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Eslicarbazepine acetate as monotherapy in clinical practice: Outcomes from Euro-Esli

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Abstract

Objectives: To assess the effectiveness and safety/tolerability of eslicarbazepine acetate (ESL) monotherapy in clinical practice in Europe.

Materials and methods: Euro-Esli was a pooled analysis of 14 European clinical practice studies. Responder rate (≥50% seizure frequency reduction) and seizure freedom rate (seizure freedom at least since prior visit) were assessed after 3, 6 and 12 months of ESL treatment and at last visit. Adverse events (AEs) and AEs leading to ESL discontinuation were assessed throughout follow-up. A subanalysis was conducted to assess outcomes for patients treated initially with ESL monotherapy and for patients treated at the last visit with ESL monotherapy.

Results: ESL was used as monotherapy in 88/2045 (4.3%) patients initially and in 229/1340 (17.1%) patients at the last visit. At 12 months, responder and seizure freedom rates were 94.1% and 88.2%, respectively, in patients treated initially with ESL monotherapy, and 93.2% and 77.4%, respectively, in patients treated at the last visit with ESL monotherapy. Corresponding values for patients treated initially with ESL adjunctive therapy were 74.8% and 39.0%, respectively; and for patients treated at the last visit with ESL adjunctive therapy, corresponding values were 70.4% and 25.9%, respectively. Safety and tolerability were generally comparable in patients treated with ESL as monotherapy or adjunctive therapy. The most commonly reported AEs (≥5% of patients in any group) were dizziness, somnolence, instability/ataxia, and fatigue.

Conclusions: These clinical practice data support the use of ESL as monotherapy, as well as adjunctive therapy, for focal-onset seizures, complementing evidence from clinical trials.

KEYWORDS

adjunctive therapy, antiepileptic drug, clinical practice, eslicarbazepine acetate, Euro-Esli, focal epilepsy, monotherapy

1 | INTRODUCTION

Eslicarbazepine acetate (ESL) is a once-daily antiepileptic drug (AED) that is approved in Europe as monotherapy in the treatment of focal-onset seizures, 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-onset seizures, with or without secondary generalization.[1] ESL was approved for use as monotherapy in Europe on the basis of a phase III, randomized, double-blind, non-inferiority trial, in which once-daily monotherapy

with ESL was shown to be non-inferior to twice-daily monotherapy with controlled-release carbamazepine.[2] These findings are supported by the results of two phase III withdrawal to monotherapy trials,[3,4] which resulted in approval for ESL in the monotherapy setting in the United States.[5]

Clinical trials are essential for the development and approval of new AEDs, but due to the strict inclusion and exclusion criteria typically employed, they may not always represent the entire breadth of patient types encountered in clinical practice.[6,7] Furthermore, individualized treatment approaches are used in clinical practice, and protocol-defined dosing strategies may restrain assessment of this in clinical trials. Therefore, clinical practice studies complement evidence from clinical trials by further elucidating an agent's effectiveness when used under everyday conditions.

The Euro-Esli study addressed the need for clinical practice data by conducting an audit of clinical practice studies conducted across Europe, thereby providing insights into how the evidence obtained from ESL clinical trials has translated into the clinical practice setting.[8] Euro-Esli represents the largest study into the effectiveness of ESL in clinical practice to date, with over 2000 patients included in the study population,[8] similar to the total number of patients recruited into ESL clinical trials (approximately 2400[1]), and thereby providing strong evidence of how ESL performs in this setting. The size of the Euro-Esli cohort has allowed meaningful, statistically robust subanalyses to be conducted, providing further insights into the use of ESL in clinical practice.[8]

Since evidence for the use of ESL as monotherapy in clinical practice is currently scarce, we present here the results of a subanalysis of data from patients included in Euro-Esli who were either treated with ESL as initial monotherapy, or converted to ESL monotherapy after initially receiving ESL as adjunctive therapy.

2 | MATERIAL AND METHODS

2.1 | Study design

The Euro-Esli study was an exploratory, retrospective, pooled analysis of data from European clinical practice studies,[9-21] conducted to audit the effectiveness, safety, and tolerability of ESL as an adjunctive treatment for focal-onset seizures in clinical practice, details of which have been published previously.[8] In brief, effectiveness was assessed after 3, 6, and 12 months of ESL treatment and at final follow-up, and safety and tolerability were assessed for the duration of ESL treatment. The study protocol was approved by the Ethics Committee of Hospital Universitario y Politécnico La Fe, Valencia, Spain.[8]

A subanalysis was conducted of data from patients included in Euro-Esli who were treated with ESL as initial monotherapy and patients who were being treated with ESL monotherapy at the last visit. Corresponding data were assessed for patients treated initially with ESL as adjunctive therapy and for those who were being treated with ESL as adjunctive therapy at the last visit. In addition, a further subanalysis of patients treated initially with ESL as adjunctive therapy was conducted, to compare outcomes for patients who subsequently withdrew to ESL monotherapy with those who continued to receive ESL as adjunctive therapy throughout follow-up.

2.2 | Study population

The studies included in Euro-Esli had broad inclusion/exclusion criteria, in order to be representative of the variety of patients encountered in clinical practice.[8] The current analysis included all patients from Euro-Esli for whom the number of AEDs used initially and at the last visit was known.

2.3 | Study assessments

Effectiveness was evaluated by assessing responder and seizure freedom rates. Response was defined as ≥50% seizure frequency reduction from baseline (ie, prior to ESL initiation), and seizure freedom was defined as having no seizures since at least the prior visit (either 3 or 6 months, depending on the time point at which seizure freedom was assessed).

Safety and tolerability were assessed by the evaluation of adverse events (AEs) and rate of ESL discontinuation due to AEs, respectively. AEs of special interest (hyponatremia and rash) were specifically evaluated. AEs (including hyponatremia and rash) were classified by participating clinicians according to Medical Dictionary for Regulatory Activities definitions. Sodium levels were evaluated, when recorded.

2.4 | Statistical analyses

Details of the statistical methodology employed in Euro-Esli have been published previously.[8] The safety population was defined as all patients who initiated ESL treatment and the effectiveness population was defined as all patients who initiated ESL treatment and had at least one effectiveness assessment. There was great heterogeneity in the particular objectives of the studies included in the analysis and, thus, in the information each study reported. The current analysis attempted to combine the reported information in the most complete way possible. Missing data were not imputed, except in cross-sectional studies, in which the last visit data were captured and included in the established cutoff points (3, 6, or 12 months). When the observation timepoint of a study did not match the established cutoff points, the following allocations were made: observations performed between 1.5 and <4.5 months were allocated to the 3-month visit; those performed between 4.5 and <9 months were allocated to the 6-month visit; and those performed between 9 and 15 months were allocated to the 12-month visit. A "final" variable was also created, in which the last observation of each patient was included, independently of the timepoint when it occurred. Since this was an exploratory study, no hypothesis was defined. No systematic review of the individual patients was undertaken due to the heterogeneity of the individual samples and objectives of each study. Therefore, individual studies were not treated as clusters.[8]

A descriptive analysis of quantitative and qualitative variables was performed.[8] For each variable, the total number of patients for whom the data in question were available was stated and this value was used as the denominator for analysis. Quantitative variables were described as mean, standard deviation (SD), median, minimum and maximum values, together with the number of valid cases and confidence intervals (CIs) or interquartile range (25th percentile to 75th percentile). Qualitative variables (responder rate, seizure freedom rate, incidence of AEs, rate of discontinuation due to AEs) were described as means of absolute frequencies and percentages. In the sub-analysis of patients who were initially treated with ESL as adjunctive therapy, demographic and baseline characteristics were compared between the subgroups of patients who withdrew to ESL monotherapy versus those who continued to receive ESL as adjunctive therapy using the Student's *t* test, Mann–Whitney *U* test, or chi-squared test, as appropriate. ESL dosing levels were similarly compared using the Mann–Whitney *U* test. Duration of ESL treatment was assessed using Kaplan-Meier analysis and compared between the subgroups of patients who did versus did not withdraw to ESL monotherapy using the log-rank test. Effectiveness, safety, and tolerability assessments were compared between the subgroups of patients who did versus did not withdraw to ESL monotherapy using the chi-squared test. The Statistical Package for the Social Sciences version 19.0 was used for all analyses, and the significance level was 5%.[8]

3 | RESULTS

Euro-Esli included a total of 2058 patients from 14 European clinical practice studies.[8] These studies included patients treated with ESL between November 2009 and December 2016. The number of initial AEDs patients were receiving at study entry was known for 2045 patients, of whom 88 (4.3%) received ESL as initial monotherapy. The number of previous AEDs received was known for 49 of these 88 patients, of whom 17 (34.7%) had not been treated with another AED prior to starting ESL monotherapy. The number of AEDs patients were receiving at the last visit was known for 1340 patients, of whom 229 (17.1%) were being treated with ESL monotherapy. These included patients treated with ESL as initial monotherapy and those who converted to ESL monotherapy after initially receiving ESL as adjunctive therapy.

Of the 1957 patients who received ESL as initial adjunctive therapy, information on whether or not patients subsequently withdrew to ESL monotherapy was known for 1309 patients, of whom 199 (15.2%) withdrew to ESL monotherapy and 1110 (84.8%) continued to receive ESL as adjunctive therapy.

3.1 | Study population

Demographic and baseline characteristics of patients who received ESL as initial monotherapy and monotherapy at the last visit are summarized in Table 1, together with the corresponding data for patients treated with ESL as initial adjunctive therapy and adjunctive therapy at the last visit. For the subanalysis of patients who were treated with ESL as initial adjunctive therapy, corresponding data for those who did versus did not subsequently withdraw to ESL monotherapy are presented in Table 2, together with results of statistical comparisons.

Several of the baseline characteristics of patients who received ESL as initial monotherapy differed from those of patients who received ESL as initial adjunctive therapy (Table 1). Age at onset of epilepsy was higher for patients who received ESL as initial monotherapy versus initial adjunctive therapy (mean [SD] age at onset, 27.9 [18.6] vs 23.1 [19.2] years), and duration of epilepsy was shorter (mean [SD] duration, 13.4 [15.2] vs 21.2 [16.3] years). In addition, the baseline frequency of partial seizures was lower in patients who received ESL as initial monotherapy versus initial adjunctive therapy (mean [SD] monthly frequency, 5.2 [12.4] vs 13.9 [50.7]). The proportion of patients with psychiatric comorbidity was higher in patients who received ESL as initial monotherapy versus initial adjunctive therapy (46.7% vs 24.3%).

Similarly, there were differences in a number of demographic and baseline characteristics between patients who received ESL as monotherapy at the last visit, compared with those who received ESL as adjunctive therapy at the last visit (Table 1). The proportion of male-to-female patients differed between groups (percentage of male patients, 59.8% for patients who received ESL as monotherapy vs 50.3% for patients who received ESL as adjunctive therapy). The age of patients was higher for patients treated with ESL as monotherapy versus adjunctive therapy at the last visit (mean [SD] age, 46.4 [18.7] vs 43.4 [15.2] years). The age of patients at onset of epilepsy was also higher for patients who received ESL as monotherapy versus adjunctive therapy at the last visit (mean [SD] age at onset, 34.3 [22.5] vs 21.5 [18.3] years), and the duration of epilepsy was shorter (mean [SD] duration, 12.3 [14.8] vs 21.9 [16.7] years). Monthly seizure frequencies were lower for patients who received ESL as monotherapy versus adjunctive therapy at the last visit, for any type of partial seizure and across partial seizure subtypes. The number of previous AEDs used was fewer in patients who received ESL as monotherapy versus adjunctive therapy at the last visit (mean [SD] number of previous AEDs, 1.5 [1.2] vs 4.1 [3.5]), and the proportion of patients with psychiatric comorbidity was higher (28.6% vs 18.9%).

In the subanalysis of patients who were treated with ESL as initial adjunctive therapy, there were significant differences in demographic and baseline characteristics between patients who withdrew to ESL monotherapy compared with those who received ESL as adjunctive therapy throughout follow-up (Table 2). Patients who withdrew to monotherapy were older than those who did not (mean [SD] age, 47.2 [18.6] vs 43.4 [15.2]; $P = 0.006$) and a greater proportion of patients who withdrew to monotherapy were male compared with those who did not (60.8% vs 50.2%; $P = 0.006$). In addition, patients who withdrew to monotherapy, compared with those who did not, had a later onset of epilepsy (mean [SD] age at onset, 34.3 [22.8] vs 21.4 [18.3] years; $P < 0.001$), shorter duration of epilepsy (mean [SD]

TABLE 1 Patient demographics and baseline characteristics of patients treated with ESL as initial monotherapy, ESL as monotherapy at the last visit, ESL as initial adjunctive therapy and ESL as adjunctive therapy at the last visit

	ESL as initial monotherapy	ESL as monotherapy at last visit	ESL as initial adjunctive therapy	ESL as adjunctive therapy at last visit
Baseline demographics				
Sex				
N[a]	88	229	1956	1110
Male, n (%)	41 (46.6)	137 (59.8)	1022 (52.2)	558 (50.3)
Female, n (%)	47 (53.4)	92 (40.2)	934 (47.8)	552 (49.7)
Age				
N[a]	88	229	1956	1110
Mean (SD), years	41.2 (15.7)	46.4 (18.7)	44.2 (15.5)	43.4 (15.2)
Median (range), years	40.5 (14-79)	46.0 (14.0-87.0)	43.0 (14-88)	41.4 (15.0-88.0)
Epilepsy-related characteristics				
Age at onset of epilepsy				
N[a]	76	221	1782	1067
Mean (SD), years	27.9 (18.6)	34.3 (22.5)	23.1 (19.2)	21.5 (18.3)
Median (range), years	23.5 (0-76)	28.0 (0-87)	18.0 (0-87)	17.0 (0-87)
Duration of epilepsy				
N[a]	76	221	1782	1067
Mean (SD), years	13.4 (15.2)	12.3 (14.8)	21.2 (16.3)	21.9 (16.7)
Median (range), years	7.5 (0.0-70.0)	7.0 (0.0-70.5)	19.0 (0.0-81.8)	19.0 (0.0-81.8)
Etiology[b]				
N[a]	81	205	1574	873
Structural-metabolic, n (%)	35 (43.2)	111 (54.1)	911 (57.9)	483 (55.3)
Genetic, n (%)	4 (4.9)	3 (1.5)	32 (2.0)	17 (1.9)
Unknown, n (%)	42 (51.9)	91 (44.4)	631 (40.1)	373 (42.7)
Baseline seizure type				
Any partial seizure				
N[a]	83	227	1897	1098
Yes, n (%)	57 (68.7)	193 (85.0)	1787 (94.2)	1082 (98.5)
Simple partial seizures				
N[a]	83	222	1747	1098
Yes, n (%)	13 (15.7)	59 (26.6)	464 (26.6)	329 (30.0)
Complex partial seizures				
N[a]	83	222	1747	1098
Yes, n (%)	30 (36.1)	85 (38.3)	1106 (63.3)	761 (69.3)
Secondarily generalized seizures				
N[a]	83	222	1747	1098
Yes, n (%)	26 (31.3)	87 (39.2)	759 (43.4)	443 (40.3)
Baseline monthly seizure frequency				
Any partial seizure				
N[a]	55	193	1787	1076
Mean (SD)	5.2 (12.4)	4.6 (20.6)	13.9 (50.7)	13.9 (50.4)

(Continues)

TABLE 1 (Continued)

	ESL as initial monotherapy	ESL as monotherapy at last visit	ESL as initial adjunctive therapy	ESL as adjunctive therapy at last visit
Median (range)	1.3 (0.3-66.7)	1.0 (0.1-240.0)	3.0 (0.1-1230.0)	3.3 (0.1-1230.0)
Simple partial seizures				
N[a]	9	55	386	298
Mean (SD)	12.3 (19.9)	6.8 (20.8)	14.7 (60.4)	10.9 (23.3)
Median (range)	1.0 (0.3-60.0)	1.5 (0.3-150.0)	3.0 (0.3-900.0)	3.1 (0.3-210.0)
Complex partial seizures				
N[a]	25	81	954	704
Mean (SD)	5.2 (9.7)	5.6 (26.6)	8.4 (22.4)	8.3 (22.1)
Median (range)	1.3 (0.3-40.0)	1.5 (0.3-240.0)	2.9 (0.2-300.0)	3.0 (0.3-300.0)
Secondarily generalized seizures				
N[a]	22	83	604	379
Mean (SD)	1.1 (0.8)	0.6 (0.5)	2.6 (6.3)	3.0 (7.1)
Median (range)	1.0 (0.3-4.0)	0.3 (0.2-3.3)	0.9 (0.1-70.0)	1.0 (0.2-70.0)
Comorbidities				
Intellectual disability				
N[a]	32	48	918	511
Yes, n (%)	4 (12.5)	3 (6.3)	104 (11.3)	51 (10.0)
Psychiatric comorbidity[c]				
N[a]	30	175	1106	635
Yes, n (%)	14 (46.7)	50 (28.6)	269 (24.3)	120 (18.9)
Depression				
N[a]	30	175	1102	635
Yes, n (%)	6 (20.0)	19 (10.9)	135 (12.3)	59 (9.3)
AED treatment				
Total number of previous AEDs				
N[a]	49	220	1837	1088
Mean (SD)	1.8 (2.2)	1.5 (1.2)	4.1 (3.4)	4.1 (3.5)
Median (range)	1.0 (0-9)	1.0 (0-10)	3.0 (0-20)	3.0 (0-20)
Reason for ESL treatment initiation				
N[a]	8	196	1309	813
Lack of effectiveness, n (%)	2 (25.0)	81 (41.3)	972 (74.3)	658 (80.9)
Adverse reaction, n (%)	1 (12.5)	81 (41.3)	184 (14.1)	58 (7.1)
Both, n (%)	3 (37.5)	17 (8.7)	109 (8.3)	87 (10.7)
Other, n (%)	2 (25.0)	17 (8.7)	44 (3.4)	10 (1.2)

AED, antiepileptic drug; ESL, eslicarbazepine acetate; SD, standard deviation.
[a]Total number of patients for whom data in question were available.
[b]International League Against Epilepsy 2010 classification.
[c]Including depression.

duration, 13.1 [15.3] vs 21.9 [16.6] years; $P < 0.001$), lower baseline seizure frequency across all seizure types ($P \leq 0.001$ for all comparisons), and had been treated with fewer previous AEDs (mean [SD] number of previous AEDs, 1.4 [1.1] vs 4.1 [3.5]; $P < 0.001$). The proportion of patients with psychiatric comorbidity was also higher in patients who withdrew to monotherapy compared with those who did not (26.4% vs 18.9%; $P = 0.035$).

3.2 | ESL treatment

In the majority of patients, ESL was initiated due to lack of effectiveness of previous treatment and/or adverse reaction(s) to previous treatment (Table 1). In the subanalysis of patients treated with ESL as initial adjunctive therapy, there was a significant difference between patients who did versus did not withdraw to ESL monotherapy in

the reasons for initiating ESL treatment (Table 2; $P < 0.001$), primarily because a higher proportion of patients who withdrew to ESL monotherapy, compared with those who did not, initiated ESL treatment due to adverse reaction(s) to previous treatment (42.0% vs 7.1%) and a lower proportion initiated ESL due to lack of effectiveness of previous treatment (41.5% vs 80.9%). Details of ESL dosing during the course of follow-up are summarized in Table 3. The mean (SD) ESL dose at baseline was 800.0 (253.0) mg/day (median, 800; range, 400-1200) in patients treated with ESL as initial monotherapy and 527.0 (247.7) mg/day (median, 400; range, 150-1600) in patients treated with ESL as initial adjunctive therapy. The mean (SD) ESL dose at the last visit was 878.9 (275.9) mg/day (median, 800; range, 400-2400) in patients treated with ESL as monotherapy at the last visit and 962.2 (315.7) mg/day (median, 800; range, 200-2800) in patients treated with ESL as adjunctive therapy at the last visit.

The mean duration of ESL treatment was 36.8 months (95% confidence interval [CI], 33.5-40.0) in patients who received ESL as initial monotherapy and 27.9 months (95% CI, 27.0-28.8) in patients who received ESL as monotherapy at the last visit. The proportions of patients who discontinued ESL treatment during follow-up were 18.1% (15/83) for those who received ESL as initial monotherapy and 8.8% (20/228) for those who received ESL as monotherapy at the last visit. Among patients who received ESL as initial monotherapy, reasons for ESL discontinuation were AEs (9.6%; n = 8), lack of efficacy (3.6%; n = 3), other (3.6%; n = 3), and unknown (1.2%; n = 1). Among patients who received ESL as monotherapy at the last visit, reasons for ESL discontinuation comprised AEs (4.4%; n = 10), lack of efficacy (2.2%; n = 5), AEs and lack of efficacy (0.4%; n = 1), and other (1.8%; n = 4).

The mean duration of ESL treatment was 49.2 months (95% CI, 44.2-54.3) in patients who received ESL as initial adjunctive therapy and 34.7 months (95% CI, 30.9-38.6) in those who received ESL as adjunctive therapy at the last visit. The proportions of patients who discontinued ESL treatment during follow-up were 26.6% (512/1924) for those who received ESL as initial adjunctive therapy and 25.4% (280/1104) for those who received ESL as adjunctive therapy at the last visit. Among patients who received ESL as initial adjunctive therapy, reasons for ESL discontinuation comprised AEs (10.1%; n = 195), lack of efficacy (8.0%; n = 154), AEs and lack of efficacy (3.3%; n = 64), other (2.2%; n = 42 [most commonly, patient decision (n = 9) and lack of compliance (n = 3)]) and unknown (3.0%; n = 57). Among those who received ESL as adjunctive therapy at the last visit, reasons for ESL discontinuation were AEs (9.6%; n = 106), lack of efficacy (8.4%; n = 93), AEs and lack of efficacy (4.7%; n = 52), other (1.9%; n = 21 [most commonly, patient decision (n = 8) and lack of compliance (n = 2)]), and unknown (0.7%; n = 8).

3.3 | Effectiveness

Responder rates in patients who received ESL as initial monotherapy were 94.1% (48/51) at 12 months and 76.3% (58/76) at the last visit (Figure 1A). The corresponding responder rates in patients who received ESL as monotherapy at the last visit were 93.2% (177/190) and 90.4% (206/228), respectively (Figure 1B). At all timepoints, responder rates were lower in patients who received ESL as adjunctive therapy than in those who received ESL as monotherapy: responder rates in patients who received ESL as initial adjunctive therapy were 74.8% (748/1000) at 12 months and 63.1% (1136/1800) at the last visit (Figure 1C), and the corresponding values for patients who received ESL as adjunctive therapy at the last visit were 70.4% (421/598) and 63.4% (684/1079), respectively (Figure 1D).

Seizure freedom rates in patients who received ESL as initial monotherapy were 88.2% (45/51) at 12 months and 59.0% (49/83) at the last visit (Figure 1A). The corresponding seizure freedom rates in patients who received ESL as monotherapy at the last visit were 77.4% (147/190) and 70.2% (160/228), respectively (Figure 1B). At all timepoints, seizure freedom rates were lower in patients who received ESL as adjunctive therapy than in those who received ESL as monotherapy: seizure freedom rates in patients who received ESL as initial adjunctive therapy were 39.0% (390/1000) at 12 months and 31.3% (589/1879) at the last visit (Figure 1C), and the corresponding values for patients who received ESL as adjunctive therapy at the last visit were 25.9% (155/598) and 26.1% (283/1085), respectively (Figure 1D).

In the subanalysis of patients who received ESL as initial adjunctive therapy, responder and seizure freedom rates were significantly higher in patients who withdrew to monotherapy compared with those who received ESL as adjunctive therapy throughout follow-up, at all timepoints ($P < 0.001$ for all comparisons; Figure 2).

3.4 | Safety and tolerability

A summary of AEs and AEs leading to discontinuation is presented in Table 4. The overall incidence of AEs was similar in patients treated with ESL as initial monotherapy and patients treated with ESL monotherapy at the last visit (29.4% [25/85] and 27.1% [62/229]). The rate of ESL discontinuation due to AEs was higher in patients treated with ESL as initial monotherapy than in those treated with ESL as monotherapy at the last visit (9.8% [8/82] and 4.8% [11/228]).

The overall incidence of AEs was similar in patients treated with ESL as initial adjunctive therapy and those treated with ESL as adjunctive therapy at the last visit (34.4% [665/1933] and 30.8% [342/1109]). The rate of ESL discontinuation due to AEs was also similar in patients treated with ESL as initial adjunctive therapy and those treated with ESL adjunctive therapy at the last visit (13.9% [259/1867] and 14.4% [158/1096]).

The most commonly reported AEs (≥5% of patients in any group) were dizziness, somnolence, instability/ataxia and fatigue, and the most commonly reported AEs leading to discontinuation (≥2% of patients in any group) were dizziness and fatigue. In patients who received ESL as monotherapy, either as initial treatment or at the last visit, no individual AE led to discontinuation of ≥2% of patients.

The incidences of hyponatremia and rash were low, although, in general, slightly higher in patients who received ESL as adjunctive therapy versus monotherapy (Table 4). Similarly, hyponatremia and rash led to discontinuation of a low proportion of patients (<2% across subgroups), although the rates of discontinuation were higher

TABLE 2 Patient demographics and baseline characteristics of patients treated with ESL as initial adjunctive therapy who did and did not subsequently withdraw to ESL monotherapy

	Withdrawal from ESL adjunctive therapy to ESL monotherapy	ESL adjunctive therapy throughout follow-up	*P*-value[a]
Baseline demographics			
Sex			
N[b]	199	1109	0.006[c]
Male, n (%)	121 (60.8)	557 (50.2)	
Female, n (%)	78 (39.2)	552 (49.8)	
Age			
N[b]	199	1109	0.006[d]
Mean (SD), years	47.2 (18.6)	43.4 (15.2)	
Median (range), years	47.0 (17.0-87.0)	41.3 (15.0-88.0)	
Epilepsy-related characteristics			
Age at onset of epilepsy			
N[b]	198	1066	<0.001[e]
Mean (SD), years	34.3 (22.8)	21.4 (18.3)	
Median (range), years	28.0 (0.0-87.0)	17.0 (0.0-87.0)	
Duration of epilepsy			
N[b]	198	1066	<0.001[e]
Mean (SD), years	13.1 (15.3)	21.9 (16.6)	
Median (range), years	8.0 (0.0-70.5)	19.0 (0.0-81.8)	
Etiology[f]			
N[b]	176	872	NS[c]
Structural-metabolic, n (%)	99 (56.3)	482 (55.3)	
Genetic, n (%)	3 (1.7)	17 (1.9)	
Unknown, n (%)	74 (42.0)	373 (42.8)	
Baseline seizure type			
Any partial seizure			
N[b]	199	1097	<0.001[c]
Yes, n (%)	167 (83.9)	1081 (98.5)	
Simple partial seizures			
N[b]	192	1097	NS[c]
Yes, n (%)	50 (26.0)	329 (30.0)	
Complex partial seizures			
N[b]	192	1097	<0.001[c]
Yes, n (%)	73 (38.0)	760 (69.3)	
Secondarily generalized seizures			
N[b]	192	1097	NS[c]
Yes, n (%)	73 (38.0)	443 (40.4)	
Baseline monthly seizure frequency			
Any partial seizure			
N[b]	167	1075	<0.001[e]
Mean (SD)	4.9 (22.2)	13.9 (50.4)	
Median (range	1.0 (0.1-240.0)	3.3 (0.1-1230.0)	
Simple partial seizures			

(Continues)

TABLE 2 (Continued)

	Withdrawal from ESL adjunctive therapy to ESL monotherapy	ESL adjunctive therapy throughout follow-up	*P*-value[a]
N[b]	49	298	0.001[e]
Mean (SD)	7.2 (22.0)	10.9 (23.3)	
Median (range)	1.7 (0.3-150.0)	3.1 (0.3-210.0)	
Complex partial seizures			
N[b]	71	703	0.001[e]
Mean (SD)	6.2 (28.4)	8.3 (22.1)	
Median (range)	1.7 (0.3-240.0)	3.0 (0.3-300.0)	
Secondarily generalized seizures			
N[b]	71	379	<0.001[e]
Mean (SD)	0.6 (0.5)	3.0 (7.1)	
Median (range)	0.3 (0.2-3.3)	1.0 (0.2-70.0)	
Comorbidities			
Intellectual disability			
N[b]	32	511	NS[c]
Yes, n (%)	1 (3.1)	51 (10.0)	
Psychiatric comorbidity[g]			
N[b]	159	635	0.035[c]
Yes, n (%)	42 (26.4)	120 (18.9)	
Depression			
N[b]	159	635	NS[c]
Yes, n (%)	15 (9.4)	59 (9.3)	
AED treatment			
Total number of previous AEDs			
N[b]	191	1087	<0.001[e]
Mean (SD)	1.4 (1.1)	4.1 (3.5)	
Median (range)	1.0 (0-10)	3.0 (0-20)	
Reason for ESL treatment initiation			
N[b]	193	812	<0.001[c]
Lack of effectiveness, n (%)	80 (41.5)	657 (80.9)	
Adverse reaction, n (%)	81 (42.0)	58 (7.1)	
Both, n (%)	16 (8.3)	87 (10.7)	
Other, n (%)	16 (8.3)	10 (1.2)	

AED, antiepileptic drug; ESL, eslicarbazepine acetate; NM, not measured; NS, not significant; SD, standard deviation.
[a]Withdrawal to ESL monotherapy versus ESL as adjunctive therapy throughout follow-up.
[b]Total number of patients for whom data in question were available.
[c]Chi-squared test.
[d]Student's *t* test.
[e]Mann–Whitney *U* test.
[f]International League Against Epilepsy 2010 classification.
[g]Including depression.

with adjunctive therapy than with monotherapy. Hyponatremia was reported in 68 patients in the total Euro-Esli population. Sodium levels were recorded for 52 of these patients, among whom the mean (SD) sodium level was 127.3 (4.5) mEq/L (median, 127.0; range, 117-137). A total of 15 patients had sodium levels <125 mEq/L recorded (range, 116-124 mEg/L). None of the patients treated with ESL as initial monotherapy or ESL monotherapy at the last visit had sodium levels <125 mEq/L recorded. One (1.2%) patient treated with ESL as initial monotherapy and none of the patients treated with ESL monotherapy at the last visit developed rash. Rash developed

in 43 (2.2%) patients treated with ESL as initial adjunctive therapy and 25 (2.3%) patients treated with ESL as adjunctive therapy at the last visit.

In the subanalysis of patients who received ESL as initial adjunctive therapy, the overall incidence of AEs was similar in patients who withdrew to ESL monotherapy and those who received ESL adjunctive therapy throughout follow-up (28.6% [57/199] vs 30.9% [342/1108]; $\chi^2 = 0.39$; P = not significant). However, the rate of ESL discontinuation due to AEs was significantly lower in patients who withdrew to ESL monotherapy compared with those who received ESL adjunctive therapy throughout follow-up (4.5% [9/199] vs 14.4% [158/1095]; $\chi^2 = 14.70$; $P < 0.001$).

4 | DISCUSSION

Euro-Esli is the largest ESL clinical practice study conducted to date.[8] The findings of this subanalysis of Euro-Esli data demonstrate that ESL monotherapy was effective when used under everyday clinical practice conditions in Europe. Responder and seizure freedom rates were higher in patients treated with ESL as monotherapy than in those treated with ESL as adjunctive therapy. The safety and tolerability of ESL were generally comparable in patients treated with ESL as monotherapy or adjunctive therapy.

The higher responder and seizure freedom rates observed in patients treated with monotherapy in comparison with adjunctive therapy are likely to have been because patients on monotherapy were less refractory to treatment and/or had less severe epilepsy than those who required adjunctive therapy. For example, subanalysis of patients who received ESL as initial adjunctive therapy demonstrated that those who subsequently withdrew to monotherapy, compared with those who received ESL adjunctive therapy throughout follow-up, had a significantly later onset of epilepsy, shorter duration of epilepsy, and lower baseline seizure frequency across all seizure types, and had been treated with significantly fewer previous AEDs. Similar patterns of difference were observed between patients who received ESL as initial monotherapy and those who received ESL as initial adjunctive therapy, and between patients who received ESL as monotherapy at the last visit and those who received ESL as adjunctive therapy at the last visit. Taken together, these findings appear to support the notion that patients treated with ESL monotherapy were either less refractory to treatment and/or had less severe epilepsy, or were being treated earlier in their disease course, than those who received ESL as adjunctive therapy. This hypothesis is supported by the findings of a previous subanalysis of Euro-Esli data, which demonstrated that responder and seizure rates were higher in patients treated with less than two versus two or more concomitant AEDs, where the number of concomitant AEDs was employed as a marker for treatment refractoriness.[8] It is also notable that the incidence of psychiatric comorbidity at baseline was higher in patients who received ESL as monotherapy than in those who received ESL as adjunctive therapy. Although the reasons for this are unclear, it might be hypothesized that clinicians specifically chose ESL as monotherapy for patients with psychiatric comorbidity, since it is associated with fewer psychiatric side effects than some other AEDs (eg, levetiracetam, topiramate, valproate).[1,22-24]

In terms of ESL dosing, it is important to point out that baseline dose levels used for ESL monotherapy and adjunctive therapy were only accurate for those patients initiating treatment with monotherapy and adjunctive therapy (since some patients treated with ESL as initial monotherapy would have subsequently received concomitant AED treatment and some of those treated with ESL as initial adjunctive therapy would have subsequently withdrawn to ESL monotherapy). Likewise, the ESL dose levels used as monotherapy and adjunctive therapy at the last visit were only accurate for the subgroups of patients who received ESL as monotherapy and adjunctive therapy at the last visit. Taking these factors into consideration, the mean (SD) dose of ESL used as monotherapy increased from 800.0 (253.0) mg/day at baseline to 878.9 (275.9) mg/day at the last visit, and the mean (SD) dose of ESL used as adjunctive therapy increased from 527.0 (247.7) mg/day at baseline to 962.2 (315.7) mg/day at the last visit. The relatively small increase in mean ESL dose when used as monotherapy, in comparison with adjunctive therapy, is likely to reflect the relatively high responder and seizure freedom rates observed in patients treated with ESL as monotherapy in comparison with adjunctive therapy, since patients experiencing inadequate seizure control were likely to have had their dosing increased. Tolerability is also generally better in the monotherapy setting, compared with the adjunctive therapy setting, regardless of the initial dosage. Therefore, patients treated with ESL as initial monotherapy may have been started on a higher dosage in order to reach therapeutic levels as soon as possible and/or because clinicians preferred to start treatment immediately at a therapeutic dosage (800 mg/day) and avoid titration. The duration of ESL treatment was shorter in patients who received monotherapy than in those who received adjunctive therapy. This is likely to be because the first patients included in this study were treated with ESL as adjunctive therapy (as happens with all AEDs), and there was a delay before ESL became consolidated as a viable treatment option as clinicians gained experience with the drug and subsequently started to use it as monotherapy. Furthermore, patients who are relatively early in their disease course (with a relatively short duration of treatment) are less likely to have relapsed than those with more long-standing epilepsy (with a longer duration of treatment), and are therefore more likely to be on monotherapy. The proportion of patients who discontinued ESL was also lower in patients who received ESL as monotherapy than in those who received ESL as adjunctive therapy, primarily because a higher proportion of patients treated with ESL as adjunctive therapy discontinued due to lack of efficacy. These findings again support the idea that patients who received ESL as adjunctive therapy were more refractory to treatment than those treated with ESL as monotherapy.

The proportion of patients treated with ESL as monotherapy increased from 4.3% at baseline to 17.1% at the last visit, consistent with the significant reduction in the number of concomitant AEDs patients used at the last visit, compared with baseline, previously

TABLE 3 Summary of ESL dosing

	ESL as initial monotherapy	ESL as monotherapy at last visit	ESL as initial adjunctive therapy	ESL as adjunctive therapy at last visit
Baseline				
N	6	171	813	623
Mean (SD) dose, mg/day	800.0 (253.0)	499.4 (185.8)	527.0 (247.7)	515.3 (235.8)
Median (range)	800 (400-1200)	400 (200-1200)	400 (150-1600)	400 (150-1600)
3 months				
N	17	165	910	650
Mean (SD) dose, mg/day	823.5 (299.0)	784.2 (216.4)	875.2 (271.2)	883.1 (266.0)
Median (range)	800 (400-1600)	800 (400-1600)	800 (400-2000)	800 (400-1600)
6 months				
N	16	191	1002	770
Mean (SD) dose, mg/day	900.0 (230.9)	851.8 (264.5)	947.9 (293.2)	965.1 (292.6)
Median (range)	800 (800-1600)	800 (400-2400)	800 (200-2800)	800 (200-2800)
12 months				
N	21	183	814	530
Mean (SD) dose, mg/day	895.2 (215.6)	862.3 (235.0)	1004.7 (307.2)	1022.6 (294.3)
Median (range)	800 (800-1600)	800 (400-1600)	800 (400-2400)	1200 (400-2400)
Last visit				
N	50	227	1857	1099
Mean (SD) dose, mg/day	1000.0 (315.6)	878.9 (275.9)	977.2 (329.8)	962.2 (315.7)
Median (range)	800 (400-1600)	800 (400-2400)	800 (200-2800)	800 (200-2800)
Maximum dose				
N	50	227	1857	1099
Mean (SD) dose, mg/day	1000.0 (315.6)	887.7 (266.6)	986.2 (327.2)	975.2 (313.8)
Median (range)	800 (400-1600)	800 (400-2400)	800 (300-2800)	800 (300-2800)

ESL, eslicarbazepine acetate; SD, standard deviation.

reported for the overall Euro-Esli population.[8] The decrease in use of concomitant AEDs and associated increase in the proportion of patients treated with monotherapy following ESL initiation are encouraging, since it is recommended that polytherapy levels be reduced wherever possible, due to the potentially increased risk of pharmacokinetic interactions and toxicity associated with an increased drug burden.[25-27] The study's findings appear to support the value of such a recommendation, because although the incidence of AEs was similar regardless of whether ESL was used as monotherapy or adjunctive therapy, the rate of ESL discontinuation due to AEs was lower in patients treated with ESL monotherapy at the last visit, compared with those treated with adjunctive therapy at the last visit. This may therefore reflect an improvement in overall tolerability as patients withdrew from AED polytherapy to monotherapy (since the majority of patients treated with ESL monotherapy at the last visit had previously received concomitant AED treatment[s] prior to withdrawing to ESL monotherapy). This idea is supported by the results of the subanalysis of patients who received ESL as initial adjunctive therapy, since the rate of ESL discontinuation was significantly lower in patients who did versus did not withdraw to ESL monotherapy. These findings are consistent with those of a previous Euro-Esli subanalysis, which demonstrated that the incidence of AEs leading to discontinuation (as well as the overall incidence of AEs) was significantly lower in patients treated with less than two concomitant AEDs than in those treated with two or more concomitant AEDs.[8] In the current study, the most commonly reported AEs (dizziness, somnolence, instability/ataxia, fatigue) and AEs leading to discontinuation (dizziness and fatigue) were generally typical of those associated with sodium channel modulation (ESL's primary mechanism of action) and consistent with ESL's known safety profile.[1,26] For example, in the phase III monotherapy trial conducted in patients with newly diagnosed epilepsy, the most frequently reported ESL-related AEs (≥5% of patients) were dizziness, headache, somnolence, and fatigue, and the AEs that most frequently led to ESL discontinuation (≥1% of patients) were fatigue, nausea, dizziness, somnolence, and rash.[2] Combining drugs that block voltage-dependent sodium channels is known to increase the likelihood of neurotoxic side effects (such as dizziness).[26] Therefore, it is perhaps unsurprising that the incidence of AEs leading to discontinuation was higher when ESL was used as adjunctive therapy versus monotherapy, since sodium channel blocking is the most common mechanism of

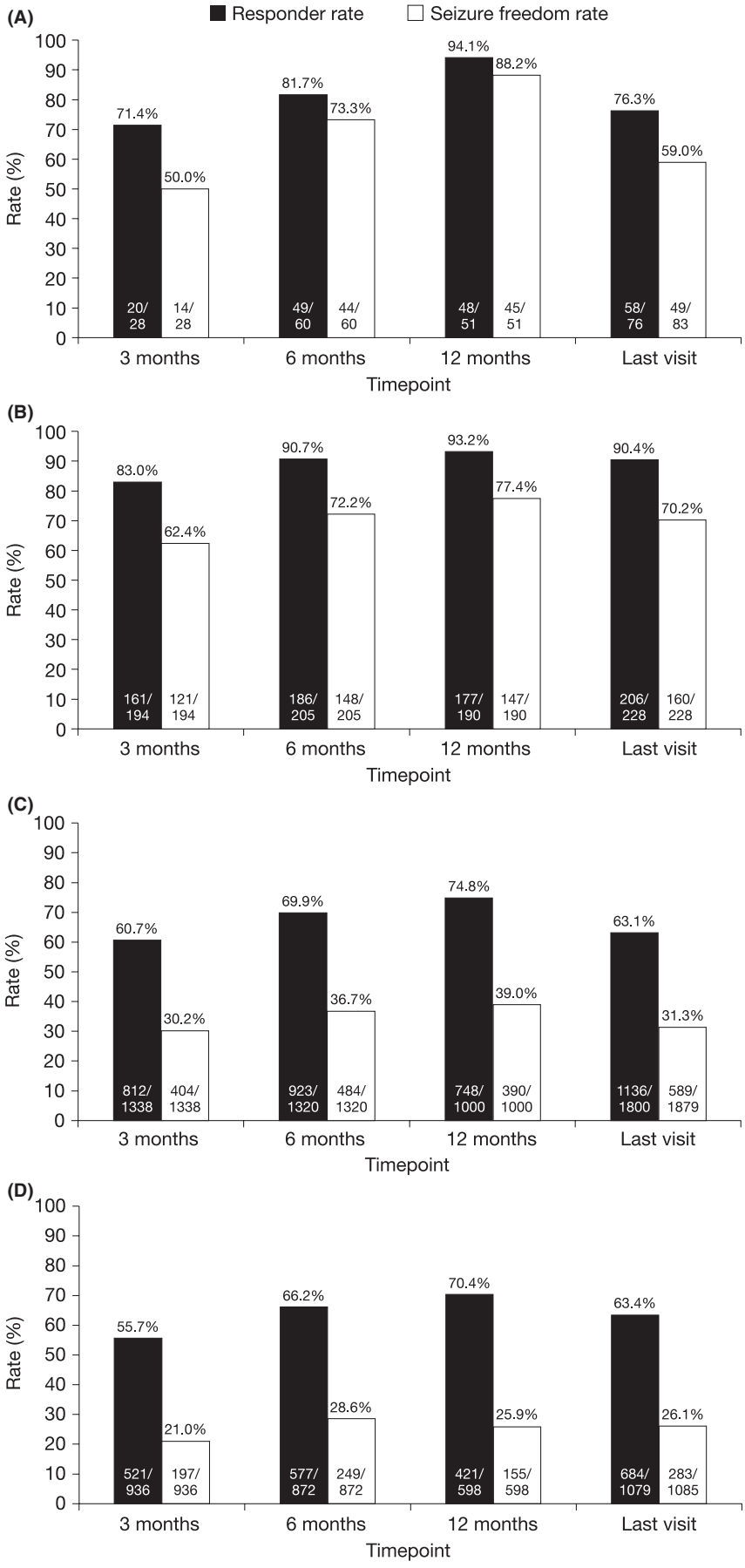

FIGURE 1 Responder and seizure freedom rates at 3 months, 6 months, 12 months and the last visit for (A) patients who received ESL as initial monotherapy, (B) patients who received ESL as monotherapy at the last visit, (C) patients who received ESL as initial adjunctive therapy and (D) patients who received ESL as adjunctive therapy at the last visit. Response was defined as ≥50% seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit

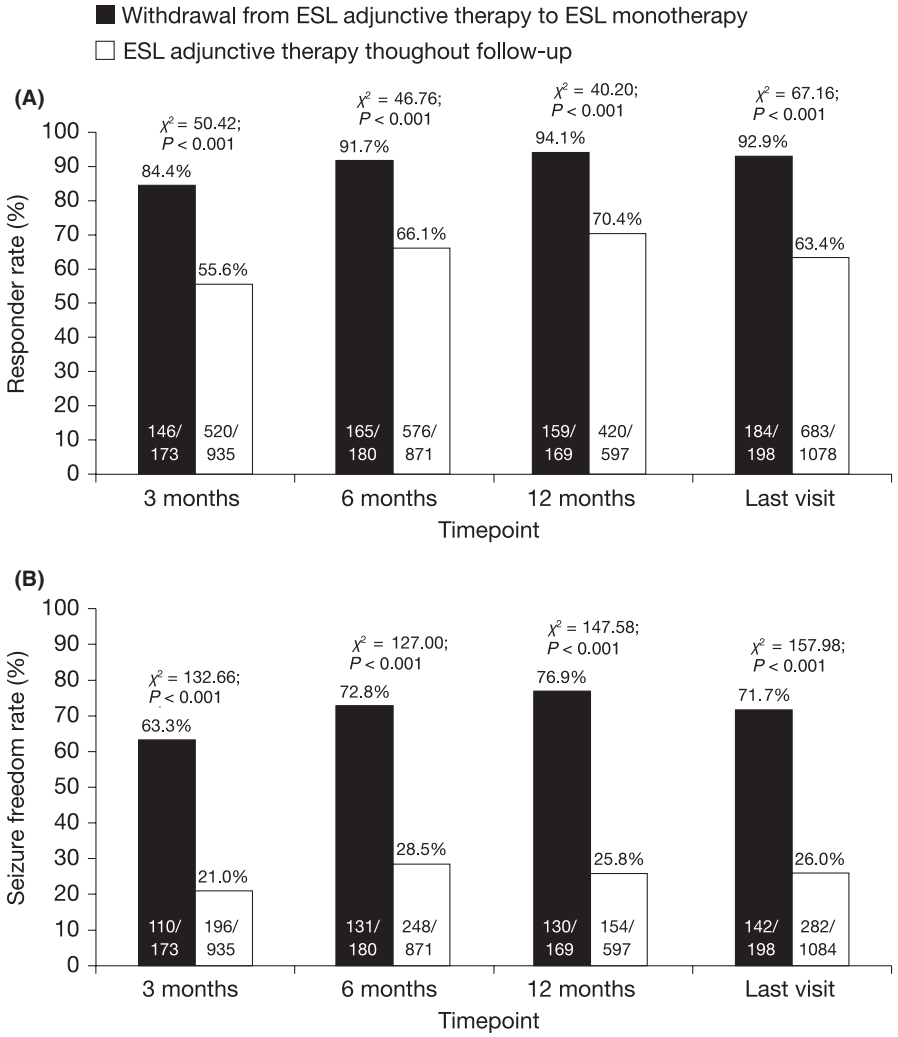

FIGURE 2 Subanalysis of patients who received ESL as initial adjunctive therapy: responder rates (A) and seizure freedom rates (B) at 3 months, 6 months, 12 months and the last visit for patients who withdrew to ESL monotherapy and those who received ESL as adjunctive therapy throughout follow-up. Response was defined as ≥50% seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit

action among currently available AEDs.[26] This is supported by a previously reported subanalysis of Euro-Esli, which compared data from patients using other sodium channel blockers with those not using other sodium channel blockers.[8] This found that the overall incidence of AEs was similar between the groups, but the rate of discontinuation due to AEs was significantly higher in patients treated with other sodium channel blockers versus those who were not.[8] Overall, no new or unexpected safety signals emerged in either the monotherapy or adjunctive therapy settings in the current study.

The findings of this study complement evidence from clinical trials, which have demonstrated that ESL is efficacious and generally well tolerated when used as initial monotherapy in patients with newly diagnosed focal-onset seizures,[2] and when used in patients with uncontrolled focal-onset seizures who have withdrawn to ESL monotherapy following treatment with other AEDs.[3,4] In the current analysis, the seizure freedom rates at 6 months for patients treated with ESL as monotherapy at the last visit (72.2%) and those who withdrew from ESL adjunctive therapy to ESL monotherapy (72.8%) were similar to the 26-week seizure freedom rate observed in the phase III monotherapy trial conducted in patients with newly diagnosed epilepsy (71.1%).[2] Moreover, the median ESL dose at 6 months in patients treated with ESL as monotherapy at the last visit (800 mg/day) was the same as the target ESL dose achieved by the majority of patients in the phase III trial, and the rates of hyponatremia were also comparable (2.6% in the current analysis, 2.5% in the phase III trial).[2] In the current analysis, the incidences of TEAEs and TEAEs leading to discontinuation were lower in patients treated with ESL as monotherapy at the last visit (27.1% and 4.8%, respectively) and in those who withdrew from ESL adjunctive therapy to ESL monotherapy (28.6% and 4.5%, respectively) than in those treated with ESL monotherapy in the phase III trial (76.3% and 14.0%, respectively),[2] which is likely to reflect the more individualized approach to treatment adopted in clinical practice in comparison with clinical trials.

The overall seizure freedom rates for patients treated with ESL as monotherapy at the last visit (70.2%) and patients who withdrew from ESL adjunctive therapy to ESL monotherapy (71.7%) in the current analysis were substantially higher than the seizure freedom rates observed in the phase III withdrawal to monotherapy trials conducted in patients with uncontrolled focal-onset seizures (13.3%-17.0% during last 4 weeks of monotherapy).[3,4] Similarly, the overall responder rates for patients treated with ESL as monotherapy

TABLE 4 Summary of AEs and AEs leading to discontinuation

	ESL as initial monotherapy	ESL as monotherapy at last visit	ESL as initial adjunctive therapy	ESL as adjunctive therapy at last visit
AEs				
N	85	229	1933	1109
Patients with any AE, n (%)	25 (29.4)	62 (27.1)	665 (34.4)	342 (30.8)
Most frequently reported AEs,[a] n (%)				
Dizziness	1 (1.2)	9 (3.9)	131 (6.8)	67 (6.0)
Somnolence	3 (3.5)	13 (5.7)	97 (5.0)	52 (4.7)
Instability/ataxia	7 (8.2)	1 (0.4)	59 (3.1)	17 (1.5)
Fatigue	2 (2.4)	5 (2.2)	103 (5.3)	39 (3.5)
AEs of special interest[c]				
Hyponatremia[d]	0	6 (2.6)	68 (3.5)	28 (2.5)
Hyponatremia (sodium level <125 mEq/L)	0	0	15 (0.8)	7 (0.6)
Rash	1 (1.2)	0	43 (2.2)	25 (2.3)
AEs leading to discontinuation				
N	82	228	1867	1096
Patients with any AE leading to discontinuation, n (%)	8 (9.8)	11 (4.8)	259 (13.9)	158 (14.4)
Most frequently reported AEs leading to discontinuation,[b] n (%)				
Dizziness	0 (0.0)	1 (0.4)	46 (2.5)	29 (2.6)
Fatigue	1 (1.2)	0	38 (2.0)	14 (1.3)
AEs of special interest leading to discontinuation[c]				
Hyponatremia[d]	0	2 (0.9)	19 (1.0)	12 (1.1)
Rash	1 (1.2)	0	29 (1.6)	21 (1.9)

AE, adverse event; ESL, eslicarbazepine acetate
[a]≥5% of patients in any group.
[b]≥2% of patients in any group.
[c]Any patients in any group.
[d]As reported by participating clinicians. Sodium levels were recorded for 52/68 patients reported as having hyponatremia; mean (SD) sodium level in these 52 patients was 127.3 (4.5) mEq/L (median, 127.0; range, 117-137).

at the last visit (90.4%) and patients who withdrew from ESL adjunctive therapy to ESL monotherapy (92.9%) in the current analysis were substantially higher than the responder rates observed in the phase III withdrawal to monotherapy trials (32.2%-46.0% during 10-week monotherapy treatment periods).[3,4] These findings are perhaps unsurprising since the phase III withdrawal to monotherapy trials was conducted using a design in which baseline concomitant AEDs were down-titrated and withdrawn regardless of patients' prior response to treatment or clinical characteristics, and which therefore differed fundamentally from the individualized approach to treatment used in clinical practice (ie, as used in the studies included in Euro-Esli). The similar seizure freedom rates observed in the current study and the phase III trial of ESL as initial monotherapy in patients with newly diagnosed focal-onset seizures[2] may nevertheless provide further evidence to suggest that the patients treated with ESL monotherapy in Euro-Esli were likely to have mostly comprised newly diagnosed patients, rather than patients with more long-standing, refractory focal epilepsy.

The findings of the study are also consistent with those of a recent multicenter, prospective, clinical practice study, conducted in 17 hospitals in Spain, in which 117 patients with focal seizures, aged 9-87 years, were treated with ESL monotherapy.[28] The responder rates (where response was defined as ≥50% seizure frequency reduction) after 3, 6, and 12 months were 82.0%, 79.7% 83.0%, respectively[28] (the corresponding responder rates in patients who received monotherapy at the last visit in the current study were 83.0%, 90.7%, and 93.2%, respectively, and in those who withdrew from ESL adjunctive therapy to ESL monotherapy, the corresponding values were 84.4%, 91.7%, and 94.1%, respectively). AEs were reported by 15.3% of patients and those reported by more than one patient comprised instability and dizziness (n = 9), somnolence (n = 3), and mild hyponatremia (n = 3).[28]

It is difficult to directly compare the findings of the current analyses with those of studies that have assessed the effectiveness of monotherapy with other AEDs in clinical practice, primarily due to differences in study designs and patient populations. Some studies

have reported outcomes for the use of monotherapy with another member of the dibenzazepine family of AEDs, oxcarbazepine, in the clinical practice setting.[29,30] For example, in a retrospective evaluation of 61 outpatients, aged ≥16 years, with focal or generalized epilepsy (simple or complex partial seizures, with or without secondary generalization, and generalized seizures induced by sleep) who were treated with oxcarbazepine in clinical practice in Italy, 12-month seizure freedom rates were 76.9% in patients treated with oxcarbazepine monotherapy (n = 52) and 11.1% in those treated with oxcarbazepine as adjunctive therapy (n = 9).[29] Furthermore, several studies have assessed the effectiveness of monotherapy with another sodium channel blocker, lacosamide, in clinical practice.[31-33] In a retrospective, non-interventional chart review of 439 patients with focal seizures, aged ≥16 years, who were treated with lacosamide monotherapy according to standard clinical practice in Italy, Spain, and the Netherlands, 6-month seizure freedom rates were 66.3% in patients treated with lacosamide as initial monotherapy and 63.0% in those who converted to lacosamide monotherapy from another AED, and the corresponding 12-month seizure freedom rates were 60.2% and 52.5%, respectively.[31] Even considering the limited comparability of these studies to the current data, ESL seems to be at least as effective as other sodium channel blockers.

The current analyses were limited because the monotherapy and adjunctive therapy subgroups were not "pure" throughout the duration of follow-up, since some patients initially treated with monotherapy or adjunctive therapy converted to adjunctive therapy or monotherapy, respectively, during the course of the study, but were included in the subgroup to which they were initially allocated for the purposes of "initial treatment" analyses. Similarly, some of the patients treated with monotherapy and adjunctive therapy at the last visit were previously treated with adjunctive therapy and monotherapy, respectively, but were included in the subgroup that applied to them at the last visit (ie, monotherapy or adjunctive therapy) for all the "treatment at last visit" analyses. These limitations are, however, vindicated by the results of the subanalysis of patients treated initially with ESL adjunctive therapy who did and did not subsequently withdraw to ESL monotherapy, since these were consistent with the other findings of the study. As with the overall Euro-Esli study,[8] the study has additional limitations, primarily because it was a subanalysis of a retrospective pooled analysis. Moreover, there was great heterogeneity in the studies included in Euro-Esli, and although individual patient data were previously reviewed by the authors of the individual studies, they were not reviewed systematically post hoc.[8] The heterogeneous nature of the studies included in Euro-Esli also meant that, across all endpoints and assessments, data were not available for all patients at all timepoints. However, the large number of patients included in Euro-Esli allowed a meaningful number of patients to be assessed in the current analysis, mitigating some of these limitations.

In summary, taking into account the aforementioned limitations, these findings provide further evidence supporting the use of ESL as monotherapy, as well as adjunctive therapy, for focal-onset seizures, complementing evidence from regulatory clinical trials.

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CONFLICT OF INTEREST

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