 (37.4)
12–17 years	66 (58.9)	82 (36.4)	148 (43.9)
Height, cm; median (range)	154.0 (110–192)	140.0 (84–190)	143.0 (84–192)
Body weight, kg; median (range)	46.0 (19–99)	33.0 (12–121)	37.5 (12–121)
Body weight subgroup; n (%)			
11–21 kg	5 (4.5)	49 (21.8)	54 (16.1)
22–31 kg	14 (12.6)	54 (24.0)	68 (20.2)
32–38 kg	20 (18.0)	29 (12.9)	49 (14.6)
>38 kg	72 (64.9)	93 (41.3)	165 (49.1)
Number of baseline ASDs used; n (%)			
1	55 (49.1)	33 (14.7)	88 (26.1)
2	55 (49.1)	170 (75.6)	225 (66.8)
≥3	2 (1.8)	22 (9.8)	24 (7.1)
Baseline ASD use; n (%)			
Valproic acid	59 (52.7)	109 (48.4)	168 (49.9)
Carbamazepine	38 (33.9)	66 (29.3)	104 (30.9)
Lamotrigine	18 (16.1)	68 (30.2)	86 (25.5)
Topiramate	26 (23.2)	59 (26.2)	85 (25.2)
Levetiracetam	14 (12.5)	48 (21.3)	62 (18.4)

ASD, antiseizure drug; ESL, eslicarbazepine acetate; OLE, open-label extension.

^a 1-year OLE baseline.

ESL dose and incidence of individual TEAEs. During the post-1-year OLE, although the overall incidence of TEAEs appeared to be lower in patients taking the lowest ESL dosages (<15 mg/kg/day: 31%) compared with higher dosages (15–25 mg/kg/day: 55%; ≥25 mg/kg/day: 54%), there was no clear relationship between ESL dose and incidence of individual TEAEs (Table 3).

There were no clinically significant changes from baseline in any vital sign parameters during the 1-year or post-1-year OLEs.

3.3. Serious AEs and deaths

The overall incidence of serious AEs was 9% during the 1-year OLE and 10% during the post-1-year OLE (Table 4). The most frequently reported serious AEs were similar during the 1-year and post-1-year OLEs; partial seizures and pneumonia were reported in >1% (but fewer than 2%) of patients during both study periods, and status epilepticus was reported in >1% of patients in the post-1-year OLE (1.1% vs 0.6% of patients during the 1-year OLE).

One patient died during the post-1-year OLE because of infection and disseminated intravascular coagulation (Table 4); the sponsor judged

Table 2
ESL exposure according to patient weight category.

	Weight category				Total ^a
	11–21 kg	22–31 kg	32–38 kg	>38 kg	
1-year OLE					
Mean daily dosage, mg/day, mean (SD)	444.4 (114.8)	632.6 (160.6)	830.8 (221.6)	1000.9 (221.1)	822.1 (287.8)
Exposure, days, mean (SD)	307.1 (86.0)	315.8 (80.8)	305.6 (101.8)	318.1 (95.9)	314.2 (92.3)
Post-1-year OLE					
Mean daily dosage, mg/day, mean (SD)	540.8 (108.7)	736.0 (190.0)	981.1 (218.0)	1118.5 (153.8)	949.2 (274.4)
Exposure, days, mean (SD)	455.3 (409.6)	675.0 (440.0)	808.8 (487.2)	665.5 (335.2)	653.3 (390.4)

ESL, eslicarbazepine acetate; OLE, open-label extension; SD, standard deviation.

^a All patients, regardless of weight.

the fatal event of bronchopneumonia (with aspiration, decreased respiratory rate, and unresponsive to stimuli) as unlikely related to the study drug. The patient was 5 years of age, weighed 19.0 kg, and had been taking ESL for >4 years in Study 305. The sponsor judged the multiple occurrences of pneumonia (including one while taking placebo) as not related to ESL but related to the patient's baseline medical conditions of epilepsy, Dandy–Walker syndrome, and cerebral palsy. There were no cases of sudden unexpected death in epilepsy (SUDEP).

3.4. TEAEs leading to discontinuation

The overall incidence of TEAEs leading to discontinuation was 4.2% during the 1-year OLE and 0.6% during the post-1-year OLE (Table 4). One TEAE leading to discontinuation occurred in >1% of patients during the 1-year OLE (partial seizures, 1.5%). During the post-1-year OLE, a total of one TEAE leading to discontinuation was reported (splenomegaly, n = 1, 0.6%).

3.5. TEAEs of special interest

Allergic reaction TEAEs were reported in 8 patients (2.4%) during the 1-year OLE and in 1 patient (0.6%) during the post-1-year OLE. Rash was the most frequently reported allergic reaction TEAE (1-year OLE, 1.2%; post-1-year OLE, 0.6%); the cases of rash occurred between study days 177 and 998 and were not related to an ESL dose increase (Table 5). There were no cases of drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, or toxic epidermal necrolysis. The investigator-reported TEAE hyponatremia was reported in 1 patient during the 1-year OLE (0.3%) and was not related to treatment with ESL but to diagnosis of syndrome of inadequate secretion of vasopressin. There was one report of serum sodium levels ≤125 mEq/L during the post-1-year OLE (0.6%) which was unlikely related to treatment with ESL; initiation of carbamazepine may have been a contributing factor (Table 5). The investigator-reported TEAE of hypothyroidism was reported in 3 patients (0.9%) during the 1-year OLE and 2 patients (1.1%) during the post-1-year OLE but not confirmed via laboratory testing (Table 5); all patients were treated with thyroid supplementation, and none discontinued the study because of hypothyroidism. One TEAE related to cytopenia (0.3%) was reported during the 1-year OLE and three (1.7%) during the post-1-year OLE; one pancytopenia event in the post-1-year OLE was a recurrence of the event reported during the 1-year OLE in the same patient (Table 5). The cases of pancytopenia were not serious and were possibly related to treatment with ESL; one patient was taking concomitant carbamazepine and valproic acid (ASDs with documented associations with pancytopenia and similar hematopoietic disorders). Abnormal liver function tests (LFTs; postdose serum alanine aminotransferase or aspartate aminotransferase >3× the upper limit of normal) were reported in 1 patient (0.3%) during the 1-year OLE and 4 patients (2.3%) during the post-1-year OLE (Table 5). Seizure-related TEAEs were reported in 25 patients (7.4%) during the 1-year OLE and 12 patients (6.8%) during the post-1-year OLE (Table 5).

Table 3
Most frequently reported TEAEs according to mean daily dose.^a

n (%)	ESL				Post-1-year OLE			
	1-year OLE N = 337				N = 177			
	<15 mg/kg/day n = 42	15–25 mg/kg/day n = 148	≥25 mg/kg/day n = 147	Total n = 337	<15 mg/kg/day n = 13	15–25 mg/kg/day n = 75	≥25 mg/kg/day n = 89	Total n = 177
Any TEAE	31 (73.8)	107 (72.3)	78 (53.1)	216 (64.1)	4 (30.8)	41 (54.7)	48 (53.9)	93 (52.5)
Nasopharyngitis	2 (4.8)	21 (14.2)	11 (7.5)	34 (10.1)	0	7 (9.3)	8 (9.0)	15 (8.5)
Partial seizures	6 (14.3)	17 (11.5)	11 (7.5)	34 (10.1)	1 (7.7)	9 (12.0)	9 (10.1)	19 (10.7)
Vomiting	3 (7.1)	15 (10.1)	14 (9.5)	32 (9.5)	2 (15.4)	5 (6.7)	5 (5.6)	12 (6.8)
Pyrexia	3 (7.1)	13 (8.8)	13 (8.8)	29 (8.6)	0	6 (8.0)	10 (11.2)	16 (9.0)
Headache	2 (4.8)	17 (11.5)	8 (5.4)	27 (8.0)	1 (7.7)	9 (12.0)	4 (4.5)	14 (7.9)
Somnolence	6 (14.3)	13 (8.8)	4 (2.7)	23 (6.8)	0	1 (1.3)	1 (1.1)	2 (1.1)
Respiratory tract infection	2 (4.8)	8 (5.4)	7 (4.8)	17 (5.0)	1 (7.7)	2 (2.7)	1 (1.1)	4 (2.3)
Bronchitis	0	5 (3.4)	9 (6.1)	14 (4.2)	0	6 (8.0)	4 (4.5)	10 (5.6)
Pharyngitis	1 (2.4)	10 (6.8)	3 (2.0)	14 (4.2)	0	2 (2.7)	7 (7.9)	9 (5.1)
Rhinitis	0	9 (6.1)	3 (2.0)	12 (3.6)	0	6 (8.0)	5 (5.6)	11 (6.2)
Cough	0	4 (2.7)	5 (3.4)	9 (2.7)	0	6 (8.0)	3 (3.4)	9 (5.1)
Diarrhea	1 (2.4)	4 (2.7)	3 (2.0)	8 (2.4)	0	6 (8.0)	4 (4.5)	10 (5.6)
Upper respiratory tract infection	2 (4.8)	1 (0.7)	4 (2.7)	7 (2.1)	2 (15.4)	1 (1.3)	7 (7.9)	10 (5.6)

ESL, eslicarbazepine acetate; OLE, open-label extension; TEAE, treatment-emergent adverse event.

^a ≥5% overall incidence during the 1-year or post-1-year OLE.

4. Discussion

During this long-term study, 337 children were treated with ESL for ~1 year, and 177 were treated with ESL for ~2 years. The large amount of data generated during this extended time period provide valuable information about the safety and tolerability of ESL in children. Patients were exposed to a mean daily dosage of ESL 822 mg/day during the 1-year OLE and ESL 949 mg/day during the post-1-year OLE; mean daily dose increased with increasing weight, explaining the higher dose during the post-1-year OLE, when patients will have been older and heavier than during the 1-year OLE. Alternatively, doses may have increased over time due to changing therapeutic need.

Overall, TEAEs were reported in 64% of patients taking ESL during the 1-year OLE and 53% of patients during the post-1-year OLE. These overall incidences were similar to those in the placebo-controlled portion of the studies (ESL, 68%; placebo, 66%) [4]. Similar TEAEs were reported during the 1-year and post-1-year OLEs. There were more TEAEs related to infection during these long-term OLEs than during the 12–18-week placebo-controlled portions of the trials [4] as might be expected when monitoring for long periods of time. There was no clear relationship between ESL dose and TEAE incidence during the OLEs, consistent with analyses conducted during the placebo-controlled portion of the trials [4].

Serious AEs were reported in 9% of patients during the 1-year OLE and 10% during the post-1-year OLE. TEAEs leading to discontinuation were reported in 4% of patients during the 1-year OLE and 1% during the post-1-year OLE. Allergic reactions, hypothyroidism, cytopenia, and

Table 4
Most frequently reported serious AEs and TEAEs leading to discontinuation.^a

n (%)	ESL	
	1-year OLE n = 337	Post-1-year OLE n = 177
Any serious AE	30 (8.9)	18 (10.2)
Partial seizures	4 (1.2)	3 (1.7)
Pneumonia	4 (1.2)	2 (1.1)
Status epilepticus	2 (0.6)	2 (1.1)
Death	0	1 (0.6)
Any TEAE leading to discontinuation	14 (4.2)	1 (0.6)
Partial seizures	5 (1.5)	0

AE, adverse event; ESL, eslicarbazepine acetate; OLE, open-label extension; TEAE, treatment-emergent adverse event.

^a ≥1% incidence during the 1-year or post-1-year OLE.

abnormal LFTs were reported in few patients taking ESL in these OLEs. There were 2 hyponatremia-related reports. The investigator-reported TEAE hyponatremia was reported in 1 patient during the 1-year OLE and was not related to treatment with ESL. Serum sodium levels ≤125 mEq/L were reported in 1 patient during the post-1-year OLE and were unlikely related to treatment with ESL; initiation of carbamazepine may have been a contributing factor. Overall, 7% of patients in both the 1-year and post-1-year OLEs were reported to have experienced seizures

Table 5
TEAEs of special interest.

n (%)	ESL	
	1-year OLE n = 337	Post-1-year OLE n = 177
Allergic reactions	8 (2.4)	1 (0.6)
Rash ^{a,b}	4 (1.2)	1 (0.6)
Urticaria ^a	2 (0.6)	0
Allergic dermatitis ^a	1 (0.3)	0
Vesicular rash ^{a,b}	1 (0.3)	0
Hypersensitivity ^a	1 (0.3)	0
Hyponatremia	1 (0.3)	1 (0.6)
Hyponatremia ^a	1 (0.3)	0
Postdose serum sodium ≤125 mEq/L ^c	0	1 (0.6)
Hypothyroidism	3 (0.9)	2 (1.1)
Hypothyroidism ^a	3 (0.9)	2 (1.1)
Cytopenia	1 (0.3)	3 (1.7)
Pancytopenia ^a	1 (0.3)	2 (1.1)
Anemia ^a	0	1 (0.6)
Hepatic events	1 (0.3)	4 (2.3)
Postdose serum ALT > 3 × ULN ^c	1 (0.3)	4 (2.3)
Postdose serum AST > 3 × ULN ^c	1 (0.3)	1 (0.6)
Seizures	25 (7.4)	12 (6.8)
Partial seizures ^a	13 (3.9)	6 (3.4)
Convulsion ^a	6 (1.8)	3 (1.7)
Epilepsy ^a	5 (1.5)	1 (0.6)
Partial seizures with secondary generalization ^a	4 (1.2)	0
Status epilepticus ^a	2 (0.6)	2 (1.1)
Febrile convulsion ^a	1 (0.3)	1 (0.6)
Simple partial seizures ^a	1 (0.3)	0
Complex partial seizures ^a	0	1 (0.6)
Grand mal convulsion ^a	0	1 (0.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESL, eslicarbazepine acetate; OLE, open-label extension; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

^a Investigator-reported TEAE.^b The cases of rash occurred on study days 177, 207, 230, 258, and 998. Vesicular rash occurred on study day 277.^c Laboratory analysis.

as TEAEs, and 2% of patients discontinued during the 1-year OLE and 1% during the post-1-year OLE due to seizure TEAEs. However, if ESL were suspected to induce or worsen seizures, patients would have been unlikely to have remained in the OLE studies; therefore, the seizures reported during the 1- and post-1-year OLEs are more likely to be evidence of incomplete or absent therapeutic effect than drug-induced exacerbation of seizures. This is consistent with a previous analysis of data pooled from three phase III trials in adults, which concluded that treatment with adjunctive ESL did not appear to aggravate focal or secondarily generalized tonic-clonic seizures [9].

It is of note that only patients in whom ESL was at least somewhat effective and relatively well tolerated would likely have continued into the 1-year and post-1-year OLE periods (1-year OLE: N = 337 of 362 patients in the double-blind studies; post-1-year OLE: N = 177 of 257 who completed the 1-year OLE), suggesting that these data are somewhat biased in favor of those patients. Further limitations of OLE studies in general include difficulties measuring treatment compliance and potential underreporting of TEAEs by clinicians (including serious AEs). In the current study, few patients (34%) completed the post-1-year OLE, partly due to the introduction of a compassionate use program; patients primarily exited the study because ESL became available through the compassionate use program, not due to safety or efficacy concerns. More TEAEs might have been reported if the mean duration of treatment was longer than 653 days.

Overall, long-term treatment with ESL was generally well tolerated in pediatric patients aged 4–17 years with focal seizures. TEAEs were comparable with those observed in adults with no new events of concern [10].

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Declaration of competing interest

RS reports employment at the University of California; receiving honoraria from Sunovion Pharmaceuticals Inc., Supernus, Eisai, Greenwich Biosciences, UCB, LivaNova, BioMarin, and Encoded; receiving consulting fees from Sunovion Pharmaceuticals Inc., Supernus, UCB, BioMarin, Encoded, West Therapeutic Development, and Aquestive Therapeutics; and receiving grants or funds from SK Life Science. FK reports being on advisory councils or committees and receiving honoraria from BIAL and Eisai; and receiving grants from Action Medical Research. GH reports being on advisory councils or committees for Eisai (Data Safety Monitoring Board), Marinus, Ovid, and Zogenix. JEP-G reports being on an advisory council or committee for and receiving honoraria and consulting fees from Aquestive, Eisai, Greenwich, Sunovion Pharmaceuticals Inc., Supernus, and UCB. JW reports receiving grants from Shainberg

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Data sharing statement

Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability, please visit: <https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx> and click on Sunovion.

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