

Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: Results of a phase III, double-blind, randomized, placebo-controlled trial

*Michael R. Sperling, †Bassel Abou-Khalil, ‡Jay Harvey, §Joanne B. Rogin, ¶Arnaud Biraben, #Carlo A. Galimberti, **Pedro A. Kowacs, ††Seung Bong Hong, ‡‡Hailong Cheng, ‡‡David Blum, §§Teresa Nunes, §§¶¶Patrício Soares-da-Silva, and on behalf of the 304 Study Team

Epilepsia, 56(2):244–253, 2015
doi: 10.1111/epi.12894

SUMMARY

Objective: To evaluate the efficacy and safety of adjunctive eslicarbazepine acetate (ESL) in patients with refractory partial-onset seizures.

Methods: This randomized, placebo-controlled, double-blind, parallel-group, phase III study was conducted at 173 centers in 19 countries, including the United States and Canada. Eligible patients were aged ≥ 16 years and had uncontrolled partial-onset seizures despite treatment with 1–2 antiepileptic drugs (AEDs). After an 8-week baseline period, patients were randomized to once-daily placebo ($n = 226$), ESL 800 mg ($n = 216$), or ESL 1,200 mg ($n = 211$). Following a 2-week titration period, patients received ESL 800 or 1,200 mg once-daily for 12 weeks. Seizure data were captured and documented using event-entry or daily entry diaries.

Results: Standardized seizure frequency (SSF) during the maintenance period (primary end point) was reduced with ESL 1,200 mg ($p = 0.004$), and there was a trend toward improvement with ESL 800 mg ($p = 0.06$), compared with placebo. When data for titration and maintenance periods were combined, ESL 800 mg ($p = 0.001$) and 1,200 mg ($p < 0.001$) both reduced SSF. There were no statistically significant interactions between treatment response and geographical region ($p = 0.38$) or diary version ($p = 0.76$). Responder rate ($\geq 50\%$ reduction in SSF) was significantly higher with ESL 1,200 mg (42.6%, $p < 0.001$) but not ESL 800 mg (30.5%, $p = 0.07$) than placebo (23.1%). Incidence of treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation increased with ESL dose. The most common TEAEs were dizziness, somnolence, nausea, headache, and diplopia.

Significance: Adjunctive ESL 1,200 mg once-daily was more efficacious than placebo in adult patients with refractory partial-onset seizures. The once-daily 800 mg dose showed a marginal effect on SSF, but did not reach statistical significance. Both doses were well tolerated. Efficacy assessment was not affected by diary format used.

KEY WORDS: Adjunctive therapy, Antiepileptic drugs, Eslicarbazepine acetate, North America, Partial-onset seizures, Refractory epilepsy.



Dr. Michael R. Sperling, is Baldwin Keyes Professor of Neurology at Thomas Jefferson University.

Accepted November 12, 2014; Early View publication December 22, 2014.

*Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; †Vanderbilt University Medical Center, Nashville, Tennessee, U.S.A.; ‡Texas Epilepsy Group, Dallas, Texas, U.S.A.; §Midwest Center for Seizure Disorders, Minneapolis Clinic of Neurology, Golden Valley, Minnesota, U.S.A.; ¶C.H.U. de Rennes, Rennes, France; #I.R.C.C.S., C. Mondino National Neurological Institute, Pavia, Italy; **Curitiba Neurological Institute, Curitiba, Brazil; ††Samsung Medical Center, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Seoul, South Korea; ‡‡Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts, U.S.A.; §§BIAL-Portela & C^a S.A., S. Mamede do Coronado, Portugal; and ¶¶MedInUP – Center for Drug Discovery and Innovative Medicines, University of Porto, Porto, Portugal

Address correspondence to Michael Sperling, Thomas Jefferson University, Philadelphia, PA, U.S.A. E-mail: michael.sperling@jefferson.edu

© 2014 The Authors. *Epilepsia* published by Wiley Periodicals, Inc. on behalf of International League Against Epilepsy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Eslicarbazepine acetate (ESL) is a new molecular entity belonging to the dibenzazepine carboxamide chemical class of antiepileptic drugs. ESL, carbamazepine (CBZ), and oxcarbazepine (OXC) all contain a dibenzazepine nucleus bearing a 5-carboxamide substitute, but ESL is structurally different at the 10,11 position.^{1,2} This molecular variation results in differences in metabolism and pharmacology. Following oral administration, ESL is rapidly and extensively converted to the major active metabolite, (S)-licarbazepine (eslicarbazepine) via hydrolytic first-pass metabolism;^{2,3} consequently, ESL is undetectable in plasma as early as 15 min postdose.⁴ Approximately 95% of oral ESL exposure is accounted for by eslicarbazepine, and <1% by OXC.⁵ In contrast, the major metabolite of OXC is the monohydroxy derivative (MHD: a racemic mixture of 4:1 eslicarbazepine to (R)-licarbazepine);⁶ 3% of OXC exposure is accounted for by residual oxcarbazepine.⁵ In contrast to CBZ, ESL is not metabolized to potentially toxic epoxide metabolites,³ and is not susceptible to metabolic autoinduction.^{7,8}

Eslicarbazepine is believed to act by stabilizing the inactivated state of voltage-gated sodium channels (VGSCs), and shows higher selectivity for the inactivated state of the channel versus the resting state³ ($K_i[\text{resting}]/K_i[\text{inactivated}] = 60$) than CBZ ($K_i[r]/K_i[i] = 19$), OXC ($K_i[r]/K_i[i] = 44$), and the enantiomer (R)-licarbazepine ($K_i[r]/K_i[i] = 28$).⁹ The greater selectivity of eslicarbazepine for the inactivated state of VGSCs is thought to confer a greater inhibitory effect on rapidly firing (or “epileptic”) neurons compared with neurons in the resting state.¹⁰

Previous double-blind placebo-controlled studies demonstrated that ESL (800 or 1,200 mg once-daily [QD]) is well-tolerated as adjunctive therapy and is significantly more effective than placebo in patients with partial-onset seizures refractory to treatment with between one and three concomitant antiepileptic drugs (AEDs).^{11,12} In these studies, ESL significantly reduced standardized seizure frequency (per 4 weeks) during a maintenance period of 12 weeks, and increased the rate of response (defined as the proportion of patients with $\geq 50\%$ reduction in seizure frequency) compared with placebo.

This article reports primary efficacy and safety data from an additional double-blind placebo-controlled trial (the trial is registered at ClinicalTrials.gov, number NCT00988429) that was undertaken to evaluate further the efficacy, safety, and tolerability of ESL as adjunctive therapy in patients aged ≥ 16 with refractory partial-onset (focal) seizures receiving one or two AEDs. The impact of an alternative seizure diary format on evaluation of ESL efficacy was also assessed. Previous trials of ESL made use of event-entry (EE) diaries (in which patients provide entries only when seizures occur); however, when using EE diaries, it is not possible to determine whether days with no entry reflect a true absence of seizures, or failure of the patient to make a diary entry. To address this issue, the current trial mainly

used daily entry (DE) diaries, in which patients were instructed to document seizure data every day, irrespective of whether a seizure had occurred. To our knowledge, this is the first clinical trial to report efficacy data of an AED in patients with partial-onset seizures using either EE or DE diaries.

METHODS

Study design

This randomized, placebo-controlled, double-blind, parallel-group study was conducted at 173 centers in 19 countries (Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and the United States) between December 2008 and January 2012.

Patients aged ≥ 16 years were eligible for screening if they satisfied all of the following criteria: in general good health except for a documented diagnosis of epilepsy for a minimum of 12 months; had ≥ 4 simple or complex partial-onset seizures (with or without secondary generalization) within the 4-week period prior to screening; treated with a stable dose of one to two AEDs (except OXC) for ≥ 1 month prior to screening (vagus nerve stimulation therapy was not considered to be an AED and was permitted, as was vigabatrin, if the patients were stable and safety was monitored). Eligibility criteria for randomization included the following: ≥ 8 partial-onset seizures that were documented in a diary during the baseline period (with ≥ 3 seizures during each 4-week period and no seizure-free interval exceeding 28 consecutive days) and satisfactorily completed diaries.

Criteria for exclusion included the following: simple partial seizures with no motor symptoms; primarily generalized seizures; known progressive neurologic disorder; status epilepticus or cluster seizures within 3 months before screening, or seizures of nonepileptic or psychogenic origin within 2 years; history of schizophrenia or suicide attempts; current treatment with OXC (Patients taking OXC were excluded from study participation to avoid the possibility of excessive exposure to eslicarbazepine.), or using benzodiazepines >2 times per week (except when used chronically as an AED); hypersensitivity to CBZ or CBZ derivatives; second- or third-degree atrioventricular block not corrected with a pacemaker; relevant clinical laboratory abnormalities; a positive major histocompatibility complex, class I, B*1502 test (for patients of Asian ancestry); at randomization, inadequate compliance to the study protocol during the baseline period.

Following screening, patients entered an observational 8-week baseline period, during which they were instructed on how to complete their seizure diaries. Patients with at least eight seizures during the baseline period then entered a double-blind phase that comprised a 2-week titration per-

iod, a 12-week maintenance period, and a 2-week tapering-off period. At the start of the titration period, eligible patients were randomized in a 1:1:1 ratio to receive placebo, ESL 800 mg, or ESL 1,200 mg (all QD). Randomization and allocation to treatment group was performed using an interactive voice-response system. The randomization code was prepared by a third party using a computer-generated schedule, and followed a permuted-block design (block size = 8). Each patient was assigned a unique screening number that was used for identification purposes throughout the study. Investigators were provided with a sealed envelope for each patient containing the patient's unique randomization number but were blinded to study treatment. Treatment codes remained blinded throughout the study. During the titration period, patients in the ESL 800 mg group started treatment at 400 mg QD, and those in the ESL 1,200 mg group started at 800 mg QD (in each group, the dose was increased by 400 mg at the end of the first week). Patients who completed the maintenance phase could enter a 1-year open-label extension study.

When the study was first initiated, EE diaries were used to record seizures; patients (with or without assistance) recorded each seizure by date, type, and time of occurrence during the baseline and double-blind treatment phases. Following a protocol amendment, EE diaries were replaced with DE diaries. Patients who were already enrolled prior to the protocol amendment continued to use EE diaries for the duration of the study. Both types of diary were provided in printed form. Of the intent-to-treat (ITT) population, approximately 29% and 71% of patients used EE and DE diaries, respectively. EE and DE subgroups were well matched in terms of demographics and baseline clinical characteristics, although the proportion of patients using vagus nerve stimulation at baseline (8% vs. 0.3%) and the proportion of Asian patients (27% vs. 1.6%) were greater for the DE than for the EE group.

Seizure types were classified according to the International League Against Epilepsy (ILAE) Revised Clinical and Electroencephalographic Classification of Epileptic Seizures (1981) into simple partial seizures, complex partial seizures, partial seizures evolving to secondarily generalized seizures, and unclassified.¹³ In addition, investigators could indicate "other" if the seizure type was unknown or not otherwise captured.

Assessments

Efficacy

The primary efficacy variable was seizure frequency, standardized per 4 weeks (standardized seizure frequency). The primary assessment of efficacy was based on the least squares (LS) mean-adjusted seizure frequency during the maintenance period. For the primary end point, all patients with diaries (of either type) were considered. Secondary efficacy variables included the following: seizure frequency

during the 2-week titration period and the maintenance period combined; proportion of responders (patients with $\geq 50\%$ reduction in seizure frequency vs. baseline); reduction in seizure frequency from baseline; proportion of patients with exacerbations in seizure frequency $\geq 25\%$ versus baseline; reduction in seizure frequency according to seizure type; proportion of seizure-free patients during the maintenance period; change in Clinical Global Impression (CGI) score from baseline;¹⁴ and change in Quality of Life in Epilepsy Inventory-31 (QOLIE-31) total score from baseline.¹⁵ CGI scores (global improvement [CGI-I], severity of illness [CGI-S], and therapeutic effect [CGI-efficacy]) and QOLIE-31 ratings were evaluated at randomization and the end of the maintenance period.

Safety and tolerability

Adverse events (AEs) were reported at each clinic visit (irrespective of whether they were considered to be related to the study drug) and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. Treatment-emergent AEs (TEAEs) were defined as AEs that occurred on or after the first dose of study drug. Other safety assessments included the following: clinical laboratory tests; vital signs; 12-lead electrocardiography measurements; and Columbia Suicide Severity Rating Scale (C-SSRS) scores.

Statistical analyses

Determination of sample size

For the primary efficacy analysis, the required sample size was calculated such that a treatment difference of 0.174 (standard deviation [SD] = 0.4) in the primary efficacy variable could be detected with 90% power (using DE diaries). Using Bonferroni adjustment for two comparisons of the two doses of active drug with placebo ($\alpha = 0.025$ for each), 130 patients would be required per group to achieve 89.4% power. Assuming a drop-out rate of 10% based on previous phase III studies,^{11,12} 435 patients using DE diaries (145 patients per group) were required. Therefore, a total enrollment of 615 patients was required (435 using DE diaries and 185 using EE diaries [the latter group was enrolled prior to the protocol amendment]).

Definitions

The primary efficacy analysis was based on the ITT population (all randomized patients who received at least one dose of the study drug and had at least one post-baseline seizure frequency assessment). The ITT population included patients who used either EE or DE diaries. In addition, the EE and DE diary ITT populations were analyzed separately. Supportive analyses were performed in the per-protocol (PP) population (patients in the ITT population with no major protocol deviations/violations) and the DE diary ITT population. The safety population

consisted of all randomized patients who received at least one dose of study drug.

Analysis

For the primary efficacy variable, the natural logarithm of seizure frequency was compared between groups using an analysis of covariance (ANCOVA), which models seizure frequency as a function of baseline seizure frequency and treatment (with diary type as an additional covariate). Estimates from the ANCOVA model were back-transformed using the exponential function. A two-stage gate-keeping multiple-testing procedure¹⁶ was used for comparisons between ESL treatment LS means and placebo LS means for the ITT and DE diary ITT populations in the primary analysis. *p*-values were subject to Bonferroni adjustment in the first stage; Dunnett's multiple comparison procedure was used in the second stage (*p*-values from other analyses were not corrected for multiplicity). The proportion of responders, the proportion of patients with exacerbations in seizure frequency $\geq 25\%$, and the proportion of patients who were seizure-free were analyzed using a Cochran-Mantel-Haenszel test. The group comparisons in the reduction in seizure frequency and the change in CGI score were analyzed by ANCOVA.

This study (BIA 2-093-304) was approved by the appropriate institutional review boards, and was conducted in accordance with international and local regulations of the countries involved. Informed consent was obtained from each patient.

RESULTS

Patients

The number of patients randomized and their disposition (for the safety, ITT, and PP populations) are summarized in Figure S1. The placebo and active-treatment groups were well balanced in terms of demographics and baseline characteristics (Table 1).

Efficacy

Seizure frequency

In the ITT population (Table 2), during the 12-week maintenance period seizure frequency was significantly lower in the ESL 1,200 mg group (LS mean: 6.00) than the placebo group (LS mean: 7.88; log difference: -0.26 ; $p = 0.004$). Seizure frequency was also numerically lower in the ESL 800 mg group (LS mean: 6.54) than the placebo group ($p = 0.06$). In the PP population, similar statistically significant effects were observed during the 12-week maintenance period with ESL 1,200 mg (LS mean 5.78, log difference: -0.29 , $p = 0.001$), but not ESL 800 mg (LS mean: 6.83; log difference: -0.13 ; $p = 0.12$) versus placebo (LS mean: 7.85).

When analyzed for the titration and maintenance periods combined, seizure frequency was significantly lower for both the ESL 1,200 mg group (LS mean: 6.31; log difference: -0.31 ; $p < 0.001$) and the ESL 800 mg group (LS mean: 6.60; log difference: -0.26 ; $p = 0.001$) than for the placebo group (LS mean: 8.68).

A separate ANCOVA demonstrated that there was no significant interaction between treatment and diary version used ($p = 0.76$); nevertheless the primary end point was analyzed separately in the EE and DE populations. Both diary groups showed similar trends across treatment groups (Table 2). Although the influence of geographic region on treatment response was also not statistically significant ($p = 0.38$), seizure frequency was nevertheless analyzed separately for patients enrolled in North America ($n = 229$) and the rest of the world ($n = 411$). In the North American subgroup there was no statistically significant difference in seizure frequency between the ESL 1,200 mg group (LS mean: 6.57; log difference: -0.18 ; $p = 0.18$) or the ESL 800 mg group (LS mean: 7.63; log difference: -0.03 ; $p = 0.79$) and placebo (LS mean: 7.90). In the rest of the world subgroup, seizure frequency was significantly lower in both the ESL 1,200 mg group (LS mean: 5.59; log difference: -0.32 , $p = 0.003$) and the ESL 800 mg group (LS mean: 5.87; log difference: -0.27 ; $p = 0.010$) than the placebo group (LS mean: 7.80).

Responder rate

The responder rate in the ITT population during the maintenance phase was significantly higher in the ESL 1,200 mg group (42.6%; $p < 0.001$) but not the ESL 800 mg group (30.5%; $p = 0.07$) compared with the placebo group (23.1%; Fig. 1). In patients taking ESL 1,200 mg, a significantly greater response rate than placebo was observed in both DE (43.0% vs. 26.0%; $p = 0.002$) and EE (41.7% vs. 15.5%; $p = 0.002$) diary groups.

Reduction in seizure frequency

Overall, the median percent reduction in seizure frequency was 21.8% in the placebo group, 29.7% in the ESL 800 mg group, and 35.6% in the ESL 1,200 mg group. The difference from placebo was significant for the 1,200 mg group ($p = 0.02$) but not for the ESL 800 mg group ($p = 0.07$). A similar pattern was observed for different seizure types: simple partial seizures were reduced by 26.5%, 36.6%, and 34.1%; complex partial seizures were reduced by 17.2%, 28.2%, and 34.1%; and partial seizures evolving to secondarily generalized seizures were reduced by 18.7%, 35.9%, and 37.0% (for placebo, ESL 800 mg, and ESL 1,200 mg, respectively). A $\geq 25\%$ increase in seizure frequency occurred in 31 (14.6%), 26 (13.0%), and 24 (13.1%) patients (placebo, ESL 800 mg, and ESL 1,200 mg, respectively); differences between treatment groups were not statistically significant in the subgroup analyses.

Table 1. Demographic and baseline characteristics (safety population)

Characteristic	Placebo (n = 224)	ESL 800 mg (n = 216)	ESL 1,200 mg (n = 210)
Age, years (median [range])	39.0 (16–67) ^a	38.5 (16–71)	38.0 (16–69)
Male, n (%)	112 (50.0)	109 (50.5)	105 (50.0)
Ethnicity, n (%)			
Caucasian	142 (63.4)	137 (63.4)	134 (63.8)
Black	8 (3.6)	8 (3.7)	8 (3.8)
Asian	46 (20.5)	41 (19.0)	39 (18.6)
Other	28 (12.5)	30 (13.9)	29 (13.8)
BMI, kg/m ^{2b}			
Mean ± SD	25.7 ± 5.8	26.3 ± 5.6	26.5 ± 7.0
Median (range)	24.8 (16.2–46.5)	25.7 (16.0–55.2)	25.4 (15.5–71.4)
Duration of epilepsy (years) ^c			
Mean ± SD	21.3 ± 14.6	21.6 ± 13.0	21.2 ± 13.0
Median (range)	18.3 (1.1–63.4)	19.6 (1.4–53.9)	18.3 (1.1–57.3)
Seizure frequency in the 4 weeks prior to screening ^d			
Mean ± SD	18.1 ± 28.7	18.0 ± 35.9	17.6 ± 30.2
Median (range)	8 (4–282)	8 (1–420)	9 (4–351)
Seizure type in the 4 weeks prior to screening, ^{d,e} n (%) ^f			
Simple partial ^g	81 (36.8)	84 (39.3)	66 (32.2)
Complex partial ^h	175 (79.5)	170 (79.4)	170 (82.9)
Partial evolving to secondarily generalized ⁱ	57 (25.9)	59 (27.6)	63 (30.7)
Unclassifiable	2 (0.9)	0	3 (1.5)
Other	2 (0.9)	1 (0.5)	0
Missing	0	1	0
Median (range) SSF during the baseline period ^{d,j}	9.0 (2.4–131.8)	8.6 (2.0–412.3)	8.9 (3.7–163.5)
Number of AEDs used during the baseline period, ^k n (%)			
1	64 (28.6)	60 (27.8)	59 (28.1)
2	158 (70.5)	153 (70.8)	151 (71.9)
≥3	1 (0.4)	0	0
AEDs during baseline used by >15% of patients, ^l n (%)			
Carbamazepine	77 (34.4)	84 (38.9)	89 (42.4)
Levetiracetam	66 (29.5)	58 (26.9)	43 (20.5)
Lamotrigine	57 (25.4)	51 (23.6)	57 (27.1)
Valproic acid	42 (18.8)	46 (21.3)	41 (19.5)

AED, antiepileptic drug; BMI, body mass index; ESL, eslicarbazepine acetate; ILAE, International League Against Epilepsy; SD, standard deviation; SSF, standardized seizure frequency.

^an = 223.

^bn = 222, 215, and 208 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

^cn = 215 for ESL 800 mg.

^dIntention-to-treat population.

^ePatients may have had more than one type of seizure.

^fn = 220, 214, and 205 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

^gFocal seizures without impairment of consciousness or awareness.

^hDyscognitive seizures.

ⁱFocal seizures evolving to bilateral convulsive seizures (2010 ILAE classification).¹⁷

^jn = 220, 215, and 204 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

^kAn AED was considered to be used at baseline if started any time prior to first dose of study drug and continued to the titration period. AEDs used as rescue medication at baseline are not included.

^lAs specified by the study protocol, none of the patients took OXC during the baseline period.

Seizure freedom

Seizure freedom (during the maintenance period) was achieved by 0.9% of placebo-treated patients, and 2.0% and 2.2% of ESL 800- and 1,200 mg-treated patients, respectively.

CGI and QOLIE-31 scores

The proportions of patients with improvements on the CGI-I and the CGI efficacy scales are shown in Table 3, as are the changes in CGI-S and QOLIE-31 scores between baseline and the end of the maintenance period.

There were somewhat greater reductions in CGI-S scores with ESL 800 mg and ESL 1,200 mg than with placebo, although the differences were not statistically significant. Overall, 35.3% of patients taking ESL were rated either “very much improved” or “much improved” on the CGI-I scale, versus 20.7% of those taking placebo. Similarly, 44.7% of patients overall who were taking ESL had a “marked” or “moderate” improvement according to the CGI efficacy index, versus 27.8% of those on placebo. Treatment with ESL 1,200 mg and ESL 800 mg led to an increase in total QOLIE-31 scores of approximately

Table 2. Analysis of covariance of standardized seizure frequency during the 12-week maintenance period (ITT population)

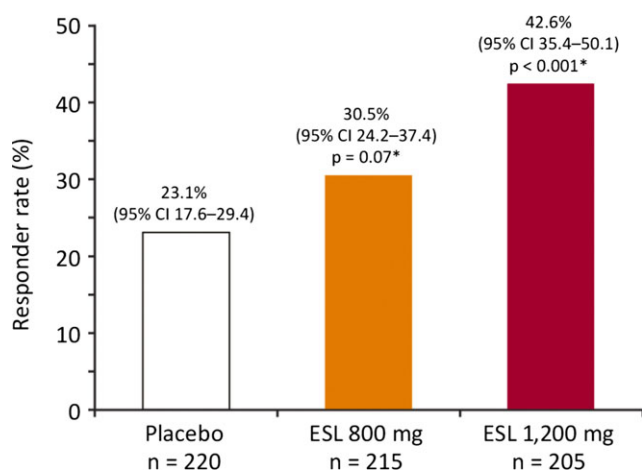
Study population	Placebo (n = 220)	ESL 800 mg (n = 215)	ESL 1,200 mg (n = 205)
Overall ITT population			
n	212	200	184
LS mean (95% CI)	7.88 (6.98–8.90)	6.54 (5.77–7.40)	6.00 (5.26–6.84)
Log difference in LS mean versus placebo	–	–0.18	–0.26
Bonferroni's procedure-adjusted p-value ^a	–	0.06	0.004
ITT population (daily entry diaries)			
n	154	137	136
LS mean (95% CI)	7.54 (6.55–8.68)	6.32 (5.44–7.35)	5.96 (5.12–6.94)
Log difference in LS mean versus placebo	–	–0.17	–0.22
Dunnett's procedure-adjusted p-value ^b	–	0.17	0.05
ITT population (event-entry diaries)			
N	58	63	48
LS mean (95% CI)	7.91 (6.43–9.72)	6.33 (5.17–7.72)	5.41 (4.28–6.81)
Log difference in LS mean versus placebo	–	–0.21	–0.36
p-value ^c	–	0.13	0.02

CI, confidence interval; ESL, eslicarbazepine acetate; ITT, intention to treat; LS, least squares.

^aBonferroni's procedure was used to calculate the p-values and the 95% CIs for log differences.

^bDunnett's procedure was used to calculate the p-values (assessed at $p = 0.025$ level) and 97.5% CIs for log differences.

^cUnadjusted p-value for pairwise comparison with placebo.



*ESL group versus placebo.

Figure 1.

Responder rate (proportion of patients with $\geq 50\%$ reduction in seizure frequency during the maintenance period versus baseline; ITT population). CI, confidence interval; ESL, eslicarbazepine acetate. *ESL group versus placebo.

Epilepsia © ILAE

five points between baseline and the end of the maintenance period.

Safety

TEAEs

The incidence of TEAEs (Table 4), TEAEs considered potentially related to treatment, and TEAEs leading to discontinuation increased with ESL dose. The majority of

TEAEs were of mild or moderate severity, the most common being dizziness, somnolence, nausea, headache, and diplopia (Table 4). The percentage of patients who had at least one severe TEAE was 6.7% for placebo, 11.1% for ESL 800 mg, and 14.8% for ESL 1,200 mg. TEAEs classed as severe and reported in $\geq 2\%$ of patients were dizziness (1.3%, 1.9%, and 3.8%) and vertigo (0%, 0.5%, and 2.9%) for placebo, ESL 800 mg, and ESL 1,200 mg, respectively. TEAEs leading to discontinuation in $\geq 2\%$ of patients taking ESL (either dose) were dizziness, nausea, vomiting, ataxia, dysarthria, and somnolence (Table 4). TEAEs of special interest included depression (reported in 2.7%, 2.3%, and 2.4% of the placebo, ESL 800 mg, and ESL 1,200 mg groups, respectively) and rash (reported in 1.8%, 1.4%, and 2.4% of the placebo, ESL 800 mg, and ESL 1,200 mg groups, respectively).

Deaths

One death occurred during the baseline period of a patient who had not received the study drug. Two deaths occurred during the double-blind period: a 29-year-old Caucasian woman randomized to placebo died of acute respiratory failure after being diagnosed with pneumonia; and a 27-year-old Caucasian man randomized to ESL 800 mg was found dead in bed with a bitten tongue (during the titration phase, while receiving 400 mg ESL). The cause of death according to the autopsy report was status epilepticus.

Serious adverse events

There were no notable differences in the types of serious TEAEs between treatment groups, and no dose-related trends (the incidence of serious TEAEs was 3.1% for placebo, 6.5% for ESL 800 mg, and 1.4% for ESL 1,200 mg).

Table 3. CGI and QOLIE-31 scores (ITT population)

	Placebo (n = 220)	ESL 800 mg (n = 215)	ESL 1,200 mg (n = 205)
CGI-S (change from baseline) ^{a,b}			
LS mean (95% CI)	-0.3 (-0.4, -0.1)	-0.5 (-0.6, -0.3)	-0.4 (-0.6, -0.3)
Unadjusted p-value		0.054	0.13
CGI-I ^{a,c}			
Very much improved, % (n)	4.2 (9)	6.9 (14)	6.1 (12)
Much improved, % (n)	16.5 (35)	27.5 (56)	30.1 (59)
CGI efficacy index (therapeutic effect) ^{a,d}			
Marked improvement, % (n)	4.4 (9)	9.8 (19)	10.5 (19)
Moderate improvement, % (n)	23.4 (48)	32.6 (63)	36.5 (66)
QOLIE-31 total score (change from baseline) ^a			
Mean ± SD	2.16 ± 25.4	5.35 ± 23.8	4.64 ± 25.7

CGI, Clinical Global Impressions; CGI-I, CGI-Improvement; CGI-S, CGI-Severity of illness; CI, confidence interval; ESL, eslicarbazepine acetate; LS, least squares; QOLIE-31, Quality of Life Epilepsy Inventory-31; SD, standard deviation.

^aBased on last assessment at the end of the maintenance period. Note that not all subjects had evaluable data; percentages are based on evaluable subjects.

^bn = 213, 205, and 198 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

^cn = 212, 204, and 196 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

^dn = 205, 193, and 181 for placebo, ESL 800 mg, and ESL 1,200 mg, respectively.

Table 4. TEAEs affecting ≥5% of patients, TEAEs leading to discontinuation in ≥2% of patients, all serious TEAEs, and deaths (safety population)

	Number (%) of patients		
	Placebo (n = 224)	ESL 800 mg (n = 216)	ESL 1,200 mg (n = 210)
Any TEAE	125 (55.8)	145 (67.1)	163 (77.6)
Dizziness	19 (8.5)	34 (15.7)	55 (26.2)
Somnolence	12 (5.4)	16 (7.4)	36 (17.1)
Nausea	11 (4.9)	16 (7.4)	32 (15.2)
Headache	17 (7.6)	20 (9.3)	24 (11.4)
Vomiting	3 (1.3)	6 (2.8)	23 (11.0)
Diplopia	4 (1.8)	14 (6.5)	22 (10.5)
Vertigo	1 (0.4)	6 (2.8)	15 (7.1)
Fatigue	6 (2.7)	8 (3.7)	11 (5.2)
Potentially related TEAE	83 (37.1)	111 (51.4)	140 (66.7)
TEAEs leading to discontinuation	18 (8)	26 (12.0)	54 (25.7)
Dizziness	1 (0.4)	11 (5.1)	19 (9.0)
Nausea	0	3 (1.4)	13 (6.2)
Vomiting	0	0	8 (3.8)
Ataxia	0	1 (0.5)	8 (3.8)
Dysarthria	0	0	5 (2.4)
Somnolence	2 (0.9)	2 (0.9)	5 (2.4)
Serious TEAEs	7 (3.1)	14 (6.5)	3 (1.4)
Deaths ^a	1 (0.4)	1 (0.5)	0

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

^aData are based on the double-blind, placebo-controlled period.

One patient with a history of suicidal tendencies had a suicide attempt but, as she had responded to the study drug, she was allowed to continue on ESL 800 mg; no other psychiatric symptoms were reported. One serious cutaneous event (leukocytoclastic vasculitis) leading to discontinuation of treatment was reported in a patient taking ESL 800 mg.

Clinical laboratory assessments

Overall, changes in clinical laboratory parameters (other than serum sodium) were not substantially different between the three groups. Data for reductions in serum sodium concentrations are shown in Table 5. Overall, 5.1% of patients taking ESL had a reduction in serum sodium of >10 mEq/L, compared with 0.9% of those taking placebo, whereas hyponatremia (serum sodium <125 mEq/L) occurred in 1.5% and 0% of patients, respectively. Between baseline and week 8 of treatment (week 6 of the maintenance period), there were greater reductions in mean serum sodium with ESL 800 mg (-1.6 mEq/L) and ESL 1,200 mg (-2.2 mEq/L) than with placebo (0.1 mEq/L); the reductions tended to stabilize after approximately 2 months of treatment. Hyponatremia was reported as an adverse event (AE) leading to discontinuation in three patients taking ESL 1,200 mg (1.4%), but no patients taking placebo or ESL 800 mg. Vital signs, body weight, and electrocardiography parameters were not substantially different across visits for the placebo and ESL groups. ESL 800 and 1,200 mg had no notable effect on C-SSRS scores.

DISCUSSION

ESL was developed to enhance the yield of the pharmacologically desirable metabolite eslicarbazepine, while reducing exposure to the less pharmacologically desirable metabolites (R)-licarbazepine and OXC.

The present study confirms and extends the findings of efficacy and safety of ESL as adjunctive treatment of partial-onset seizures as reported in two prior randomized placebo-controlled trials.^{11,12} Once-daily ESL was effective as adjunctive therapy and was generally well tolerated in patients with refractory partial-onset (focal) seizures. During the 12-week maintenance period, seizure frequency was

Table 5. Serum sodium levels (safety population)

	No. (%) of patients ^{a,b}			
	Placebo (n = 224)	ESL 800 mg (n = 216)	ESL 1,200 mg (n = 210)	Total ESL (n = 426)
Serum sodium <125 mEq/L	0	1 (0.5)	5 (2.5)	6 (1.5)
Reduction from baseline in serum sodium of >10 mEq/L	2 (0.9)	9 (4.3)	12 (5.9)	21 (5.1)

ESL, eslicarbazepine acetate; mEq/L, milliequivalent/liter.
^aData are for patients in the safety population with at least one post-baseline sodium assessment. Note that not all subjects had evaluable data; percentages are based on evaluable subjects.
^bn = 220, 209, 204, and 413 for placebo, ESL 800 mg and ESL 1,200 mg, and Total ESL, respectively.

significantly reduced in the ESL 1,200 mg group compared with placebo ($p = 0.004$), and there was a trend toward improvement in the ESL 800 mg group compared with placebo ($p = 0.06$). No statistically significant interactions between ESL treatment and geographical region or ESL treatment and diary version (DE or EE) were detected. For the majority of secondary efficacy end points, including response rate and reduction in seizure frequency, there were statistically significant differences between ESL 1,200 mg and placebo, and similar trends occurred with ESL 800 mg. We noted relatively high 50% responder rates in placebo-treated patients, approximating rates reported in other studies of similar design (e.g., perampanel, 19.3%;¹⁸ lacosamide, 23.0%;¹⁹ and OXC, 28.1%²⁰). This poses a challenge in interpreting the magnitude of effect of new AEDs. Nonetheless, substantially more patients taking ESL were rated at least “much improved” on the CGI-I scale, or had at least “moderate improvement” according to the CGI efficacy scale compared with placebo-treated patients. Patients taking ESL had improvements in QOLIE-31 scores of approximately five points (i.e., comparable to the minimal clinically important improvement described by Borghs et al.),²¹ indicating that treatment with ESL led to clinically meaningful improvements in quality of life.

In this study, seizure frequency was the primary efficacy end point. Similar clinical trials^{22,23} previously used either the median percentage change in seizure frequency from baseline, or the responder rate as the primary outcome measure. These measures are susceptible to bias when the distribution of seizure frequencies is not normally distributed. In such circumstances, the log-transformed seizure frequency is a more robust measure, as discussed in an analysis by Siddiqui and Hershkovitz.²⁴

The current safety and tolerability findings are consistent with those reported previously for ESL.^{11,12} The most commonly reported TEAEs were dizziness, somnolence, nausea, headache, vomiting, diplopia, vertigo, and fatigue. Rash was reported in 1.4% and 2.4% of patients, and hyponatremia in 0% and 1.5% of patients (taking ESL 800 and 1,200 mg, respectively). Too few cases occurred to draw conclusions regarding dose and incidence of symptomatic hyponatremia. In previous studies of OXC, rash was reported in 6% of patients²⁵ and hyponatremia in 3.8% of

adult patients.²⁶ The incidence of TEAEs and TEAEs leading to discontinuations was higher in the ESL 1,200 mg group than the ESL 800 mg group. However, somewhat more patients in the 1,200 mg group than the 800 mg group were taking other concomitant AEDs with the same mode of action as ESL (sodium channel blockers, i.e., CBZ, lamotrigine). It has been reported that combining sodium channel blockers may lead to increased toxicity.²⁷

As in previous ESL trials, these findings indicate that ESL is effective as adjunctive therapy in patients with a long history of partial seizures and poor seizure control, who are taking one or two concomitant AEDs. ESL demonstrated efficacy in patients who previously had continued to have frequent seizures, despite treatment with AEDs including CBZ, levetiracetam, lamotrigine and valproic acid. The current trial is generally consistent with previous trials^{11,12} in which once-daily ESL (800 and/or 1,200 mg) was efficacious and well-tolerated in patients with refractory partial-onset seizures. In the current trial, the ESL 800 mg dose did not reach statistical significance. It is not clear why this occurred, however, the trends toward improvements were consistent with results in previous studies. Too few patients ($n = 36$) in the entire ESL development program were taking three concomitant AEDs to assess efficacy as a function of number of AEDs.

One important methodologic difference between this trial and previous studies was the use of DE diaries to ensure that seizure data were recorded on every day of the trial, regardless of whether seizures had occurred. Reliability of seizure recording is a key issue in epilepsy trials,²⁸ but to date no formal comparisons of seizure diaries of different designs are available. In the present study, the interaction between the effect of treatment and diary version was not significant ($p = 0.76$). The results obtained with DE diaries were consistent with those obtained with EE diaries. Selection of diary type was based on time of enrollment, rather than by randomization, which represents a limitation in the method.

CONCLUSIONS

In this phase III study, daily dosing with adjunctive ESL was effective in reducing seizures in patients with refractory partial-onset (focal) seizures, and was generally well toler-

ated. The effect of ESL 1,200 mg on seizure frequency was significantly greater than that of placebo; whereas ESL 800 mg also reduced seizure frequency, the difference versus placebo was not statistically significant. The DE and EE diary methods produced similar results with regard to seizure outcomes; this is the first clinical trial providing efficacy data in patients with partial-onset seizures who used two different diary designs. ESL is a useful addition to current AED pharmacotherapy for the treatment of refractory partial-onset (focal) seizures, on the basis of clinical activity, convenient once-daily dosing, and good tolerability.

ACKNOWLEDGMENTS

The authors would like to acknowledge the writing assistance of Tracey Baskerville of FireKite, part of the Knowledge Point 360 Group, an Ashfield company, for support in drafting this manuscript. Medical writing support was funded by Sunovion Pharmaceuticals Inc.

DISCLOSURE OF CONFLICT OF INTEREST

Michael Sperling has received consultancy honoraria from UCB Pharma, ElectroCore, and Accordia Therapeutics and honoraria from Wiley Blackwell for serving as an associate editor for *Epilepsia*, and has received grants from National Institute of Neurological Disorders and Stroke (NINDS), UCB Pharma, Sunovion Pharmaceuticals Inc., Eisai, SK Life Science, Upsher-Smith, Medtronic, Lundbeck, Visualase, and Brain Sentinel. Bassel Abou-Khalil has received research grants paid to Vanderbilt University Medical Center from Sunovion Pharmaceuticals Inc., UCB Pharma, Pfizer, GlaxoSmithKline, Upsher-Smith, and SK Life Science. Jay Harvey has received financial support for research from Sunovion Pharmaceuticals Inc., UCB Pharma, Upsher-Smith, Marinus, SK Life Science, Cyberonics, Brain Sentinel, and Eisai, and speaker fees from Sunovion Pharmaceuticals Inc. and UCB Pharma. Joanne Rogin has received financial support for research from GlaxoSmithKline, Eisai, Pfizer, UCB Pharma, Sunovion Pharmaceuticals Inc., and Marinus; speaker's fees from GlaxoSmithKline, Pfizer, UCB Pharma, and Supernus; and consultancy honoraria from Pfizer and Sunovion Pharmaceuticals Inc. Arnaud Biraben serves as a member on a corporate scientific board and receives honoraria from GlaxoSmithKline, Eisai, and UCB Pharma. Carlo A. Galimberti received a grant from the Italian Ministry of Health, financial support for research from UCB Pharma, Eisai, and Bial-Portela & C^a S.A.; and speaker's fees from GlaxoSmithKline and UCB Pharma. Pedro A. Kowacs has received consultancy honoraria from Abbott, GlaxoSmithKline, and Cyberonics and financial support for research from Bial-Portela & C^a S.A. Seung Bong Hong has no potential conflicts of interest to disclose. Hailong Cheng and David Blum are paid employees of Sunovion Pharmaceuticals Inc. Teresa Nunes and Patr cio Soares-da-Silva are paid employees of Bial-Portela & C^a S.A. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Benes J, Parada A, Figueiredo AA, et al. Anticonvulsant and sodium channel-blocking properties of novel 10,11-dihydro-5H-dibenz[b, f]azepine-5-carboxamide derivatives. *J Med Chem* 1999;42:2582–2587.
2. Almeida L, Potgieter JH, Maia J, et al. Pharmacokinetics of eslicarbazepine acetate in patients with moderate hepatic impairment. *Eur J Clin Pharmacol* 2008;64:267–273.
3. Hebeisen S, Brady K, Konrad D, et al. Inhibitory effects of eslicarbazepine acetate and its metabolites against neuronal voltage-gated sodium channels. *Epilepsia* 2011;52:257–258.
4. Almeida L, Soares-da-Silva P. Safety, tolerability and pharmacokinetic profile of BIA 2-093, a novel putative antiepileptic agent, during first administration to humans. *Drugs R D* 2003;4:269–284.
5. Nunes T, Rocha JF, Falcao A, et al. Steady-state plasma and cerebrospinal fluid pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine in healthy volunteers. *Epilepsia* 2013;54:108–116.
6. Stahl SM. *Stahl's essential psychopharmacology – the prescriber's guide*. New York: Cambridge University Press; 2011.
7. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia* 2012;53:935–946.
8. Almeida L, Bialer M, Soares-da-Silva P. Eslicarbazepine acetate. In Shorvon S, Perucca E, Engel J (Eds) *The treatment of epilepsy*. 3rd Ed. Oxford: Blackwell Publishing, 2009:485–498.
9. Data on file. Marlborough, MA: Sunovion Pharmaceuticals Inc.
10. Ragsdale DS, Scheuer T, Catterall WA. Frequency and voltage-dependent inhibition of type IIA Na⁺ channels, expressed in a mammalian cell line, by local anaesthetic, antiarrhythmic, and anticonvulsant drugs. *Mol Pharmacol* 1991;40:756–765.
11. Elger C, Halasz P, Maia J, et al. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group Phase III study. *Epilepsia* 2009;50:454–463.
12. Ben-Menachem E, Gabbai AA, Hufnagel A, et al. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. *Epilepsy Res* 2010;89:278–285.
13. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981;22:489–501.
14. National Institute of Mental Health. CGI: clinical global impression. In Guy W, Bonato RR (Eds) *Manual for the ECDEU assessment battery*. 2nd Revised Ed. Chevy Chase, MD: National Institute of Mental Health, 1970:12-1–12-6.
15. Cramer JA, Perrine K, Devinsky O, et al. Development and cross-cultural translation of a 31-item quality of life questionnaire (QOLIE-31). *Epilepsia* 1998;39:81–88.
16. Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. *Biom J* 2008;50:667–677.
17. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51:676–685.
18. Perampanel (Fycompa). US prescribing information. 2013. Eisai Inc. Available at: http://www.fycompa.com/sites/all/themes/fycompa/pdf/Fycompa_Prescribing_Information.pdf. Accessed June 23, 2014.
19. Lacosamide (VIMPA). EPAR – summary for the public. 2013. European medicines Agency 710648, 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000863/WC500050339.pdf. Accessed June 23, 2014.
20. Oxcarbazepine (Oxtellar®). FDA medical review. 2012. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM328320.pdf>. Accessed 23 June, 2014.
21. Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. *Epilepsy Behav* 2012;23:230–234.
22. Brodie MJ, Lerche H, Gil-Nagel A, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010;75:1817–1824.
23. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global Phase III study 305. *Epilepsia* 2013;54:117–125.
24. Siddiqui O, Hershkowitz N. Primary efficacy endpoint in clinical trials of antiepileptic drugs: change or percentage change. *Drug Inf J* 2010;44:343–350.
25. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1000–1015.

26. Sachdeo R, Wasserstein A, Mesenbrink P, et al. Oxcarbazepine (Trileptal): effect on serum sodium. *Epilepsia* 1999; 40 (Suppl. 7):2.074 Abstract.
27. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006;61:246–255.
28. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav* 2012;24:304–310.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Patient disposition.

Appendix S1. The 304 study team.