


Pooled efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Data from four double-blind placebo-controlled pivotal phase III clinical studies

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Summary

Purpose: Pooled evaluation of the key efficacy and safety profile of eslicarbazepine acetate (ESL) added-on to stable antiepileptic therapy in adults with focal-onset seizures.

Methods: Data from 1703 patients enrolled in four phase III double-blind, randomized, placebo-controlled studies were pooled and analyzed. Following a 2 week titration period, ESL was administered at 400 mg, 800 mg, and 1200 mg once-daily doses for 12 weeks (maintenance period). Pooled efficacy variable was standardized (/4 weeks) seizure frequency (SSF) analyzed over the maintenance period as reduction in absolute and relative SSF and proportion of responders ($\geq 50\%$ reduction in SSF). Pooled safety was analyzed by means of adverse events and clinical laboratory assessments.

Results: SSF was significantly reduced with ESL 800 mg ($P < 0.0001$) and 1200 mg ($P < 0.0001$) compared to placebo. Median relative reduction in SSF was 33.4% for ESL 800 mg and 37.8% for 1200 mg (placebo: 17.6%), and responder rate was 33.8% and 43.1% (placebo: 22.2%). ESL was more efficacious than placebo regardless of gender, geographical region, epilepsy duration, age at time of diagnosis, seizure type, and type of concomitant antiepileptic drugs (AED). Incidence of adverse events (AEs) and

AEs leading to discontinuation was dose dependent. Most common AEs (>10% patients) were dizziness, somnolence, and nausea. The incidence of treatment-emergent AEs (dizziness, somnolence, ataxia, vomiting, and nausea) was lower in patients who began taking ESL 400 mg (followed by 400 mg increments to 800 or 1200 mg) than in those who began taking ESL 600 mg or 800 mg.

Conclusions: Once-daily ESL 800 mg and 1200 mg showed consistent results across all efficacy and safety endpoints, independent of study population characteristics and type of concomitant AEDs. Treatment initiated with ESL 400 mg followed by 400 mg increments to 800 or 1200 mg provides optimal balance of efficacy and tolerability.

KEYWORDS

adjunctive therapy, adults, antiepileptic drugs, eslicarbazepine acetate, focal-onset seizures, refractory epilepsy

1 | INTRODUCTION

Eslicarbazepine acetate (ESL) is a once-daily antiepileptic drug (AED) that has been approved by the European Medicines Agency (EMA), Food and Drug Administration (FDA) and Health Canada, as adjunctive therapy in adults with focal-onset seizures (FOS). Subsequently, both EMA and FDA approved ESL for monotherapy in the treatment of FOS in patients with epilepsy 18 years and older. ESL has also been approved by EMA as adjunctive therapy in children aged above 6 years old with FOS.

The adjunctive therapy program in adult patients with FOS included four pivotal, phase III, multicentre, randomized, double-blind, and placebo-controlled clinical trials: Studies BIA-2093-301 (NCT00957684), -302 (NCT00957047), -303 (NCT00957372), and -304 (NCT00988429). All studies followed a similar design with ESL administered at once-daily doses for 12 weeks (maintenance period). The only major differences in study designs were the number of ESL doses tested and the titration and tapering-off regimens (Figure 1). Studies BIA-2093-301 and -302 had three ESL dose groups (400 mg,

800 mg or 1200 mg once-daily), while study -303 and -304 had only two (800 mg or 1200 mg once-daily). The main results of each individual study have been published elsewhere.¹⁻⁴

To better understand the efficacy and safety profile of ESL in a broader population and to perform additional analyses in patient subpopulations, data from the four studies were pooled and analyzed. The results of this integrated analysis, which had been planned in the study protocols, and are reported here, had three key variables to assess efficacy over the 12-week maintenance period: (i) standardized seizure frequency (the primary efficacy variable), (ii) relative change in seizure frequency, and (iii) the responder rate ($\geq 50\%$ reduction in seizure frequency). However, as major protocol violations raised doubts on the reliability of the study results in Study BIA-2093-303 (included in the supplementary information),⁵ the main results of the present combined analysis are displayed with and without Study -303. In fact, Study -303 was endowed with a difference between intention-to-treat (ITT) and per-protocol (PP) populations (96.8% vs 56.6%) larger than in the other 3 studies (301 [98.8% vs 85.3%], 302 [99.5% vs 70.9%] and 304 [98.0% vs 83.8%]). Moreover, study 304⁴ is the only

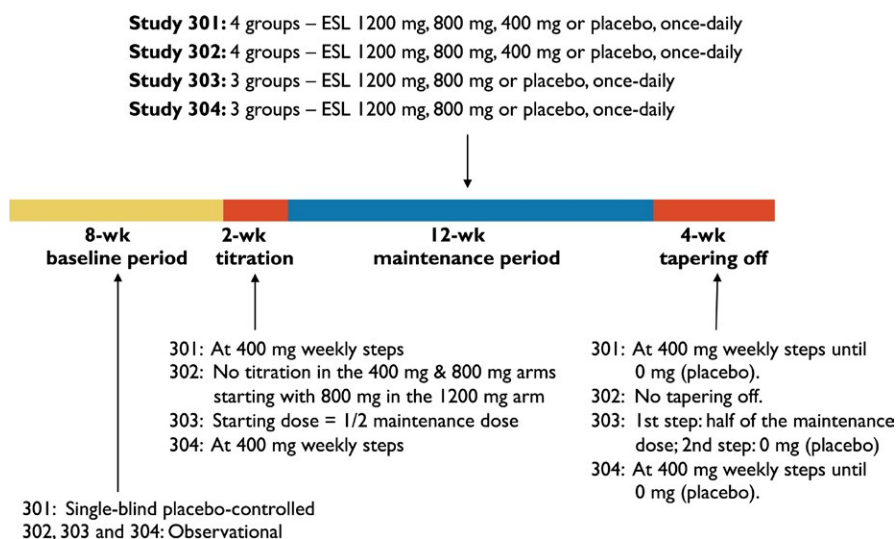


FIGURE 1 Study design

adjunctive ESL trial to include North American patients, and data from this trial were not part of the Gil-Nagel et al's pooled analysis.⁶ Also, the current pooled analysis allows the assessment of detailed safety data by titration regimen and efficacy by other subgroups.

2 | PATIENTS AND METHODS

Men and women of age ≥ 18 years (16 years or more in study 304) with simple or complex partial seizures (ie focal seizures according to the new classification of the International League Against Epilepsy) evolving or not to a generalized convulsive seizure for at least twelve months before screening, who had at least four partial seizures (three for study 304) in each 4 week period during the 8 weeks prior to screening, treated with up to three AEDs (any except oxcarbazepine [OXC] and felbamate) or vagus nerve stimulation (VNS) plus 1 AED, and had a stable dose of AEDs for at least 2 months (1 month for study 304) prior to screening (vigabatrin should have been stable for at least 1 year with no deficit in visual field based on a confirmatory test from within 1 month before study entry). Patients taking felbamate were excluded due to safety reasons. OXC was not allowed as concomitant AED as it shares the pharmacologically active main metabolite with ESL. Patients with known hypersensitivity to carbamazepine (CBZ) or OXC were excluded. Patients were excluded if they had simple partial seizures with no motor symptomatology and purely subjective symptoms that were not video-electroencephalogram documented, primarily generalized seizures, known rapid progressive neurological disorder, or a history of status epilepticus or cluster seizures (ie three or more seizures within 30 minutes) within the 3 months prior to screening. Patients were also excluded if they had seizures of psychogenic origin within the last 2 years, a history of schizophrenia or suicide attempt, been exposed to felbamate or OXC within 1 month of screening, or had used benzodiazepines on more than an occasional basis (except when used chronically as AED). Furthermore, uncontrolled cardiac, renal, hepatic, endocrine, gastrointestinal, metabolic, hematological or oncology disorders, second or third-degree atrioventricular blockade not corrected with a pacemaker, relevant clinical laboratory abnormalities (eg Na^+ <130 mEq/L, alanine or aspartate transaminases >2.0 times the upper limit of normal, white blood cell count <3000 cells/mm³), or an estimated creatinine clearance <50 mL/min (<60 mL/min in study 304) led to subject exclusion. Efficacy data were documented by means of diaries in which patients were to record all seizures by type, including date and time of their occurrence. In studies 301, 302, and 303, event diaries were used, and patients or their caregivers were not asked to confirm periods without seizures; it was assumed that no seizures occurred on study days without actively reported seizures. In study 304, event diaries and daily diaries were used. If the diary was returned and there was no seizure information available for a particular day, it was assumed as missing seizure data and the day was then excluded from the calculation of the primary endpoint. The studies were approved by the appropriate independent ethics

committees or institutional review boards and were conducted according to the international and local regulations of the countries where they were performed. Patients gave their written informed consent prior to enrolment.

The primary efficacy variable, in each of the individual studies and also for the integrated analyses, was the standardized (per 4 weeks) seizure frequency (SSF) over the 12-week maintenance period. The predefined key efficacy endpoints were reduction in absolute and relative SSF during the 12 week maintenance and proportion of responders ($\geq 50\%$ reduction in SSF). Absolute and relative reduction in SSF was compared among the treatment groups using analyses of covariance (ANCOVA) that modeled the logarithm of the variable as a function of study, baseline seizure frequency, number of concomitant AEDs at baseline and treatment (with and without treatment-by-study interaction). The model with interaction was restricted to placebo, ESL 800 mg and 1200 mg. The effect of treatment in responders was evaluated using a Cochran-Mantel-Haenszel (CMH) test stratified by study factor with chi-square. Results for all three key efficacy variables are presented for the intention-to-treat (ITT) and the per-protocol (PP) populations. In addition to these analyses, several other models were used to confirm the robustness of the findings. Other secondary efficacy outcomes included relative reduction in seizure frequency and responder rate per week, categorized relative change in seizure frequency (seizure reduction $<25\%$, 25% to $<50\%$, 50% to $<75\%$ and $\geq 75\%$, exacerbation $<25\%$ and $\geq 25\%$), number of days with seizures, and proportion of seizure-free patients (100% seizure reduction). The interaction effect of ESL and concomitant AEDs taken by at least approximately 20% of patients (carbamazepine, lamotrigine, and valproic acid) was also pooled and analyzed by an ANCOVA that modeled SSF as a function of ESL dose, study, baseline seizure frequency, concomitantly given AED, and treatment by concomitant AED interaction. Additional efficacy outcomes included the number of days with seizures and the proportion of seizure-free patients.

Safety data included adverse events (AEs) reporting as well as clinical laboratory tests (hematology, coagulation, biochemistry, thyroid function, and urinalysis). All AEs were recorded by the investigator and assessed with regards to severity (mild, moderate, or severe), causality, and seriousness. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 (for studies 301, 302, and 303) or 13.1 (for Study 304).

3 | RESULTS

3.1 | Analysis of populations

In the 4 Phase III studies combined, 1703 patients were randomized and 1675 received at least one dose of study drug (ITT population). A total of 1303 patients (77.8% ITT) completed the maintenance period without any major protocol violations, compared to 79.7% in the placebo group. The percentage of patients who completed the maintenance period without major protocol violations decreased with increasing dose of ESL, ranging from 83.7% in the 400 mg group to 68.4% in the 1200 mg group. A description of major protocol

violations is provided as supplementary information for each specific study.

Main baseline population characteristics are presented in Table S1. The population in the four studies was predominantly Caucasian (71.7% in the placebo group, 75.0% in the total ESL group) and approximately 11% Hispanic in each group (except for the ESL 400 mg group as studies 303 and 304 did not have a 400 mg group, and 303 was the only study to include Mexico). There were no relevant differences in the demographic and other baseline characteristics between the individual treatment groups. The population was approximately 50% male with a mean age of 38 years and a mean Body Mass Index of 25 kg/m². The disease characteristics at baseline were similar in each of the treatment groups. The mean duration of disease was 22 years, mean age at onset was approximately 15 years, and the majority of patients (>86% per group) did not have a family history of epilepsy. The overall seizure frequency at baseline was about 15 seizures per 4 weeks in all treatment groups. Most of these were either simple partial or complex partial, and the frequency for each seizure type was also similar in each of the treatment groups (Table S2). All patients but five were taking at least one concomitant AED at the end of the baseline period (majority were under two AEDs in parallel, Table S3). The most common AEDs being taken at the end of the baseline period were CBZ (>48% in any group), lamotrigine (LTG) (>20% in any group), and valproic acid (VPA) (>18% in any group). Table S3 lists concomitant AEDs taken by more than 3% of patients in any treatment group. During the baseline period of the studies, AEDs were discontinued only for 2.0% of patients on placebo, 2.1% of patients on ESL 400 mg, 2.6% of patients on ESL 800 mg, and 2.1% of patients on ESL 1200 mg.

3.2 | Efficacy Results

The median SSF at baseline (Table 1) was similar between the full (Studies 301 + 302 + 303 + 304 pooled: 7.6 to 8.4) or partial (only Studies 301 + 302 + 304 pooled: 8.0 to 8.5) integrated dataset of the ITT population. At the end of the maintenance period, the median SSF was lowest in the ESL 1200 mg group (full pooled analysis: 4.8; partial pooled analysis: 5.3) and highest in the placebo group (full: 6.9; partial: 7.0) (Table 1). The ANCOVA of SSF is presented in Table S4. Compared to the placebo group the change in SSF during the maintenance period was statistically significant for the ESL 800 mg and 1200 mg groups in the ITT and PP populations (Figure 2A for full and Figure 2B for partial integrated analysis; see also Table S4). In the full ITT integrated ANCOVA analysis, the least square (LS) mean SSF was lowest in the ESL 1200 mg group (6.11) and highest in the placebo group (7.95). In the partial ITT integrated analysis, the LS mean SSF was also lowest in the ESL 1200 mg group (6.35) and highest in the placebo group (8.27) (Figure 2A for full and Figure 2B for partial integrated analysis; see also Table S4).

The LS means and 95% confidence intervals (CI) of relative reduction in SSF over the 12-week maintenance period are displayed in Figures 2C and D for full and partial integrated analysis, respectively. The relative reduction in SSF during the maintenance period was significantly higher ($P < 0.0001$) for the ESL 800 mg and 1200 mg groups

compared to the placebo group in both the ITT and PP populations (Figures 2C and D for full and partial integrated analysis, respectively). In the full integrated analysis, the median relative change was -17.6% in the placebo group compared to -23.4% in the ESL 400 mg group, -33.4% in the ESL 800 mg group, and -37.8% in the ESL 1200 mg group (Figure 2C). In the partial integrated ANCOVA analysis, the change of LS mean was also greatest in the ESL 1200 mg group (-36.6) and lowest in the placebo group (-17.3) (Figure 2D).

Figures 2E and F presents the percentage of responders (patients with $\geq 50\%$ decrease in SSF relative to baseline). The responder rate was significantly higher in the ESL 800 mg and 1200 mg groups than in the placebo group in each of the 4 studies as well as either in the full or partial integrated analyses. In either full or partial integrated analyses, the difference to placebo was statistically significant ($P \leq 0.0001$) for the ESL 800 mg and 1200 mg groups; the difference between the ESL 400 mg group and placebo was not statistically significant. The responder rate for ESL 400 mg was 22.9% for full and for partial integrated analyses, for ESL 800 mg was 33.8% for full and 33.2% for partial integrated analyses, and for ESL 1200 mg 43.1% and 43.0%, respectively (placebo: 22.2% and 21.2%).

In the full integrated analysis, a larger proportion of patients had a reduction in SSF of 25% or more in the ESL 800 mg (58.3%) and ESL 1200 mg group (60.4%) compared to placebo patients (43.0%). An exacerbation of seizure frequency was observed in less than 24% of patients for any ESL group, but in 33.4% of placebo patients (Figure 2G). In the partial integrated analysis, a larger proportion of patients had a reduction in SSF of 25% or more in the ESL 800 mg (57.1%) and ESL 1200 mg group (60.5%) compared to placebo patients (41.9%), while less than 24% of patients in any ESL group had an exacerbation of SSF compared to 33.0% of placebo patients (Figure 2H). Analyses performed to demonstrate the robustness of the findings for SSF were consistent with the results shown above for Model I without treatment-by-study interaction. There was no indication that the treatment effect was different across studies.

The ANCOVA of SSF by seizure type showed a difference compared to placebo that was statistically significant at ESL 800 mg ($P = 0.0096$) for simple partial seizures, at both ESL 800 mg ($P = 0.0108$) and 1200 mg ($P < 0.0001$) for complex partial seizures, and at ESL 1200 mg ($P = 0.0101$) for partial seizures evolving to secondarily generalized (Figure S1). A dose-dependent and statistically significant difference for both ESL 800 mg and 1200 mg compared to placebo for simple partial and complex partial seizures was observed in the previous pooled analysis conducted with studies 301, 302, and 303. The inclusion of study 304 data appears to have an impact for this particular analysis. Although the influence of geographic region on treatment response was found not to be statistically significant ($P = 0.38$), in the North American subgroup, there was no statistically significant difference in seizure frequency between the both 800 and ESL 1200 mg and placebo. In the rest of the world subgroup, seizure frequency was significantly lower in both the 800 mg and ESL 1200 mg than the placebo group [5].

In the full pooled ITT population, at baseline the mean \pm SD (median) number of days with seizures per 4 weeks was 8.7 ± 6.1 (6.2) for

TABLE 1 Standardized seizure frequency (ITT population)

Study/ Treatment	Baseline period			Maintenance period		
	N	Mean±SD	Median	N	Mean±SD	Median
301						
Placebo	102	12.4 ± 17.9	6.7	99	11.1 ± 17.2	6.7
ESL 400 mg	99	11.4 ± 9.7	7.5	97	8.9 ± 9.5	5.7
ESL 800 mg	98	11.2 ± 11.2	7.0	94	7.1 ± 8.1	4.8
ESL 1200 mg	98	11.6 ± 15.9	7.5	94	8.1 ± 15.5	4.7
302						
Placebo	100	13.5 ± 14.3	7.5	99	12.8 ± 15.0	7.0
ESL 400 mg	96	14.6 ± 19.0	8.3	95	12.3 ± 15.9	6.9
ESL 800 mg	100	15.8 ± 15.6	9.3	88	12.6 ± 19.5	5.7
ESL 1200 mg	97	15.8 ± 16.1	9.5	86	11.0 ± 12.1	6.2
303						
Placebo	84	12.9 ± 18.3	6.5	81	11.2 ± 21.6	5.7
ESL 400 mg	-	-	-	-	-	-
ESL 800 mg	84	13.1 ± 18.6	7.8	80	9.7 ± 14.4	4.6
ESL 1200 mg	77	12.1 ± 12.8	6.0	73	7.8 ± 10.5	3.7
304						
Placebo	220	16.3 ± 19.3	9.0	212	13.0 ± 16.7	7.4
ESL 400 mg	-	-	-	-	-	-
ESL 800 mg	215	18.2 ± 34.5	8.6	200	13.7 ± 27.2	5.6
ESL 1200 mg	204	17.2 ± 21.1	8.9	184	12.0 ± 16.8	5.5
Integrated 301 + 302 + 303 + 304 studies						
Placebo	506	14.4 ± 18.0	7.6	491	12.3 ± 17.4	6.9
ESL 400 mg	195	13.0 ± 15.1	8.0	192	10.6 ± 13.1	5.9
ESL 800 mg	497	15.5 ± 25.5	8.0	462	11.5 ± 21.2	5.2
ESL 1200 mg	476	15.0 ± 18.1	8.4	437	10.3 ± 14.8	4.8
Integrated 301 + 302 + 304 studies						
Placebo	422	14.7 ± 17.9	8.1	410	12.5 ± 16.4	7.0
ESL 400 mg	195	13.0 ± 15.1	8.0	192	10.6 ± 13.1	5.9
ESL 800 mg	413	16.0 ± 26.7	8.1	382	11.8 ± 22.3	5.3
ESL 1200 mg	399	15.5 ± 18.9	8.5	364	10.8 ± 15.5	5.3

ITT, intention-to-treat; N, total number of subjects; SD, standard deviation; ESL, eslicarbazepine acetate.

placebo, 8.5 ± 5.6 (6.5) for the ESL 400 mg group, 8.9 ± 6.3 (6.6) for ESL 800 mg and 8.9 ± 6.3 (6.5) for ESL 1200 mg. During the maintenance period, the mean±SD (median) number of days with seizures per 4 weeks, during the maintenance period, decreased to 7.3 ± 6.2 (5.3) for placebo, 7.0 ± 5.8 (5.1) for ESL 400 mg, 6.5 ± 6.3 (4.3) for ESL 800 mg and 6.5 ± 6.4 (4.2) for ESL 1200 mg. The decrease in the number of days with seizures was statistically significant in the ESL 800 mg once-daily ($P = 0.0005$) and ESL 1200 mg once-daily ($P = 0.0001$) groups, when compared to placebo. During the maintenance period, the proportion of patients who were seizure-free increased with increasing dose of ESL, from 2.0% for the ESL 400 mg group, 3.7% for the ESL 800 mg group to 5.7% for the ESL 1200 mg group, compared to 2.0% for placebo.

Regardless of whichever concomitant baseline AEDs were used, efficacy of ESL 800 mg and 1200 mg was demonstrated during the

maintenance period. For either the full or partial pooled data, median relative reduction in SSF by ESL was similar in patients taking CBZ or not (Figure S2). The median relative reduction in SSF was almost identical between patients taking and not taking LTG (Figure S2), and between patients taking or not taking VPA (Figure S2). These results are consistent with those reported for the responder rates.

The median relative reduction in SSF in men (placebo: 19.0%, ESL 400 mg: 22.7%, ESL 800 mg: 36.0%, ESL 1200 mg: 37.9%) was not significantly different from that in women. The responder rate in men (placebo: 22.2%, ESL 400 mg: 17.2%, ESL 800 mg: 35.9%, ESL 1200 mg: 42.4%) was not significantly different from that in women.

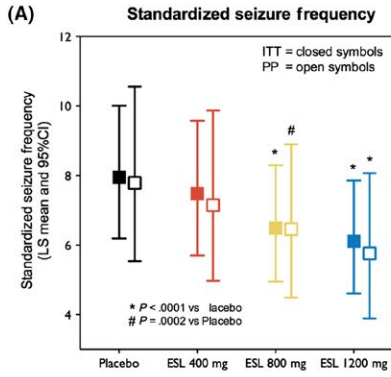
The efficacy observed in each dose group was generally comparable regardless of the duration of epilepsy. The median relative reduction

in SSF in patients whose epilepsy duration was <20 years (placebo: 20.4%, ESL 400 mg: 24.6%, ESL 800 mg: 34.1%, ESL 1200 mg: 41.9%) was not significantly different from that in patients whose epilepsy duration was 20 years or more. The responder rate was also identical in patients with an epilepsy duration <20 years (placebo: 25.0%,

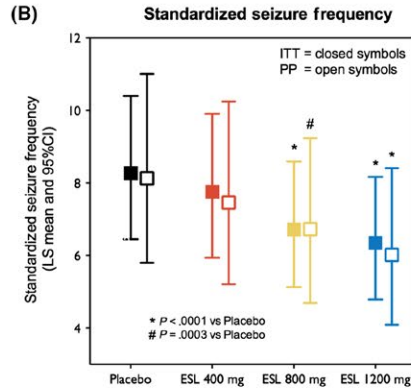
ESL 400 mg: 24.1%, ESL 800 mg: 32.9%, ESL 1200 mg: 44.3%) and 20 years or more.

The efficacy observed in each dose group was generally comparable regardless of the age at time of diagnosis. Also, in the full pooled data, the median relative reduction in SSF in patients whose age at

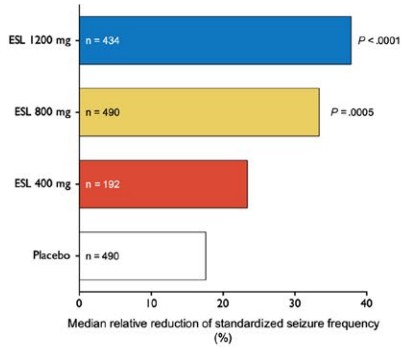
Studies 301 + 302 + 303 + 304 combined



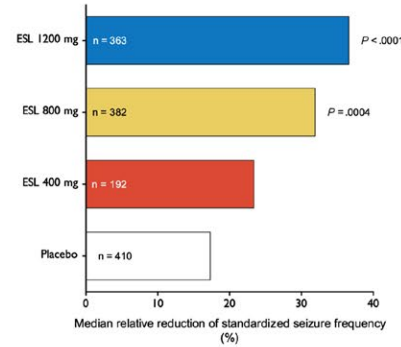
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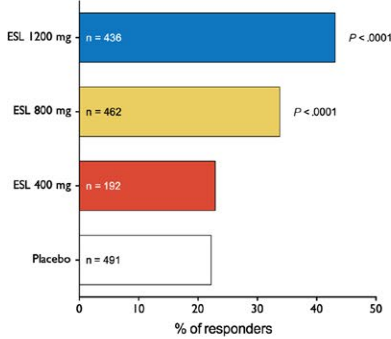
(C) Relative reduction of standardized seizure frequency



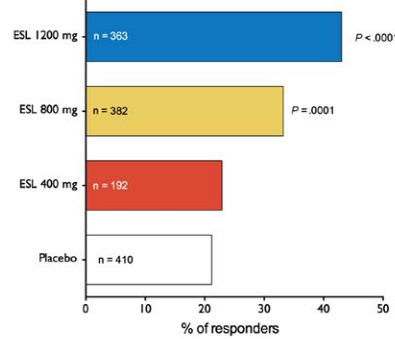
(D) Relative reduction of standardized seizure frequency



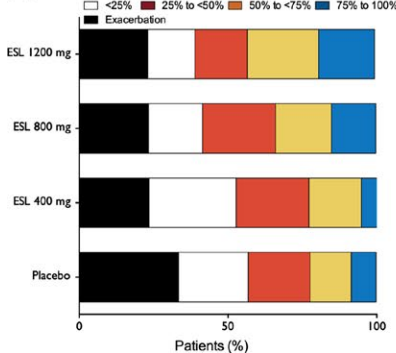
(E) Responder rate



(F) Responder rate



(G) Relative change in seizure frequency



(H) Relative change in seizure frequency

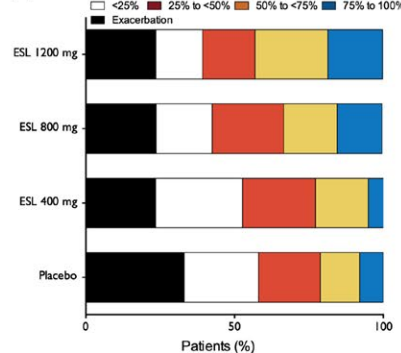


FIGURE 2 Mean and 95% CI seizure frequency per 4 weeks (A and B), mean and 95% CI relative reduction in seizure frequency (C and D), mean responder rate (ie percentage of patients with ≥50% reduction in seizure frequency) (E and F) and mean relative change in seizure frequency (G and H) over the 12week maintenance in the integrated analysis of 301 + 302 + 303 + 304 or 301 + 302 + 304 studies in the intention-to-treat (ITT) and PP populations (A, B, C, and D) or the ITT populations (E, F, G, and H)

time of diagnosis was <18 years (placebo: 14.5%, ESL 400 mg: 23.0%, ESL 800 mg: 31.9%, ESL 1200 mg: 37.8%) was not significantly different from that in patients whose age at time of diagnosis was 18 to 50 years of age. The responder rate in patients whose age at time of diagnosis was <18 years (placebo: 18.7%, ESL 400 mg: 20.0%, ESL 800 mg: 33.3%, ESL 1200 mg: 42.9.7%) was not significantly different from that in patients whose age at time of diagnosis was 18 to 50 years of age. Although there was no upper age limit in each study, very few ($n = 21$) patients ≥ 65 years of age were enrolled (Table S1). Therefore, it was not possible to make meaningful comparisons between ESL and placebo for elderly patients.

The efficacy observed in each dose group was generally comparable for patients taking 1 AED and those taking 2 AEDs. A meaningful comparison to patients who took >2 AEDs ($N = 51$) or did not take any AEDs ($N = 3$) was not possible due to the small number of patients in this sub-population. In the pooled data from ITT population of 4 studies, the median relative reduction in SSF was similar in patients taking 1 AED (placebo: 20.0%, ESL 400 mg: 17.6%, ESL 800 mg: 34.4%, ESL 1200 mg: 38.6%) and those taking 2 AEDs. The responder rate was similar in patients taking 1 AED (placebo: 27.4%, ESL 400 mg: 24.6.5%, ESL 800 mg: 38.5%, ESL 1200 mg: 45.0%) and those taking 2 AEDs.

There were marked differences in the placebo response (Western Europe: 4.9%; Eastern Europe: 17.1%; Latin America: 15.8%; North America: 25.0%; Rest of the World: 25.6%) and for ESL 400 mg (Western Europe: 17%; Eastern Europe: 26.8%; Latin America: 20.8%; Rest of the World: 24.0%), but very little differences for the other two dose groups during the maintenance period across geographical regions (Western Europe ESL 800 mg: 32.7%, ESL 1200 mg: 33.7%; Eastern Europe: ESL 800 mg: 35.6%, ESL 1200 mg: 38.7%; Latin America: ESL 800 mg: 34.0%, ESL 1200 mg: 43.1%; North America: ESL 800 mg: 30.4%, ESL 1200 mg: 37.5%; Rest of the World: ESL 800 mg: 34.1%, ESL 1200 mg: 31.7%).

3.3 | Safety results

3.3.1 | Adverse events

In the full integrated analysis, the overall incidence of treatment-emergent AEs (TEAEs) increased with increasing doses of ESL, both for all TEAEs as well as for those considered possibly related (Table 2), which was similar to that observed in the partial integrated analysis. This was also observed for TEAEs leading to study discontinuation (mainly dizziness and nausea). Hyponatremia leading to treatment discontinuation occurred in less than 1% of patients taking ESL. No dose-dependent trend was observed for serious TEAEs (SAEs), which had a similar incidence in each of the ESL treatment groups. Three deaths occurred during treatment; two in the placebo group (acute respiratory failure and possible Sudden Unexpected Death in Epilepsy [SUDEP]), and one in the ESL 800 mg group (while taking ESL 400 mg during titration [status epilepticus]). One patient drowned during the baseline period of study 304 (without having taken ESL).

The incidence of TEAEs reported by at least 10% of patients in any treatment group (dizziness, somnolence headache, and nausea) is depicted in Table 2. The majority of TEAEs were mild or moderate in severity. The difference in the frequency of TEAEs between the ESL and the placebo groups was observed mainly during the first 6 weeks of treatment. Thereafter, the frequency of TEAEs reported in the ESL and the placebo groups was similar.

The incidence of TEAEs in the pooled data from the full safety population was higher in women (73%) treated with ESL than in men (64.6%), which was comparable to the incidence in placebo treated patients (women 56.7%; men 49%). The difference in ESL group was accounted for mainly by the difference in the ESL 1200 mg group (women 79.1%; men 66.5%). The incidence of TEAEs was higher in patients treated with concomitant CBZ (placebo 54.7%, ESL 73.6%) than in patients not treated with CBZ (placebo 50.6%, ESL 61.4%). In patients treated with CBZ or not, the incidence of TEAEs increased with increasing ESL dose. The overall incidence of TEAEs was comparable in patients treated with concomitant LTG (placebo 53.3%, ESL 69.4%) and in patients not treated with LTG (placebo 52.4%, ESL 68.8%). However, in patients treated with lamotrigine, the incidence of TEAEs increased with increasing ESL dose (ESL 400 mg 58.7%, ESL 800 mg 65.7%, ESL 1200 mg 76.9%) while in patients not treated with LTG, the incidence of TEAEs was comparable between treatment groups (ESL 400 mg 65.3%, ESL 800 mg 67.3%, ESL 1200 mg 71.8%). The incidence of TEAEs was lower in patients treated with concomitant VPA (placebo 43.5%, ESL 62.2%) than in patients not treated with VPA (placebo 55.5%, ESL 71.0%); in both patients treated with VPA or not, the incidence of TEAEs increased slightly with increasing ESL dose.

Figure 3 illustrates the incidence of TEAEs in both full and partial pooled safety data during the double-blind period. The incidence of TEAEs, namely dizziness, somnolence, ataxia, vomiting, and nausea, was lower in patients who started with taking ESL 400 mg (followed by 400 mg increments to ESL 800 mg or 1200 mg) than in those who started on ESL 600 mg or 800 mg, regardless of dosing schedule or eventual maintenance dose.

3.3.2 | Clinical laboratory assessments

No clinically relevant findings were found to be associated with changes in mean clinical laboratory parameters (hematology, blood chemistry, urine, and coagulation). An incidence of clinically significant hematologic abnormalities of less than 4% in any treatment group was observed, while reviewing individual data. No dose dependency was observed with respect the hematology parameters. Clinically significant abnormalities in biochemistry parameters (<1.8% in any treatment group) or liver function tests (<1% in any treatment group) were observed in very few patients.

For most parameters, there was a natural degree of fluctuation in the population around the normal ranges, with no consistent patterns, as shown shift tables summarizing laboratory values that fell outside clinical significance. In the full safety pooled data, a shift of sodium levels from normal at baseline to low (<135 mEq/L) at the end of the maintenance treatment period was reported in 1.8% of

TABLE 2 Pooled safety analysis (safety population)

Studies 301 + 302 + 303 + 304 combined				
MedDRA preferred term	Placebo (n = 513)	ESL 400 mg (n = 196)	ESL 800 mg (n = 500)	ESL 1200 mg (n = 490)
Any TEAEs, n (%) ^a	270 (52.7)	125 (63.8)	335 (67.0)	358 (73.1)
Dizziness, n (%)	43 (8.4)	31 (15.8)	98 (19.6)	137 (28.0)
Somnolence, n (%)	43 (8.4)	23 (11.7)	59 (11.8)	83 (16.9)
Headache, n (%)	44 (8.6)	20 (10.2)	54 (10.8)	68 (13.9)
Nausea, n (%)	21 (4.1)	11 (5.6)	40 (8.0)	63 (12.9)
Possibly related TEAEs, n (%) ^a	149 (29.0)	87 (44.4)	252 (50.4)	296 (60.4)
Dizziness, n (%)	35 (6.8)	27 (13.8)	92 (18.4)	127 (25.9)
Somnolence, n (%)	37 (7.2)	21 (10.7)	54 (10.8)	78 (15.9)
Nausea, n (%)	14 (2.7)	7 (3.6)	33 (6.6)	58 (11.8)
Serious TEAEs, n (%) ^b	12 (2.3)	9 (4.6)	25 (5.0)	12 (2.4)
Diplopia, n (%)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Ataxia, n (%)	0 (0.0)	2 (1.0)	2 (0.4)	1 (0.2)
TEAEs leading to treatment discontinuation, n (%) ^c	32 (6.2)	17 (8.7)	61 (12.2)	109 (22.2)
Dizziness, n (%)	4 (0.8)	2 (1.0)	24 (4.8)	40 (8.2)
Nausea, n (%)	0 (0.0)	0 (0.0)	11 (2.2)	26 (5.3)
TEAEs leading to death, n (%)	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Death, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus, n (%)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Acute respiratory failure, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Studies 301 + 302 + 304 combined				
MedDRA preferred term	Placebo (n = 426)	ESL 400 mg (n = 196)	ESL 800 mg (n = 415)	ESL 1200 mg (n = 410)
Any TEAEs, n (%) ^a	229 (53.8)	125 (63.8)	285 (68.7)	306 (74.6)
Dizziness, n (%)	33 (7.2)	31 (15.8)	78 (18.8)	112 (27.3)
Somnolence, n (%)	32 (7.5)	23 (11.7)	45 (10.8)	68 (16.6)
Headache, n (%)	33 (7.5)	20 (10.2)	47 (11.3)	57 (13.9)
Nausea, n (%)	19 (4.5)	11 (5.6)	34 (8.2)	55 (13.4)
Possibly related TEAEs, n (%) ^a	122 (28.6)	87 (44.4)	209 (50.4)	253 (61.7)
Dizziness, n (%)	26 (6.1)	27 (13.8)	75 (18.1)	104 (25.4)
Somnolence, n (%)	30 (7.0)	21 (10.7)	41 (9.9)	66 (16.1)
Nausea, n (%)	13 (3.1)	7 (3.6)	28 (6.7)	50 (12.2)
Serious TEAEs, n (%) ^b	11 (2.6)	9 (4.6)	25 (6.0)	11 (2.7)
Diplopia, n (%)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Ataxia, n (%)	0 (0.0)	2 (1.0)	2 (0.5)	1 (0.2)
TEAEs leading to treatment discontinuation, n (%) ^c	26 (6.1)	17 (8.7)	54 (13.0)	100 (24.4)
Dizziness, n (%)	2 (0.5)	2 (1.0)	23 (5.5)	37 (9.0)
Nausea, n (%)	0 (0.0)	0 (0.0)	8 (1.9)	24 (5.9)
TEAEs leading to death, n (%)	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Death, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus, n (%)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Acute respiratory failure, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

ESL, eslicarbazepine acetate.

^aIn at least 10% of patients in any treatment group.^bIn at least 1% of patients in any treatment group.^cIn at least 5% of patients in any treatment group.

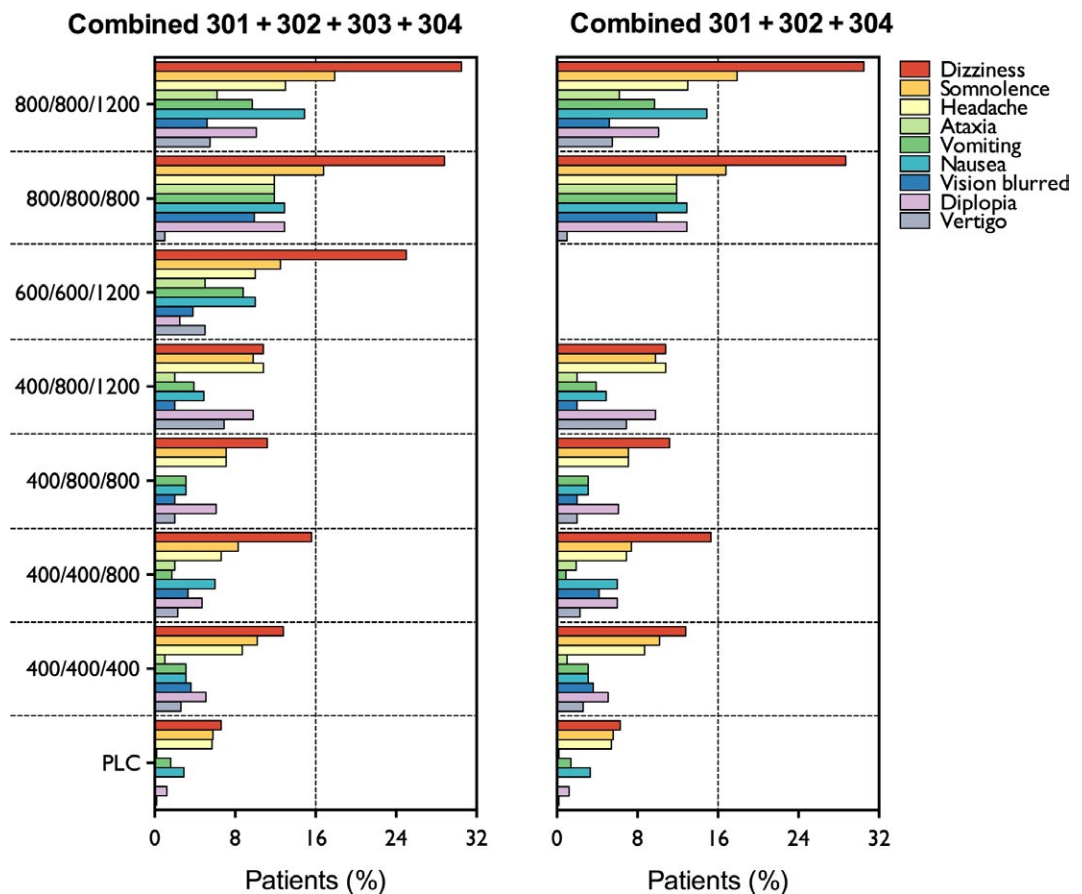


FIGURE 3 Proportion of patients reporting treatment emergent adverse events by titration regimen in the integrated analysis of the 301 + 302 + 303 + 304 or 301 + 302 + 304 studies

patients treated with placebo, and in 6.1%, 4.8%, and 6.6% of patients treated with ESL 400 mg, 800 mg, and 1200 mg, respectively. A shift from normal at baseline to high (>146 mEq/L) at the end of the maintenance period was reported in 1.1%, 0.0%, 1.4%, and 0.3% of patients treated with ESL 400 mg, 800 mg, and 1200 mg, respectively. Hyponatremia <125 mEq/L was reported in 17 patients: 1 (0.5%) on ESL 400 mg, 6 (1.2%) on 800 mg, and 10 (2.0%) on 1200 mg. The increase and decrease in LDL-cholesterol from normal at baseline to high or low at the end of the maintenance treatment period were comparable between the ESL groups and the placebo group. For HDL-cholesterol, the increase from normal at baseline to high at the end of the maintenance treatment period was dose dependent in the ESL groups and higher than in the placebo group; no trend was observed for decreases from normal at baseline to low at the end of the maintenance treatment period. No changes in vital signs or body weight were of clinical concern.

4 | DISCUSSION

The pooling of data from multiple studies with similar designs and similar patient populations can be a powerful tool to address clinical questions not readily answered in the individual studies.⁷ Therefore,

a combined analysis of the pivotal studies of ESL as adjunctive therapy in adults with FOS with or without secondary generalization was planned in the study protocols.

This integrated analysis demonstrated that adjunctive therapy with 800 mg and 1200 mg ESL once-daily doses was efficacious and well tolerated in treatment of patients with partial-onset seizures refractory to stable AED treatment. The efficacy of ESL 800 mg and 1200 mg once-daily doses clearly showed consistent results across all efficacy endpoints and was independent of study population characteristics as well as the type and number of concomitant AEDs used. SSF was significantly reduced with ESL 800 mg once-daily ($P < 0.0001$) and 1200 mg once-daily ($P < 0.0001$) compared to placebo.

The integrated analysis did not identify any patient characteristic that would predict a decrease or increase in ESL efficacy. ESL 800 mg and 1200 mg were more efficacious than placebo regardless of gender, geographical region, epilepsy duration, age at time of diagnosis, seizure type, and number and type of concomitant AEDs. However, there were differences in the placebo response rates between Western Europe and Rest of the World, suggestive that not only were patients more refractory in Western Europe, but also that diagnosis of epilepsy is likely not correct in parts of North America and Rest of the World (placebo responder=25%).

Though current knowledge on the mechanisms of action of various AEDs is too limited to allow a rational combining of AEDs with different mechanisms of action it has been suggested this should be beneficial.⁸ However, AEDs are usually combined mainly on empirical grounds.⁹ Hence, our rationale was not to exclude CBZ or other VGSC modifiers [except OXC, because it shares metabolites with ESL^{10,11}] from the add-on Phase III studies with ESL. In fact, ESL in humans undergoes extensive first pass hydrolysis to its major active metabolite eslicarbazepine that represents approximately 95% of circulating active moieties.¹⁰⁻¹⁵ Even though ESL on its own preferentially blocks VGSC in rapidly firing neurons,¹⁶ the *in vivo* effects of ESL may be limited to its extensive conversion to eslicarbazepine. Mechanistically, however, it is important to underscore that eslicarbazepine, in contrast to CBZ, reduces VGSC availability through enhancement of slow inactivation, instead of alteration of fast inactivation of VGSC.¹⁷ Other distinctive properties of eslicarbazepine over CBZ include 10- to 60-fold higher potency for the blockade of low and high affinity hCa_v3.2 inward currents, being devoid of effects upon submaximal gamma-amino butyric acid (GABA) currents in Ltk cells stably expressing $\alpha 1\beta 2\gamma 2$, $\alpha 2\beta 2\gamma 2$, $\alpha 3\beta 2\gamma 2$, or $\alpha 5\beta 2\gamma 2$ GABA_A receptors and lacking inhibitory effects upon K_v7.2 outward currents.¹⁸ Eslicarbazepine was found to exhibit maintained use-dependent blocking effects both in human and experimental epilepsy with significant add-on effects to CBZ. Moreover, it was shown that eslicarbazepine blocked T-type Ca_v3.2 channels and exhibited strong antiepileptogenic effects in experimental epilepsy.¹⁹⁻²¹ Additionally, CBZ and OXC were demonstrated to possess pro-epileptic actions in experimental models, at clinically relevant concentrations, through the enhancement of excitatory synaptic transmission; by comparison, eslicarbazepine has no such effect on synaptic transmission, explaining its lack of seizure exacerbation.^{18,22}

Eslicarbazepine acetate is metabolized initially solely to eslicarbazepine and then subsequently undergoes a minor chiral inversion (through oxidation to oxcarbazepine) to (R)-licarbazepine, resulting in an eslicarbazepine-to-(R)-licarbazepine area under the plasma concentration time curve (AUC) ratio of approximately 19 (95% eslicarbazepine/4.5% (R)-licarbazepine), with approximately 0.5% circulating as oxcarbazepine.²³ In contrast, OXC, a widely used AED currently approved as monotherapy or adjunct treatment for partial epilepsy, usually administered in twice- or thrice-daily doses,²⁴ is metabolized to its two enantiomer monohydroxy derivatives (MHDs)—eslicarbazepine (80%) and (R)-licarbazepine (20%).²⁵⁻²⁷ Despite the lack of head-to-head efficacy trials between ESL and OXC in patients with epilepsy, the overall incidence of discontinuations due to TEAEs was 4.5% for placebo, 8.7% for ESL 400 mg, 11.6% for ESL 800 mg, and 19.3% for ESL 1200 mg once daily in phase III studies,¹⁻³ whereas incidence of discontinuations for OXC in a large study with similar design was 8.7% for placebo and ranged from 11.9%-36.2% on similar doses of twice-daily 300 and 600 mg, respectively.²⁸ In comparison with OXC, administration of ESL resulted in more eslicarbazepine, less R-licarbazepine, and less oxcarbazepine in plasma and cerebrospinal fluid (CSF) of healthy volunteers, which may correlate with the

tolerability profile reported with ESL.²⁹ The smaller peak-to-trough fluctuation of eslicarbazepine in CSF (a measure of sustained delivery to the brain) than in plasma supports once-daily dosing of ESL.²⁹ In addition, comparison to twice-daily OXC administration of once-daily ESL resulted in 40.6% increase of plasma eslicarbazepine in association with less (R)-licarbazepine and oxcarbazepine plasma levels, which may correlate with the therapeutic profile reported with ESL.³⁰ Although a better tolerability profile has been reported with slow release vs immediate release formulations of OXC,³¹ it is unknown whether this is related to differences in exposure to oxcarbazepine and its metabolites.

A higher incidence of diplopia, nausea, abnormal coordination, dizziness, headache, and somnolence in the 800 mg and ESL 1200 mg groups was the primary reason for the observed dose-dependent increase in the frequency of TEAEs. The difference in the frequency of TEAEs between the ESL treatment groups and the placebo group was observed mainly during the first weeks of treatment. Patients who started titration at a higher dose of ESL showed a higher incidence of TEAEs. Discontinuation due to TEAEs was dose-dependent, ranging from 6% in the placebo group to 22% in the ESL 1200 mg group in the pooled data from safety population of four studies. Hyponatremia leading to treatment discontinuation occurred in less than 1% of patients taking ESL. The total discontinuation rate for ESL patients was 14%, which is low compared to rates reported in a study with OXC^{28,32} where incidences of discontinuation of 12%, 36%, and 67% were found following OXC daily doses of, respectively, 600 mg, 1200 mg, and 2400 mg, and similar to rates reported for other AEDs, such as LTG, topiramate, and tiagabine.³³ On the other hand, open studies have also demonstrated improvements in tolerability in patients switched overnight from OXC to ESL.^{34,35} Due to differences in pharmacokinetics, pharmacodynamics, and metabolism, there may be clinical situations in which it is appropriate to consider switching patients from OXC or CBZ to ESL.³⁶ In line with the findings from Zaccara et al, for which ESL was significantly associated with a lower withdrawal rate due to AEs than OXC.³² Changes in mean clinical laboratory parameters (hematology, blood chemistry, urine, and coagulation) did not reveal clinically relevant findings. None of the hematology parameters showed a dose dependency. Very few patients had clinically significant abnormalities in biochemistry parameters (<1.8% in any treatment group) or liver function tests (<1% in any treatment group). Hyponatremia <125 mEq/L was reported in \leq 2% of patients taking ESL. Changes in HDL- and LDL-cholesterol were comparable between the ESL groups and the placebo group; however, for HDL-cholesterol, the increase from normal at baseline to high at the end of the maintenance treatment period was dose-dependent in the ESL groups and higher than in the placebo group.

In conclusion, once-daily ESL 800 mg and 1200 mg showed consistent results across all efficacy and safety endpoints, independent of study population characteristics and type of concomitant AEDs. Treatment initiated with ESL 400 mg followed by 400 mg increments to 800 or 1200 mg provides optimal balance of efficacy and tolerability.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was supported by BIAL—Portela & C^a, SA.

CONFLICTS OF INTEREST

C. Elger, M. Koepp, E. Trinka (reports speakers honoraria and consultancy fees from Eisai, Everpharma, Medtronic, Bial, Newbridge, UCB Pharma, Boehringer, and his institution received grants from Biogen Idec, Eisai, Red Bull, and Merck. He or his institution received grants from European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, Bundesministerium für Wissenschaft und Forschung, and the Jubiläumsfond der Österreichischen Nationalbank, outside the submitted work), V. Villanueva, J. Chaves, E. Ben-Menachen, P. A. Kowacs, and A. Gil-Nagel, have received research grants from BIAL, the sponsor of the studies. J. Moreira, H. Gama, J.F. Rocha, and P. Soares-da-Silva were employees of BIAL at the time of the studies.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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