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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Long-term efficacy and safety of eslicarbazepine acetate monotherapy for adults with newly diagnosed focal epilepsy: An open-label extension study

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Abstract

Objective: To assess the efficacy, safety, and tolerability of eslicarbazepine acetate (ESL) monotherapy during long-term treatment.

Methods: An open-label extension (OLE) study was conducted in adults completing a phase 3, randomized, double-blind, noninferiority trial, during which they had received monotherapy with either once-daily ESL or twice-daily controlled-release carbamazepine (CBZ-CR) for newly diagnosed focal epilepsy. In the OLE study, all patients received ESL (800-1600 mg/d) for 2 years. Primary efficacy outcome was retention time (from baseline of the OLE study). Secondary efficacy assessments included seizure freedom rate (no seizures during the OLE study) and responder rate (≥50% seizure frequency reduction from baseline of double-blind trial). Safety assessments included evaluation of treatment-emergent adverse events (TEAEs).

Results: Of 206 randomized patients, 96 who received ESL in the double-blind trial (ESL/ESL) and 88 who received CBZ-CR in the double-blind trial (CBZ-CR/ESL) were treated with ESL monotherapy (89.3% overall). Treatment retention time was similar between groups, with low probability of ESL withdrawal overall (<0.07 at any time). After 24 months, the probability of ESL withdrawal was 0.0638 (95% confidence interval [CI] = 0.0292-0.1366) in the ESL/ESL group and 0.0472 (95% CI = 0.0180-0.1210) in the CBZ-CR/ESL group. Seizure freedom rates were 90.6% (ESL/ESL) and 80.7% (CBZ-CR/ESL; $P = .0531$). Responder rates remained >80% in both groups throughout the study. Incidence of serious TEAEs was similar between groups (7.3% vs 5.7%; 0% vs 1.1% possibly related), as were the incidences of TEAEs considered at least possibly related to treatment (17.7% vs 18.2%) and TEAEs leading to discontinuation (3.1% vs 4.5%). The types of TEAEs were generally consistent with the known safety profile of ESL.

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Significance: ESL monotherapy was efficacious and generally well tolerated over the long term, including in patients who transitioned from CBZ-CR monotherapy. No new safety concerns emerged.

KEYWORDS
antiseizure medication, carbamazepine, focal seizures, responder rate, retention, seizure freedom rate

1 | INTRODUCTION

Eslicarbazepine acetate (ESL) is a once-daily (QD) antiseizure medication (ASM) that is approved for the treatment of focal-onset seizures as monotherapy or adjunctive therapy.[1,2] In Europe, monotherapy approval for adult patients with newly diagnosed focal epilepsy was based on the results of a phase 3, randomized, double-blind, noninferiority trial (Study BIA-2093-311), in which QD monotherapy with ESL was noninferior to twice-daily (BID) monotherapy with controlled-release carbamazepine (CBZ-CR).[3] In the USA, monotherapy approval was based on the results of two phase 3 withdrawal to monotherapy trials in patients with drug-resistant focal epilepsy.[4,5]

Open-label extension (OLE) studies provide a means of assessing retention, efficacy, safety, and tolerability during long-term treatment; this is particularly relevant for chronic treatments, as it is for the use of ASMs in epilepsy.[6] The ESL phase 3 noninferiority trial[3] was therefore followed by an OLE study (Study BIA-2093-311-EXT), reported here, the primary objective of which was to confirm the maintenance of efficacy and safety/tolerability of ESL monotherapy during long-term treatment in adult patients with focal epilepsy.

Key Points

- A phase 3 open-label extension study assessed the efficacy and safety of ESL monotherapy over 2 years
- Treatment retention was high (>80%) and the probability of ESL withdrawal was <0.07 throughout the open-label extension study
- More than 80% of patients remained seizure-free throughout the open-label extension study
- ESL monotherapy demonstrated efficacy in patients previously treated with controlled-release carbamazepine monotherapy
- ESL monotherapy was generally well tolerated, and no safety concerns emerged in the long-term monotherapy setting

2 | MATERIALS AND METHODS

2.1 | Study design

Study BIA-2093-311-EXT was a phase 3, multinational, noncontrolled, OLE study conducted in adults (≥18 years) with newly diagnosed focal epilepsy who completed a phase 3 noninferiority trial, in which they had received either QD monotherapy with ESL, or BID monotherapy with CBZ-CR (Figure 1).[3] The primary objective of the OLE study was to confirm maintenance of efficacy and tolerability of ESL monotherapy (800-1600 mg QD) during long-term treatment. Secondary objectives were to further demonstrate the efficacy and safety/tolerability of ESL in patients switching from CBZ-CR treatment to ESL.

After the 26-week maintenance period of the initial double-blind trial, patients continued in an extension phase until the last patient completed the maintenance period. Details of ESL dosing at the start of the OLE study are provided in Table S1 (Study Design). ESL dosing could be adjusted throughout the study, according to response and tolerability, within the dose range 800-1600 mg QD. Of note, ESL dosing was not required to be uptitrated in those patients who experienced seizure events and investigators could decide to introduce an additional ASM to control seizures.

Treatment continued until the end-of-study visit, which took place 24 months ± 7 days after the first visit of the OLE study. Patients who discontinued prematurely attended an early discontinuation visit within 3 days of discontinuing. The maximum study duration of the OLE study, including the follow-up phase, was 105 weeks.

The study protocol, protocol amendments, informed consent forms, and patient information sheet were reviewed and approved by independent ethics committees/institutional review boards, in accordance with local laws and regulations. The study was conducted according to the International Council for Harmonization Good Clinical practice guidelines, and in accordance with the Declaration of Helsinki and local laws and regulations. The study is registered with ClinicalTrials.gov (NCT02484001) and EudraCT (2015-001243-36).

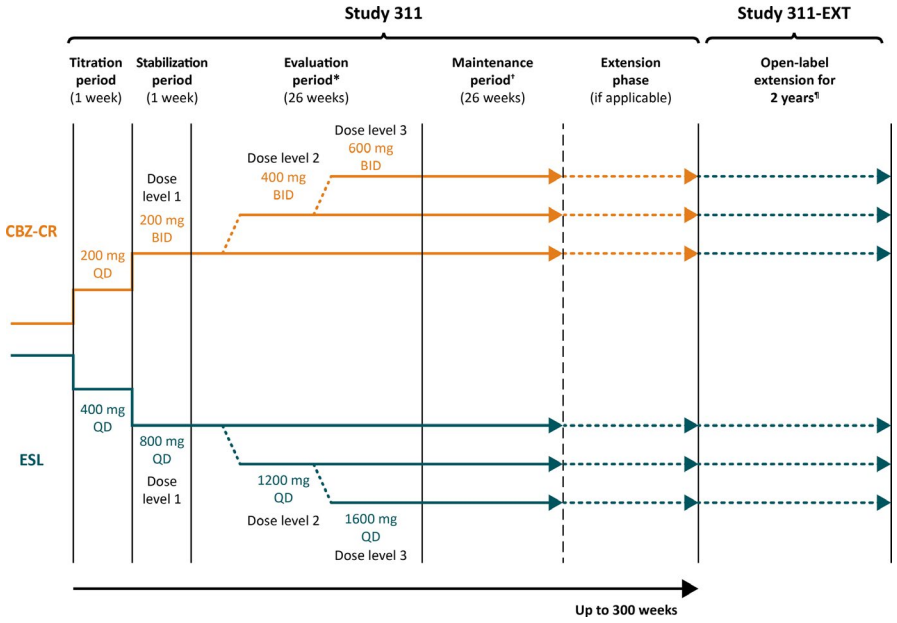

FIGURE 1 Study design. *If seizures occurred during the evaluation period of the double-blind (DB) study, patients were assigned to the next dose level using 1-week titration period (controlled-release carbamazepine [CBZ-CR] required titration, eslicarbazepine acetate [ESL] did not) and 1-week stabilization period, followed by 26-week evaluation period as before. †Patients who remained seizure-free for 26 weeks at any dose during the evaluation period entered the 26-week maintenance period. After the 26-week maintenance period, patients continued in an extension phase until the database lock (the database was locked after the last patient had completed the 26-week maintenance period). For all patients participating in the open-label extension (OLE) extension study, the last extension phase visit of the DB study was also OLE visit 1 for the OLE study. ¶Patients who received CBZ-CR during the DB phase 3 trial transitioned to ESL at the start of the open-label extension study. BID, twice daily; QD, once daily. Adapted from Trinka et al[3]

2.2 | Study population

Details of the inclusion and exclusion criteria used in the OLE study are provided in Table S1 (Study Population).

2.3 | Study assessments

The primary efficacy outcome measure was ESL retention rate, measured as treatment retention time and defined as the time from baseline of the OLE study to withdrawal of ESL due to an adverse event (AE) or lack of efficacy. The probability of seizure failure (ie, withdrawal of ESL due to an AE or lack of efficacy) was calculated. Secondary efficacy outcome measures comprised time to withdrawal, defined as the time from OLE study baseline to withdrawal of ESL for any reason; seizure freedom rate, defined as the proportion of patients without any seizures during the OLE study; seizure duration and type; standardized seizure frequency (SSF), defined as the number of seizures per 28 days; and responder rate, where response was defined as ≥50% seizure frequency reduction from the baseline of the double-blind trial. Other secondary efficacy assessments comprised quality of life (assessed using the Quality of Life in Epilepsy Inventory-31 [QOLIE-31][7]) and treatment satisfaction (assessed by investigators and patients, based on a four-point scale of "poor," "fair," "good," or "very good"[8]), both of which were evaluated throughout the OLE study.

Safety/tolerability assessments comprised evaluation of treatment-emergent AEs (TEAEs); clinical laboratory evaluations; physical (including neurological) examinations and vital sign measurements; electrocardiograms (ECGs); the Columbia-Suicide Severity Rating Scale (C-SSRS)[9]; and the Bond-Lader visual analogue scales.[10]

2.4 | Statistical methodology

The Full Analysis Set (FAS) was defined as all patients who were enrolled and treated with at least one dose of ESL during the OLE study and who had treatment retention time data available. The Monotherapy FAS was defined as all patients included in the FAS who received ESL monotherapy throughout the OLE study. The Safety Set was defined as all patients who were enrolled and treated with at least one dose of ESL during the OLE study. The Monotherapy Safety Set was defined as all patients included in the Safety Set who received ESL monotherapy throughout the OLE study. In this work, all efficacy assessments were performed for the Monotherapy FAS, whereas safety/tolerability assessments were performed for the Monotherapy Safety Set.

Details of the statistical tests employed in the OLE study are provided in Table S1 (Statistical Methodology).

3 | RESULTS

3.1 | Patient disposition

From 280 patients who completed the extension phase of a double-blind trial,[3] a total of 207 patients (73.9%) were enrolled in the OLE study (Figure 2), of whom 110 had previously been treated with ESL in the double-blind trial (ESL/ESL group) and 97 had previously been treated with CBZ-CR in the double-blind trial (CBZ-CR/ESL group). As one patient in the ESL/ESL group was a screening failure, 206 patients were randomized and received the study drug. From those, a total of 184 (89.3%) patients, 96 (88.1%) patients in the ESL/ESL group and 88 (90.7%) patients in the CBZ-CR/ESL group, remained on ESL monotherapy until the end-of-study visit or early discontinuation visit; these patients comprised the Monotherapy sets (FAS and Safety). Thirteen (11.9%) patients in the ESL/ESL group and nine (9.3%) patients in the CBZ-CR/ESL group were treated with concomitant ASMs during the study (Table S2).

Overall, 80 of 96 (83.3%) patients in the ESL/ESL group and 75 of 88 (85.2%) patients in the CBZ-CR/ESL group completed the study. The primary reasons for discontinuation (≥5% of patients in either group) were AEs (ESL/ESL, 6.3%; CBZ-CR/ESL, 4.5%) and withdrawal of consent (ESL/ESL, 5.2%; CBZ-CR/ESL, 4.5%). No patient in either group discontinued due to lack of efficacy.

3.2 | Patient demographic and baseline characteristics

Patient demographic and baseline characteristics of patients in the Monotherapy sets were generally well balanced between groups (Table 1). The total number of seizures in the 3 months prior to the baseline of the double-blind trial was higher for the CBZ-CR/ESL group than the ESL/ESL group (mean = 10.7 vs 6.7), as was the number of focal impaired awareness seizures (mean = 5.9 vs 2.9). Similarly, the total number of seizures during the 12 months prior to the baseline of the double-blind trial was higher for the CBZ-CR/ESL group than the ESL/ESL group (mean = 21.3 vs 14.9). For >50% of patients, the etiology of epilepsy was unknown; however, a lower proportion of patients in the ESL/ESL group versus CBZ-CR/ESL group had post–traumatic brain

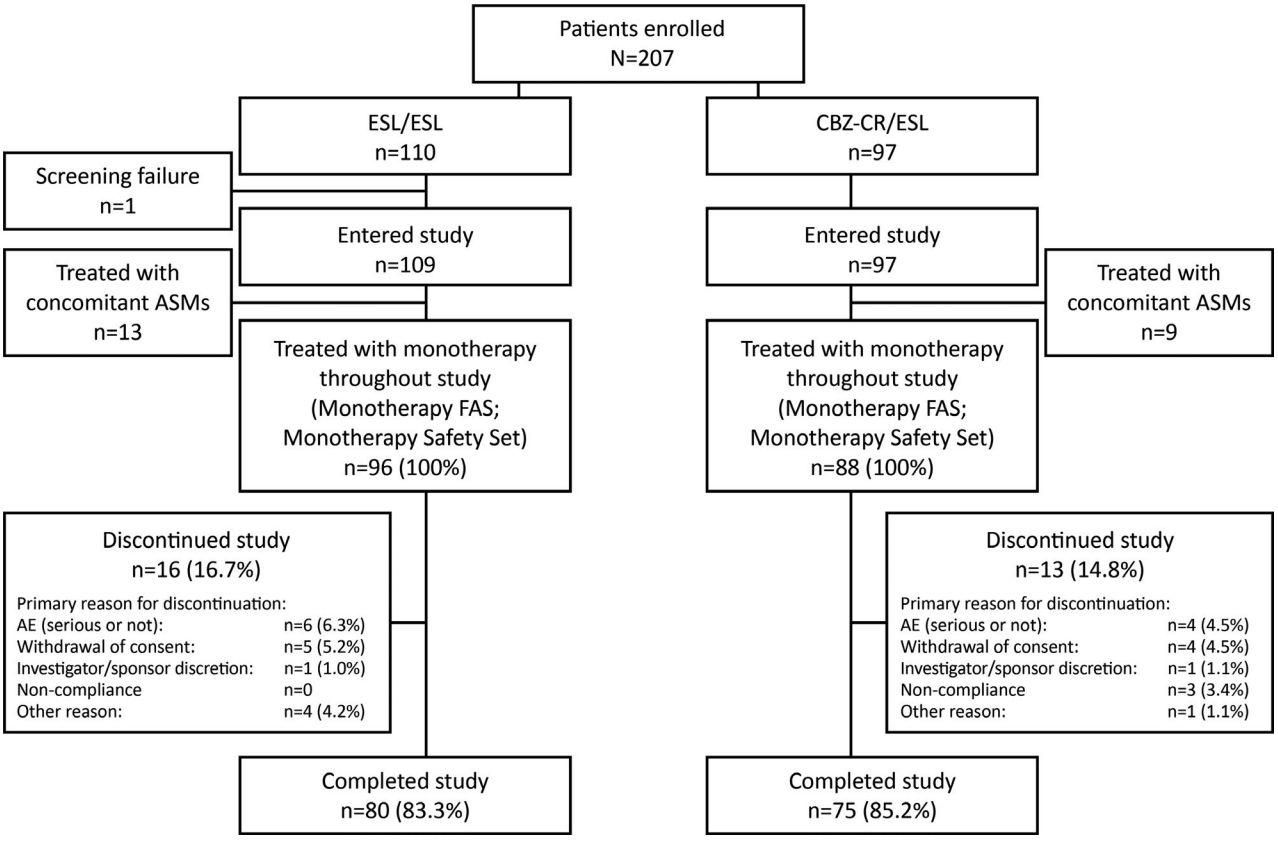

FIGURE 2 Patient disposition. AE, adverse event; ASM, antiseizure medication; CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; FAS, Full Analysis Set

TABLE 1 Demographic and baseline characteristics (Monotherapy Safety Set/Monotherapy Full Analysis Set)

	ESL/ESL, n = 96	CBZ-CR/ESL, n = 88	Total, n = 184
Demographic characteristics[a]			
Sex, n (%)			
Male	55 (57.3)	45 (51.1)	100 (54.3)
Female	41 (42.7)	43 (48.9)	84 (45.7)
Age, y			
Mean (SD)	42.5 (15.8)	41.6 (15.8)	42.1 (15.8)
Median (range)	40.0 (20-76)	39.0 (20-78)	40.0 (20-78)
Age group, n (%)			
18-<50 y	62 (64.6)	52 (59.1)	114 (62.0)
50-<65 y	22 (22.9)	30 (34.1)	52 (28.3)
65-<85 y	12 (12.5)	6 (6.8)	18 (9.8)
Ethnicity, n (%)			
Caucasian	90 (93.8)	81 (92.0)	171 (92.9)
Other	6 (6.3)	7 (8.0)	13 (7.1)
Body mass index, kg/m^2			
Mean (SD)	25.7 (4.4)	25.9 (4.6)	25.8 (4.5)
Median (range)	25.5 (17.8-36.1)	25.1 (16.4-45.2)	25.4 (16.4-45.2)
Epilepsy-related characteristics[b]			
Age at onset of epilepsy, y			
Missing data	2	1	3
Mean (SD)	39.5 (15.8)	38.9 (15.8)	39.2 (15.8)
Median (range)	37.0 (18-74)	37.0 (18-75)	37.0 (18-75)
Time since last seizure, d			
Missing data	3	5	8
Mean (SD)	19.3 (20.7)	20.6 (22.9)	19.9 (21.7)
Median (range)	11.0 (0-88)	10.0 (0-88)	11.0 (0-88)
Number of seizures during previous 3 mo, n			
Total seizures			
Mean (SD)	6.7 (12.8)	10.7 (28.3)	8.6 (21.7)
Median (range)	2.0 (1-91)	3.0 (1-230)	2.0 (1-230)
Focal aware seizures			
Mean (SD)	2.8 (6.7)	3.9 (8.8)	3.3 (7.8)
Median (range)	0.0 (0-39)	0.0 (0-47)	0.0 (0-47)
Focal impaired awareness seizures			
Mean (SD)	2.9 (11.8)	5.9 (27.9)	4.3 (21.1)
Median (range)	0.0 (0-91)	0.0 (0-230)	0.0 (0-230)
Focal to bilateral tonic-clonic seizures			
Mean (SD)	1.0 (0.9)	0.9 (1.1)	1.0 (1.0)
Median (range)	1.0 (0-5)	1.0 (0-6)	1.0 (0-6)
Number of seizures during previous 12 mo, n			
Total seizures			
Mean (SD)	14.9 (31.8)	21.3 (45.7)	18.0 (39.1)
Median (range)	4.0 (2-187)	4.0 (2-260)	4.0 (2-260)
Focal aware seizures			

(Continues)

TABLE 1 (Continued)

	ESL/ESL, n = 96	CBZ-CR/ESL, n = 88	Total, n = 184
Mean (SD)	6.4 (17.8)	9.9 (27.7)	8.0 (23.1)
Median (range)	0.0 (0-104)	0.0 (0-200)	0.0 (0-200)
Focal impaired awareness seizures			
Mean (SD)	6.9 (28.3)	9.9 (39.1)	8.3 (33.8)
Median (range)	0.0 (0-187)	0.0 (0-260)	0.0 (0-260)
Focal to bilateral tonic-clonic seizures			
Mean (SD)	1.7 (1.3)	1.6 (1.8)	1.6 (1.6)
Median (range)	2.0 (0-6)	1.0 (0-9)	1.0 (0-9)
Etiology, n (%)			
Idiopathic	2 (2.1)	0	2 (1.1)
Infectious diseases	2 (2.1)	1 (1.1)	3 (1.6)
Congenital/hereditary disorders	2 (2.1)	2 (2.3)	4 (2.2)
Brain tumors	2 (2.1)	0	2 (1.1)
Cranial trauma/injuries	5 (5.2)	21 (23.9)	26 (14.1)
Cerebrovascular disease	17 (17.7)	7 (8.0)	24 (13.0)
Other	8 (8.3)	11 (12.5)	19 (10.3)
Unknown	58 (60.4)	46 (52.3)	104 (56.5)
Family history of epilepsy, n (%)			
Yes	7 (7.3)	4 (4.5)	11 (6.0)
No	88 (91.7)	82 (93.2)	170 (92.4)
Unknown	1 (1.0)	2 (2.3)	3 (1.6)

Abbreviations: CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; SD, standard deviation.

[a]At baseline of open-label extension study.

[b]At baseline of double-blind trial.

injury epilepsy (5.2% vs 23.9%) and a higher proportion of patients in the ESL/ESL group versus CBZ-CR/ESL group had epilepsy resulting from cerebrovascular disease (17.7% vs 8.0%). The use of different concomitant medications was similar between groups (<10% difference), except for beta-blocking agents, which were more frequently used in the ESL/ESL group than in the CBZ-CR/ESL group (17.4% vs 7.2%).

3.3 | ESL treatment

The majority of patients in the ESL/ESL and CBZ-CR/ESL groups maintained the same ESL dose during the 2-year OLE study (95.8% and 89.8%, respectively). In the ESL/ESL group, four patients (4.2%) had a dose increase, and in the CBZ-CR/ESL group, nine patients (10.2%) had a dose increase. The median (interquartile range; mean; SD) daily ESL dose was similar for the ESL/ESL group (800.0 [800-800; 899.2; 205.0] mg/d) and the CBZ-CR/ESL group (796.2 [792.4-959.7; 910.3; 217.4] mg/d). The median (interquartile range; mean; SD) total duration of treatment was also similar for the ESL/ESL group (734.0 [724.5-741.5; 685.8; 129.2] days) and the CBZ-CR/ESL group (730.5 [723.0-737.0; 680.5; 160.1] days).

3.4 | Efficacy assessments

Treatment retention time was similar between groups, with a low probability of treatment failure throughout the OLE study (<0.07 at any time; Figure 3A). After 24 months of open-label ESL treatment (Day 720), the probability of treatment failure was 0.0638 (95% confidence interval [CI] = 0.0292-0.1366) in the ESL/ESL group and 0.0472 (95% CI = 0.0180-0.1210) in the CBZ-CR/ESL group.

Time to withdrawal was also similar between groups (Figure 3B). The proportion of patients who withdrew from ESL for any reason was low and similar between groups throughout the OLE study (≤17% of patients in either group), and the proportion of patients with TEAEs leading to ESL discontinuation was low in both groups (ESL/ESL, 3.1%; CBZ-CR/ESL, 4.5%). Overall, 87 of 96 (90.6%) patients in the ESL/ESL group and 71 of 88 (80.7%) patients in the CBZ-CR/ESL group remained seizure-free throughout the OLE study (95% CI for difference in seizure freedom

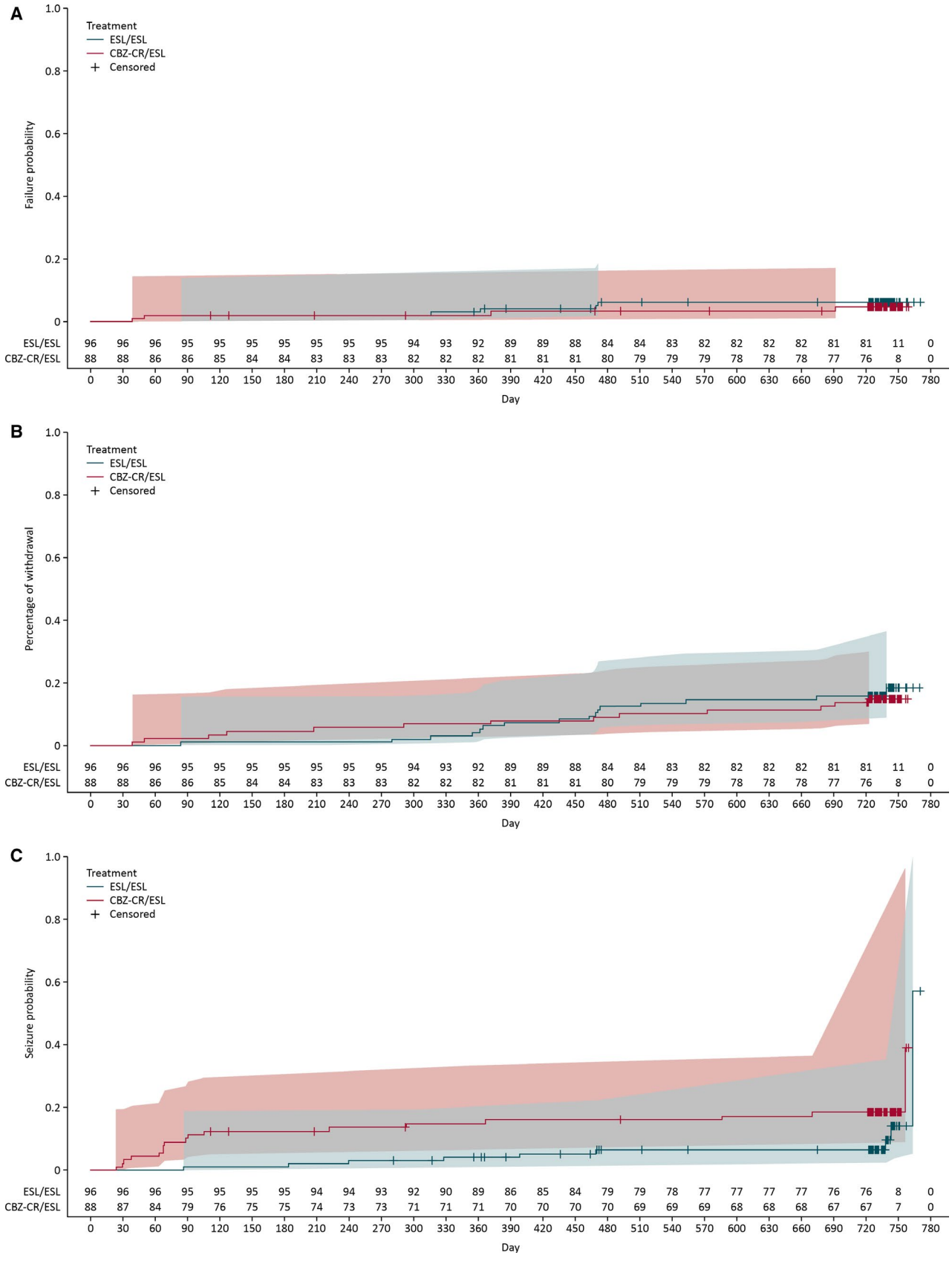

FIGURE 3 Kaplan-Meier plots of (A) treatment retention time, (B) time to withdrawal, and (C) time to first seizure (Monotherapy Full Analysis Set). CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate

rate = −0.0016 to 0.2004; $P = .0531$). After 24 months of open-label ESL treatment (Day 720), the probability of a seizure was 0.0644 (95% CI = 0.0294-0.1380) in the ESL/ESL group and 0.1851 (95% CI = 0.1177-0.2845) in the CBZ-CR/ESL group. In the CBZ-CR/ESL group, patients underwent an initial cross-tapering period for 14-21 days; the probability of a seizure in this group increased during the first 120 days of ESL treatment and thereafter stabilized (probability of a seizure at 120 days = 0.1250, 95% CI = 0.0713-0.2143; Figure 3C). The rate of seizure events after 120 days of ESL treatment was low and comparable between groups.

The proportion of patients who experienced seizures was lower in the ESL/ESL group than in the CBZ-CR/ESL group (9.4% vs 19.3%), driven by the increased occurrence of seizures in the CBZ-CR/ESL group during the first 120 days of ESL treatment, and there were also some differences between groups in type, number, and duration of seizures experienced (Table 2). The decrease in SSF observed in the double-blind trial[3] was maintained throughout the OLE study, with responder rates in both groups remaining >80% (Table S3).

Improvements in quality of life (QOLIE-31 score) observed in the double-blind trial were maintained throughout the OLE study, and most of the patients' and investigators' assessments of treatment satisfaction at all treatment visits were classified either "very good" or "good" (≥80% of patients per visit) in both groups (Table S4).

3.5 | Safety assessments

The incidence of TEAEs was lower in the ESL/ESL group than in the CBZ-CR/ESL group, but the incidence of TEAEs that were considered at least possibly related to treatment was similar between groups (Table 3). The most frequently reported TEAEs that were considered at least possibly related to treatment (≥3% of patients in any group) were γ-glutamyltransferase (GGT) increase (relative to baseline of OLE study), blood creatine phosphokinase increase (relative to baseline of OLE study), and nausea. The incidence of serious TEAEs was similar between groups, and only one serious TEAE was considered at least possibly related to treatment (a seizure in the CBZ-CR/ESL group, which resolved following a dose increase). Three patients died due to TEAEs (all in the ESL/ESL group), but no death was considered related to treatment (cerebral hemorrhage, n = 1; pulmonary embolism, n = 1; sudden death after myocardial infarction, n = 1). The majority of TEAEs were of mild or moderate intensity.

TABLE 2 Seizure information (Monotherapy Full Analysis Set)

	ESL/ESL, n = 96	CBZ-CR/ESL, n = 88	Total, n = 184
Patients with seizures, n (%)			
Total seizures	9 (9.4)	17 (19.3)	26 (14.1)
Focal aware seizures	2 (2.1)	3 (3.4)	5 (2.7)
Focal impaired awareness seizures	2 (2.1)	8 (9.1)	10 (5.4)
Focal to bilateral tonic-clonic seizures	4 (4.2)	10 (11.4)	14 (7.6)
Generalized seizures	1 (1.0)	0	1 (0.5)
Unclassifiable seizures	2 (2.1)	0	2 (1.1)
Number of total seizures, n (%)			
0	87 (90.6)	71 (80.7)	158 (85.9)
1	5 (5.2)	6 (6.8)	11 (6.0)
2	1 (1.0)	6 (6.8)	7 (3.8)
3-5	1 (1.0)	1 (1.1)	2 (1.1)
≥6	2 (2.1)	4 (4.5)	6 (3.3)
Duration of total seizures, n (%)			
<30 s	0	2 (2.3)	2 (1.1)
≥30 s to <1 min	2 (2.1)	5 (5.7)	7 (3.8)
≥1 min to <5 min	4 (4.2)	14 (15.9)	18 (9.8)
≥5 min	5 (5.2)	5 (5.7)	10 (5.4)
Unknown	1 (1.0)	0	1 (0.5)

Abbreviations: CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate.

TABLE 3 Summary of TEAEs (Monotherapy Safety Set)

	ESL/ESL, n = 96	CBZ-CR/ESL, n = 88	Total, n = 184
Any TEAE, n (%)	51 (53.1)	58 (65.9)	109 (59.2)
Most frequently reported[a] TEAEs, n (%)			
Blood creatine phosphokinase increased	7 (7.3)	5 (5.7)	12 (6.5)
Nasopharyngitis	5 (5.2)	6 (6.8)	11 (6.0)
Hypertension	5 (5.2)	6 (6.8)	11 (6.0)
Influenza	6 (6.3)	4 (4.5)	10 (5.4)
Back pain	3 (3.1)	5 (5.7)	8 (4.3)
Dizziness	3 (3.1)	5 (5.7)	8 (4.3)
Headache	3 (3.1)	5 (5.7)	8 (4.3)
Somnolence	3 (3.1)	5 (5.7)	8 (4.3)
International normalized ratio increased	2 (2.1)	5 (5.7)	7 (3.8)
Gamma-glutamyltransferase increased	5 (5.2)	1 (1.1)	6 (3.3)
Bronchitis	0	5 (5.7)	5 (2.7)
At least possibly related TEAEs, n (%)	17 (17.7)	16 (18.2)	33 (17.9)
Most frequently reported[b] at least possibly related TEAEs, n (%)			
Gamma-glutamyltransferase increased	4 (4.2)	0	4 (2.2)
Blood creatine phosphokinase increased	3 (3.1)	1 (1.1)	4 (2.2)
Nausea	0	3 (3.4)	3 (1.6)
C-reactive protein increased	0	2 (2.3)	2 (1.1)
Headache	0	2 (2.3)	2 (1.1)
Obesity	2 (2.1)	0	2 (1.1)
Somnolence	2 (2.1)	0	2 (1.1)
Serious TEAEs, n (%)	7 (7.3)	5 (5.7)	12 (6.5)
At least possibly related serious TEAEs, n (%)	0	1 (1.1)	1 (0.5)
TEAEs leading to death, n (%)	3 (3.1)	0	3 (1.6)
TEAEs by severity, n (%)			
Mild	42 (43.8)	49 (55.7)	91 (49.5)
Moderate	25 (26.0)	27 (30.7)	52 (28.3)
Severe	8 (8.3)	4 (4.5)	12 (6.5)
TEAEs leading to discontinuation, n (%)[c]	3 (3.1)	4 (4.5)	7 (3.8)

Abbreviations: CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; TEAE, treatment-emergent adverse event.

[a]≥5% of patients in any group.

[b]≥2% of patients in any group.

[c]ESL/ESL: hyponatremia (n = 1), mesenteric artery thrombosis (n = 1), renal artery thrombosis (n = 1), and somnolence (n = 1); CBZ-CR/ESL: bladder cancer (n = 1), chromaturia (n = 1), gastritis (n = 1), hematuria (n = 1), recurrent prostate cancer (n = 1), seizure (n = 1), and vertigo (n = 1).

The incidence of TEAEs leading to discontinuation was low in both groups, and no TEAE led to the discontinuation for more than one patient.

For nearly all laboratory parameters, no relevant changes over time or differences between groups were observed. Exceptions were the proportion of patients with high GGT and high total cholesterol. The proportion of patients with high GGT increased slightly in the ESL/ESL group (from 22.8% at baseline to 29.3% at the end-of-study visit), but decreased markedly in the CBZ-CR/ESL group (from 49.4% to 15.1%). A higher proportion of patients in the CBZ-CR/ESL group had high GGT values at the baseline of the OLE study versus the baseline of the double-blind trial (49.4% vs 6.8%) in comparison with the ESL/ESL group (22.8% vs 16.7%). These changes were also reflected in the mean GGT levels over time. These abnormalities were not corroborated by similar changes in other laboratory parameters, or by hepatic dysfunction (for GGT). No patient discontinued treatment due to GGT or any hepatic-related laboratory changes.

The proportion of patients with high total cholesterol decreased in both groups, but more markedly in the CBZ-CR/ESL group (from 31.0% to 17.8%) than in the ESL/ESL group (from 17.4% to 11.8%). In both groups, the proportion of patients with high total cholesterol at the end of the OLE study was similar to the proportion of patients with high total cholesterol at the start of the double-blind trial (ESL/ESL, 11.5%; CBZ-CR/ESL, 15.9%). With regard to low-density lipoprotein (LDL) cholesterol, the proportion of patients with high LDL cholesterol in the ESL/ESL group remained relatively stable during the OLE study (14.1% at baseline; 14.5% at end of study), whereas in the CBZ-CR/ESL group, the proportion decreased (26.4% at baseline; 15.1% at end of study). As with total cholesterol, the proportion of patients with high LDL cholesterol at the end of the OLE study was similar to the proportion of patients with high LDL cholesterol at the start of the double-blind in both groups (ESL/ESL, 14.6%; CBZ-CR/ESL, 14.8%).

The majority of patients in both groups had sodium values >130 mEq/L throughout the study (ESL/ESL, 93.8%; CBZ-CR/ESL, 95.5%). A sodium decrease of >10 mEq/L from open-label baseline was observed in three patients (3.4%) in the CBZ-CR/ESL group only. Sodium levels ≤125 mEq/L were observed in one patient (1.0%) in the ESL/ESL group and two patients (2.3%) in the CBZ-CR/ESL group. One patient (1.0%) in the ESL/ESL group discontinued due to hyponatremia (sodium level = 126 mEq/L).

There were no clinically meaningful changes over time or differences between groups in vital signs, neurological examinations, or ECGs. Suicidal ideation was reported via the C-SSRS for one patient in the ESL/ESL group, and improvement in suicidal ideation was reported for one patient in each group. No relevant changes in mean scores over time or differences between groups were observed for any of the Bond-Lader factors of alertness, calmness, or contentedness.

4 | DISCUSSION

This OLE study demonstrated the maintenance of efficacy of ESL during long-term treatment and the efficacy of ESL in patients who switched from CBZ-CR treatment. After 2 years of open-label treatment, the risk of withdrawal of ESL due to an AE or lack of efficacy was <7%, and, in both groups, >80% of patients who entered the OLE study remained seizure-free throughout its duration. The decrease in SSF observed in the double-blind trial was maintained throughout the OLE study, and the responder rate remained >80% in both groups under ESL monotherapy. Only a minority of the 206 randomized patients who received ESL in the OLE study (22/206, 10.7%) required treatment with concomitant ASMs; however, as per the study protocol, the ESL dosage was not necessarily uptitrated until maximum dose before the addition of a concomitant ASM. Improvements in quality of life observed in the phase 3 trial[3] were maintained throughout the OLE study, and the majority of patients and investigators rated treatment satisfaction as "good" or "very good."

Seizure freedom observed in the OLE study was higher in patients who had previously received ESL in the phase 3 trial (90.6%) than in those who had previously received CBZ-CR (80.7%). In the CBZ-CR/ESL group, the probability of having a seizure was highest during the transition to ESL treatment; thereafter, the probability of a seizure event was similar between groups. These findings are broadly consistent with those of a matched prospective study demonstrating that seizure-free patients who switched from a range of ASM monotherapies, for reasons such as side effects and costs, had approximately a 14% additional risk of seizure recurrence compared with patients who remained on the same treatment.[11] The observed difference in seizure freedom rates between the groups might have been related to dissimilarities in epilepsy etiologies between groups, because seizures with a vascular etiology may be more easily controlled than other etiologies.[12] Observed differences between groups in the types of seizures patients experienced might also have been influenced by differences in etiologies, although it is perhaps also notable that the frequency of focal impaired awareness seizures at baseline of the double-blind trial was somewhat higher in the CBZ-CR/ESL group than in the ESL/ESL group.

This study also demonstrated the safety/tolerability of ESL during long-term treatment and the safety/tolerability of ESL in patients transitioning from CBZ-CR treatment. Only one serious TEAE (a seizure) was considered at least possibly related to treatment. The three deaths that occurred

in the ESL/ESL group were not considered to be related to treatment, and all were associated with cerebrovascular or cardiovascular disease. The incidence of TEAEs leading to discontinuation was low in both groups, and no TEAE led to discontinuation for more than one patient. The types of TEAEs reported were generally consistent with the known safety profile of ESL.[1,2] Differences between groups in the proportion of patients with high GGT and changes in GGT over time were not corroborated by similar changes in other laboratory parameters, or by hepatic dysfunction; therefore, no clinically meaningful conclusions from these findings can be made. Moreover, these differences are unlikely to be related to concomitant medications, because with the exception of beta-blocking agents, the use of concomitant treatments was comparable between groups. Similarly, differences between groups in the proportion of patients with high total cholesterol and changes in total cholesterol over time were not corroborated by changes in mean cholesterol levels in either group, and there appeared to be no association of increased GGT and high total cholesterol, as only one patient (CBZ-CR/ESL group) had simultaneous increases in GGT, total cholesterol, and LDL cholesterol at one specific visit. However, the observed decreases in the proportions of patients with high total and LDL cholesterol among those switching from CBZ-CR to ESL are consistent with evidence demonstrating that CBZ is associated with significant increases in total and LDL cholesterol[13] and that patients who transition from CBZ to ESL may experience significant improvements in lipid levels.[14,15] CBZ not only appears to increase lipid levels via its effects on enzymes involved in endogenous metabolic pathways[16] but may also interfere with the ability of statins to lower cholesterol; moreover, CBZ's effects in raising levels of LDL cholesterol and triglycerides appear to be gender-related, being greater in men than in women.[13] Such evidence has led to recommendations for considering changing patients from CBZ to ESL if they develop, or if they are at risk of developing, dyslipidemia/hypercholesterolemia.[14,17] This is particularly relevant for those whose epilepsy etiology is related to cerebrovascular disease. Hyponatremia did not emerge as a safety concern with long-term ESL treatment; sodium levels ≤125 mEq/L were observed in no more than two patients in either group, and only one patient (ESL/ESL group) discontinued due to hyponatremia.

In an OLE study conducted in 140 patients completing two phase 3 withdrawal to monotherapy trials in patients with drug-resistant focal epilepsy,[4,5] median treatment retention time and time on ESL monotherapy were >5 years.[18] Median SSF reduction from baseline was 78.3%, and the responder rate was 74.3%. Long-term ESL monotherapy was also associated with improvements in quality of life and depressive symptoms. Tolerability appeared to be better in patients treated with ESL monotherapy than in those who required treatment with adjunctive ASMs.[18] Taken together with the results of the present study, evidence from clinical trials has therefore demonstrated that ESL monotherapy is effective and generally well tolerated over the long term, both in patients with newly diagnosed focal epilepsy and in those with drug-resistant focal epilepsy who subsequently convert to ESL monotherapy.

The long-term effectiveness of ESL monotherapy has also been investigated in the clinical practice setting. The MONOZEB study evaluated the effectiveness of ESL monotherapy when used for ≥1 year in routine clinical practice in Spain (N = 435).[19] The mean duration of ESL monotherapy was 66.7 months, and retention rates were 88.0% at 1 year and 81.9% at 2 years. Seizure freedom rates were 63.2% at 1 year, 65.1% at 2 years, and 50.3% during the entire follow-up. At the last visit, the mean seizure frequency reduction was 75.5%. The most frequent side effects were dizziness, hyponatremia (sodium < 135 mEq/L), and somnolence.[19] In the Euro-Esli study (the largest study of ESL in clinical practice conducted to date, with >2000 patients included), the proportion of patients treated with ESL monotherapy increased from 4.3% at baseline to 17.1% at the last visit.[20] After 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.[21] The most common AEs were dizziness, somnolence, instability/ataxia, and fatigue.[21] In a further multicenter, prospective, clinical practice study, conducted in 17 hospitals in Spain (N = 117), the responder rate after 12 months of ESL monotherapy was 83.0%.[22] The results reported in these clinical practice studies are generally comparable with those observed in the current study in terms of effectiveness and safety/tolerability.

Studies conducted primarily in the clinical practice setting have demonstrated that ESL monotherapy can be effective in patients who have transitioned from CBZ monotherapy due to lack of efficacy or poor tolerability.[23] The current study demonstrated that ESL monotherapy maintained seizure control in the majority of patients who transitioned from CBZ-CR to ESL, but the higher risk of seizures observed in the CBZ-CR/ESL group during the first 3-4 months, compared with the ESL/ESL group, illustrates the challenges associated with switching patients from one ASM to another. Published guidance has highlighted that transitioning patients from CBZ to ESL requires careful consideration on a patient-by-patient basis, primarily because CBZ may have a different mechanism of action than ESL[24–26] and is a stronger inducer of cytochrome P450 enzymes.[14,17]

The current study had several limitations. First, patients who experienced seizures were not forced to uptitrate their ESL dose, and consequently some investigators introduced concomitant ASM treatment to control seizures. Second, the length of time patients had been seizure-free varied at the

OLE study baseline, depending on how long they were in the extension phase of the double-blind trial before entering the OLE study. Third, the dose ratios used to calculate ESL target doses for patients treated with CBZ-CR in the double-blind trial varied somewhat depending on each patient's last evaluated CBZ-CR dose (2.0 for patients converting from CBZ-CR 200 mg BID to ESL 800 mg QD, 1.5 for patients converting from CBZ-CR 400 mg BID to ESL 1200 mg QD, and 1.3 for patients converting from CBZ-CR 600 mg BID to ESL 1600 mg QD), and this lack of homogeneity may have introduced bias. The double-blind trial started before the publication of articles suggesting a dose ratio of 1:1.3 for CBZ:ESL when transitioning from CBZ to ESL.[14,17] Fourth, smoker status and alcohol consumption were not captured during the study, and this might have influenced the observed differences between groups in the proportion of patients with high GGT and changes in GGT over time. Finally, the study population comprised selected patients who were already responsive to ESL or CBZ-CR monotherapy, as patients were required to achieve seizure freedom before entering the OLE study; in addition, the study population tolerated ESL or CBZ-CR well, as patients who dropped out from the double-blind trial because of TEAEs were not included in the OLE study.

In conclusion, this study demonstrated that ESL monotherapy was efficacious and generally well tolerated over the long term (2 years), with approximately 84% of patients being retained on ESL treatment and >80% of patients remaining seizure-free throughout the study. ESL monotherapy was associated with sustained improvements in quality of life and high levels of treatment satisfaction. No new safety concerns emerged with long-term ESL treatment in the monotherapy setting.

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CONFLICT OF INTEREST

E.T. reports personal fees from EVER Pharma, Marinus, Argenix, Medtronic, Bial-Portela & C[a], S.A., NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Genzyme Sanofi, and Actavis; his institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubilaumsfond der Österreichischen Nationalbank outside the submitted work. R.R. is a consultant for Eisai, Bial, UCB, GlaxoSmithKline and Shire, and receives grant and research support from Bial, Eisai, and UCB. J.C. has received speaker's honoraria and/or consultancy fees from Bial and Eisai and was granted with a Tecnifar Bursary. J.M., F.I., and P.S.d.S. are current 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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