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MONOZEB: Long-term observational study of eslicarbazepine acetate monotherapy

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ABSTRACT

Aim: The aim of the study was to evaluate the effectiveness and tolerability of eslicarbazepine acetate (ESL) when used as monotherapy for 1 year or more in routine clinical use in patients with focal seizures in epilepsy clinics in Spain.

Methods: This is a retrospective, observational, noninterventional study. Eligible patients were aged ≥18 years, had focal seizures, and started on ESL ≥1 year before database closure. Primary endpoint was the following: proportion seizure-free for ≥6 months at 1 and 2 years. Secondary endpoints included retention on ESL monotherapy at 1 and 2 years, seizure frequency change, seizure worsening, and side effects. Other analyses included seizure freedom from baseline to 1 and 2 years and outcomes in special populations.

Results: Four hundred thirty-five patients were included (127 on first-line monotherapy and 308 converting to ESL monotherapy): median daily dose was 800 mg at all time points; 63.2% were seizure-free at 1 year, 65.1% at 2 years, and 50.3% for the entire follow-up. Mean duration of ESL monotherapy was 66.7 months; retention was 88.0% at 1 year and 81.9% at 2 years. Mean reduction in seizure frequency was 75.5% at last visit. Over the entire follow-up, seizure worsening was seen in 22 patients (5.1%), side effects in 28.0%, considered severe in 1.8%, and leading to discontinuation in 5.7%. Dizziness, hyponatremia (sodium <135 mEq/l), and somnolence were the most frequent side effects. Outcomes in special populations (patients aged ≥65 years and those with psychiatric history or learning difficulty) were consistent with the overall population.

Conclusions: Patients with focal seizures taking ESL monotherapy had excellent retention, high seizure-free rates, and good tolerability up to 2 years.

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1. Introduction

Epilepsy is one of the most common neurological disorders, with an estimated risk of 3% to age 80 years [1]. Despite many new antiepileptic drug (AED) approvals, successful treatment is still hampered by problems like persistent drug resistance [2], poor adherence to treatment, and side effects that impact quality of life and can impair adherence and long-term retention [3]. The cost of poor adherence is high, both in monetary terms for payers [4], and in risk of early mortality for patients [5]. Simplifying dosage regimens can help to increase adherence [6], and therefore, the potential for once-daily administration should be an important consideration in treatment selection, particularly for patients on AED monotherapy.

Eslicarbazepine acetate (ESL) is a dibenz[b,f]azepine derivative like carbamazepine and oxcarbazepine. Eslicarbazepine acetate is rapidly de-esterified at the acetate functional group to produce the primary pharmacologically active metabolite S-licarbazepine, which accounts for around 95% of the circulating active metabolites [7].

Eslicarbazepine inhibits voltage-gated sodium channels but differently from carbamazepine and oxcarbazepine. The affinity of eslicarbazepine for voltage-gated sodium channels in the resting state is about 15- to 5-fold lower than that of carbamazepine, oxcarbazepine, and R-licarbazepine [8], instead of having a predominant effect on channel slow inactivation [9].

Eslicarbazepine acetate is approved in the USA for the treatment of focal (partial-onset) seizures in patients aged ≥4 years [10]. In Europe, ESL is approved as monotherapy in the treatment of focal or focal-to-bilateral seizures (partial-onset seizures, with or without secondary generalization) in adults with newly diagnosed epilepsy and as adjunctive therapy in adults, adolescents, and children aged >6 years with focal or focal-to-bilateral seizures (partial-onset seizures with or without secondary generalization) [11]. The program included four pivotal, phase III, multicenter, randomized, double-blind, placebo-controlled clinical trials of adjunctive ESL [12–15]. More recently, the efficacy and safety of converting to ESL monotherapy has been reported [15], and ESL monotherapy has been compared with carbamazepine controlled-release monotherapy in a randomized, double-blind, parallel-group study [16].

Clinical trials are essential to meet regulatory requirements; however, because they often use unrealistic dosing regimens and exclude patients with common comorbidities, they leave many practical questions unanswered [17]. Observational studies of routine clinical use are necessary to fill these gaps and provide information that is relevant to real-life clinical practice. Eslicarbazepine acetate, with its once-daily administration, is a good option for long-term monotherapy for many patients with focal seizures, and although large series in clinical practice with this AED have been published [18–20], there are few observational studies in monotherapy [21,22]. In particular, there is a lack of long-term data in a large patient series.

We aimed, therefore, to evaluate the effectiveness and tolerability of ESL when used as monotherapy for 1 year or more in routine clinical use in patients with focal seizures — the MONOZEB study.

2. Materials and methods

2.1. Study design and participants

MONOZEB was a multicenter, retrospective, noninterventional study involving epilepsy specialists from 18 hospitals in Spain. The study protocol was approved by the ethics committee at the University and Polytechnic Hospital La Fe. Centers were included in the study if their clinical practice matched the study methodology to allow extraction of appropriate information from clinical charts. The study is reported according to applicable STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [23].

All patients who were started on monotherapy or converted to monotherapy with ESL at least one year before database closure (August 2018) were included. Other inclusion criteria were the following: written informed consent by the patient or legal representative according to study protocol; age ≥ 18 years; and diagnosis of focal epilepsy. Exclusion criteria were unreliable clinical records and enrolment in other studies with AEDs or medical devices. Eslicarbazepine acetate was prescribed on an individual basis, at the discretion of the prescribing physician.

2.2. Data collection

Patients completed seizure diaries, and seizure counts were transcribed from these into patient clinical charts, according to usual clinical practice at each center. At each visit, patients were also asked to report any side effects, and any changes in AEDs were recorded. As part of usual clinical practice in these centers, visits included baseline, 3 months, 6 months, and 12 months during the first year, 18 months and 24 months for the second year, and the last visit available for longer follow-up. All patients had at least one blood test over the minimum one-year follow-up period, and vital signs were tested when considered necessary by physicians.

Data for this analysis were collected from patients' individual charts and kept according to usual clinical practice at each center. We recorded demographic data, seizure type (using 1981 and 2017 International League Against Epilepsy (ILAE) terminology), etiology, age at epilepsy onset, and previous AEDs. Mean seizure frequency was calculated at baseline (mean of the last 3 months or, if no seizures, over the previous year) and at each visit (as the mean monthly frequency since the prior visit).

2.3. Data analysis and endpoints

The efficacy population included all patients who fulfilled eligibility criteria, started ESL monotherapy treatment, and for whom at least one efficacy measurement was obtained after ESL initiation. The safety population included all patients who had received at least one dose of ESL and fulfilled eligibility criteria. The analysis was performed using last observation carried forward (LOCF) procedure for missing data. Data are reported for the whole population and separately for two populations: (1) first-line ESL monotherapy (patients who were taking no AEDs at the time of ESL initiation but who may have taken one or more AEDs at some point in the past) and (2) conversion to ESL monotherapy (patients who were previously taking 1 or more other AED(s) and switched to ESL monotherapy).

The primary effectiveness endpoint was the percentage of seizure-free patients at 1 and 2 years. Seizure freedom was defined as free from seizures since the previous visit (seizure-free at 1 year and since at least the 6 months visit and seizure-free at 2 years and since at least the 18 months visit). This method can underestimate the duration of seizure freedom, so a *post hoc* analysis calculated the proportion of patients who were seizure-free from baseline through to 1 year, from baseline to 2 years, and during the entire follow-up period.

Secondary effectiveness endpoints included retention rate on ESL monotherapy at 1 and 2 years; seizure-free rates at other time points; mean change in seizure frequency at each time point relative to baseline; and proportion of patients with seizure worsening (any increase from baseline seizure frequency).

The primary safety endpoint was the proportion of patients reporting 1 or more side effects over the complete follow-up period, in the overall population and each subgroup (first-line and conversion to ESL monotherapy). Secondary safety endpoints (in the overall group and subgroups) included the frequency and severity of side effects, rates of discontinuation due to side effects, and specific side effects leading to discontinuation, over the complete follow-up period and at each time point. The frequency of side effects of special interest (hyponatremia, psychiatric events, cognitive events) was also recorded.

Exploratory analyses also recorded effectiveness and safety outcomes in special populations of interest: patients switching from carbamazepine and from oxcarbazepine; patients aged ≥65 years; patients with prior or current psychiatric comorbidity; and patients with learning disability. Psychiatric comorbidity was determined from clinical charts by participating physicians — if a clear diagnosis was documented in the chart, then the patient was recorded as having a prior or current psychiatric comorbidity.

2.4. Statistical analysis

Statistical analyses used Statistical Package for the Social Sciences (SPSS) software 25. Last observation carried forward was used to handle missing seizure data, and *P*-value for significance was set at ≤0.05.

Frequency and percentages were used to summarize categorical variables (*e.g.*, seizure freedom, side effects), and mean, median, range, interquartile range, and 95% confidence intervals (CIs) were used to summarize numerical variables (age, duration of epilepsy, seizure frequency). Time-to-event analysis used the Kaplan–Meier method. Characteristics were compared between populations using the chi-square test (or Fisher's exact test) for categorical variables and Student's t test (or Mann–Whitney U) for numerical variables. Variation in the number of seizures over time was analyzed using the Wilcoxon or Friedman tests.

3. Results

3.1. Patients

Four hundred and thirty-five patients met eligibility criteria and were included: 127 patients (29.2%) with first-line ESL monotherapy and 308 patients (70.8%) who converted to ESL monotherapy, most often from levetiracetam (102/305). Of the 127 patients with first-line eslicarbazepine monotherapy, 22 (17.3%) had previously taken an AED at some point in the past but it had been discontinued. The reason for starting ESL monotherapy was lack of seizure control in all 127 patients with first-line ESL monotherapy and 52.5% of patients (160/305) in the conversion to ESL monotherapy group. Other reasons in the conversion group were poor tolerability in 30.5% (93/305) and problems with adherence in 6.2% (19/305). Patients' baseline characteristics, epilepsy and AED history (Table 1), and seizure types (Supplemental Table S.1) were similar in both subgroups, except that duration of epilepsy was longer, and more prior AEDs were reported in the conversion group (Table 1). Seventy-six patients (18.9%) reported no seizures during baseline.

The population included 105 patients included in a previously published analysis with shorter follow-up [19]. The most commonly used previous AEDs overall (N = 435) were levetiracetam (35.9%), carbamazepine (20.5%), and valproic acid (15.9%; see Supplemental Table S.2 for full details and the breakdown of previous AEDs). The most common AEDs taken immediately before switching to ESL monotherapy were levetiracetam (33.3%; 102/306), carbamazepine (21.9%; 67/306), and valproic acid (11.4%; 35/306; Supplemental Table S.3).

3.2. Retention and exposure

The retention rate on ESL monotherapy was 88.0% (383/435) at 12 months, 81.9% at 2 years (263/321), and 79.1% (344/435) at last visit (Fig. 1). Overall, 91 patients (20.9%) discontinued ESL monotherapy: 39 (8.9%) stopped taking ESL and 52 (12.0%) added another AED. The primary reasons for discontinuation of ESL monotherapy in the overall population were lack of effectiveness (12.2% of patients; 53/435); side

Table 1
Patient baseline characteristics and epilepsy history.

Characteristics	Overall (N = 435)	First-line ESL monotherapy (N = 127)	Conversion to ESL monotherapy (N = 308)
Female, n (%)[a]	196 (45.2%)	63 (49.6%)	133 (43.3%)
Mean age at baseline, years (range)[b]	48.8 (18–89)	49.1 (18–87)	48.6 (18–89)
Prior psychiatric comorbidity[c]	116 (27.7%)	37 (29.8%)	79 (26.8%)
Learning disability[d]	33 (8.8%)	7 (6.7%)	26 (9.6%)
Mean age at epilepsy onset, years (range)[e]	40.7 (0–86.9)	45.0 (4.4–86.9)	38.9 (0–86.8)
Median duration of epilepsy, years (range)[f]	4.5 (0–54.7)	0.9 (0–34.1)	6.5 (0.5–54.7)
Mean baseline seizure frequency/month (SD) [median][g]	1.63 (4.0) [0.33]	2.12 (5.1) [0.50]	1.44 (3.5) [0.33]
Epilepsy etiology[h]			
Vascular	63 (14.5%)	20 (15.7%)	43 (14.1%)
Tumoral	37 (8.5%)	11 (8.7%)	26 (8.5%)
Mesial temporal sclerosis	31 (7.2%)	8 (6.3%)	23 (7.5%)
Cortical developmental malformation	31 (7.2%)	6 (4.7%)	25 (8.2%)
Cavernoma	25 (5.8%)	5 (3.9%)	20 (6.5%)
Trauma	25 (5.8%)	4 (3.1%)	21 (6.9%)
Perinatal anoxia	18 (4.2%)	1 (0.8%)	17 (5.6%)
Vascular malformation	10 (2.3%)	5 (3.9%)	5 (1.6%)
Infectious	7 (1.6%)	0 (0%)	7 (2.3%)
Other	7 (1.6%)	3 (2.4%)	4 (1.3%)
Unknown	179 (41.3%)	64 (50.4%)	115 (37.6%)
Mean number of previous AEDs (SD) [range]	1.2 (1.3) [0–12]	0.3 (0.7) [0–5]	1.6 (1.2) [1–12]
Number of previous AEDs, n (%)			
0	105 (24.1%)	105 (82.7%)	0
1	213 (49.0%)	17 (13.4%)	196 (63.6%)
2	76 (17.5%)	2 (1.6%)	74 (24.0%)
3	23 (5.3%)	2 (1.6%)	21 (6.8%)
≥4	18 (4.1%)	1 (0.8%)	17 (5.5%)

AED, antiepileptic drug; ESL, eslicarbazepine acetate; SD, standard deviation.
[a] Gender data unavailable for 1 patient.
[b] Age data unavailable for 1 patient.
[c] Psychiatric history data unavailable for 16 patients.
[d] Learning disability data unavailable for 58 patients.
[e] Age at epilepsy onset unavailable for 1 patient.
[f] Epilepsy duration data unavailable for 44 patients.
[g] Seizure frequency data unavailable for 10 patients.
[h] Etiology data unavailable for 2 patients.

effects (5.7%; 25/435); both lack of effectiveness and side effects (0.9%; 4/435); and other reasons (2.1%; 9/435) — reasons were similar across the subgroups (Supplemental Table S.4).

The mean duration of ESL monotherapy was 66.7 months (95% CI: 63.6–69.8). Duration of treatment was slightly higher for patients on first-line ESL monotherapy (66.5 months, 95% CI: 60.7–72.3) than patients converting to ESL monotherapy (60.4 months, 95% CI: 57.2–63.6), but confidence intervals overlapped.

3.3. Eslicarbazepine acetate dosing

The median daily dose of ESL was 800 mg at all time points in the overall population, as well as in those with first-line monotherapy and those converting to ESL monotherapy (range: 400–2000 mg/day). The mean ESL dose was significantly lower in patients on first-line monotherapy than conversion to ESL monotherapy at day 1, 3 months, 6 months, and 12 months but not at later time-points ($P < 0.01$, Mann–Whitney U-test; Supplemental Fig. S-1).

The most common titration schedule was an increase of 400 mg every 2 weeks (42.3% of patients overall; 48.8% of patients on first-line monotherapy; 39.6% conversion to monotherapy). Most other patients either achieved target dose on the first day (21.4%; 22.8%; 20.8%) or were titrated by 400 mg every week (29.9%; 23.6%; 32.6%).

Overall, adherence to treatment was considerate adequate in 92.8% of patients at the baseline visit (283/305) and in 92.9% of patients at the last visit (398/427).

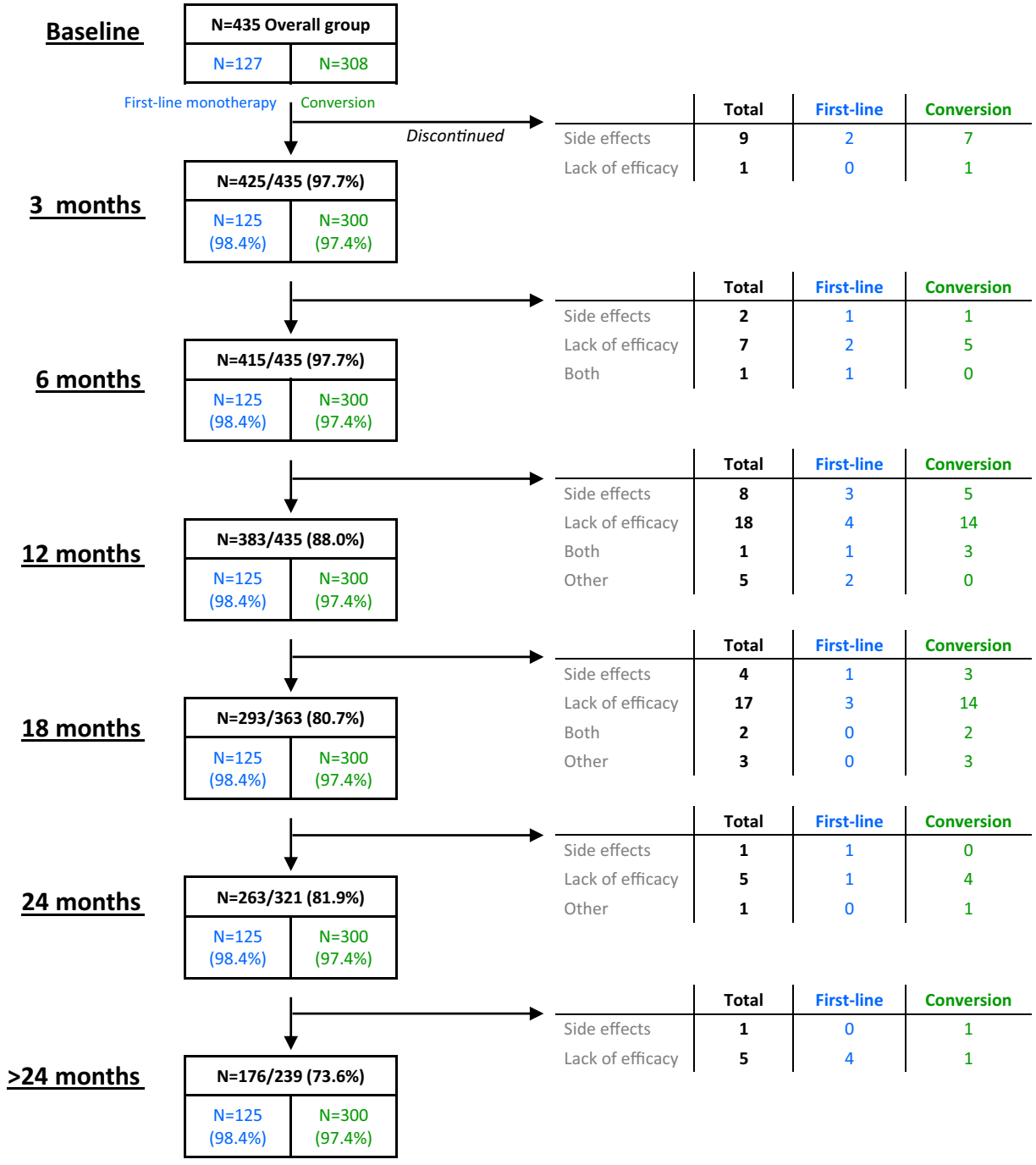

Fig. 1. Patient disposition. Disposition of all patients over time, overall, and by subgroup (first-line eslicarbazepine acetate monotherapy and conversion to eslicarbazepine acetate monotherapy). First-line, first-line eslicarbazepine acetate monotherapy; Conversion, conversion to eslicarbazepine acetate monotherapy.

3.4. Effectiveness

The effectiveness population comprised 433 patients.

3.4.1. Seizure freedom

Seizure freedom was achieved in 63.2% of patients at 1 year (265/419) and 65.1% of patients at 2 years (205/315; Fig. 2). At the final visit, seizure freedom was recorded in 66.7% of patients (289/433), of whom 67 had no seizures at baseline (Fig. 2). *Post hoc* analysis showed that 50.3% of patients with available data were seizure-free for the entire follow-up period (218/433; Table 2). Seizure-free rates, regardless of how it was defined, tended to be higher in patients with first-line monotherapy than those converting to eslicarbazepine monotherapy.

3.4.2. Seizure frequency change

The mean monthly seizure frequency was significantly reduced from baseline to last visit in the overall population (Friedman test, Fr = 284.42, $P < 0.001$), as well as in patients with first-line ESL monotherapy (Fr = 144.83, $P < 0.001$) and those converting to ESL (Fr = 184.84, $P < 0.001$; Table 3). The mean reduction in seizure frequency was 75.5% overall, 87.3% in patients with first-line ESL therapy, and 68.8% in patients converting to ESL. This significant reduction in seizure frequency was maintained when just those patients with seizures during baseline were included (Supplemental Table S.5).

The mean seizure frequency was also significantly reduced from baseline to last visit for each seizure type in the overall population (focal aware [70.6%], focal impaired awareness [80.6%], and focal-to-bilateral [89.6%]), and in patients with first-line monotherapy, and those converting to ESL monotherapy (Supplemental Information A).

3.4.3. Seizure worsening

Seizure worsening (any increase in seizure frequency relative to baseline) occurred in 19 patients at 12 months (4.5% of 419), 24 patients at 2 years (7.6% of 315), and 22 patients at the last available visit (5.1% of 433). In patients on first-line ESL, seizure worsening occurred in 3 patients at the last available visit (2.4% of 126) and in patients converting to ESL monotherapy, in 19 patients (6.2% of 307).

3.5. Safety/tolerability

During the entire observation period, 122 patients (28.0% of the safety population, N = 435) reported 1 or more side effects, of which 8 (1.8%) were severe (Table 4). The most frequent events were hyponatremia (sodium: <135 mEq/l), dizziness, and somnolence.

Discontinuations due to side effects occurred relatively evenly throughout the follow-up, with 9 of the 25 discontinuations in the first 3 months and another 10 between 3 and 12 months (discontinuation rate over 1 year 4.4%, 19/435; over entire follow-up 5.7%, 25/435). The most common reason for discontinuation of ESL monotherapy was hyponatremia (7 patients, 1.6%), followed by gastrointestinal disturbance (7, 1.6%), dizziness (5, 1.1%), insomnia (4, 0.9%), headache (3, 0.7%), and somnolence (2, 0.5%). Other side effects leading to discontinuation in 1 patient each were memory disturbance, anxiety, fatigue, depression, irritability, impotence, paresthesia in the tongue, and confusional state.

3.5.1. Side effects of special interest

Hyponatremia (sodium: <135 mEq/l) occurred in 20 patients (4.6%; mean: 126.0 mEq/l; median: 127.0 mEq/l; range: 113–134 mEq/l), and 7 patients discontinued ESL monotherapy as a result. Fifteen patients (3.4%) had levels <130 mEq/l, and 3 patients (0.7%) had levels <120 mEq/l. No other laboratory disturbances led to discontinuation. There was no difference in mean final dose of ESL between patients with (920.0 mg) and without (922.7 mg) hyponatremia (Mann–Whitney U test; U = 4090.0; $P = 0.920$) in the overall group or in either subgroup (initial monotherapy and conversion).

Psychiatric events were reported by 19 patients (4.4%) over the entire follow-up period (6.3% of first-line monotherapy patients and 3.6% of conversion to monotherapy patients). Events were mild in 7 patients, moderate in 9, severe in 1 (unclassified in 2), and led to discontinuation of eslicarbazepine monotherapy in 2 patients (both within the first 3 months). The most frequent psychiatric side effects were anxiety, depression, and irritability (1.6% each, Table 4). Overall, there was no difference in mean final dose of ESL between patients with (905.3 mg) and without (923.4 mg) psychiatric side effects (Mann–Whitney U test; U = 3919.0; $P = 0.962$). In patients with initial ESL monotherapy, the final mean dose was significantly higher in patients with psychiatric

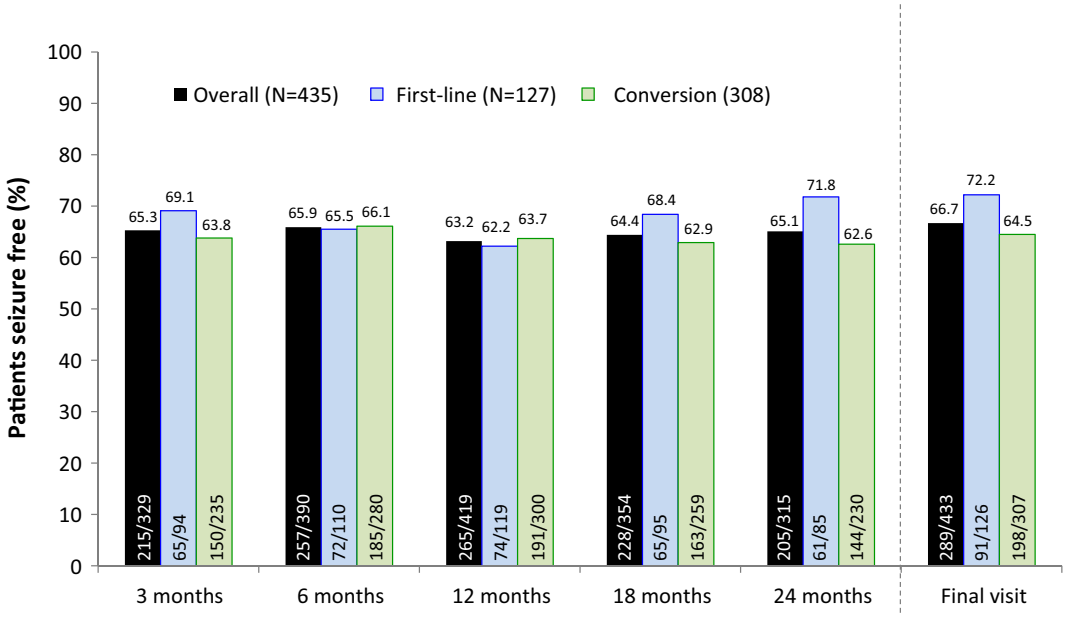

Fig. 2. Seizure freedom by visit. Proportion of patients free of seizures at each visit (and since previous visit) for the overall population (N = 435 patients with data available), and those with first-line eslicarbazepine acetate monotherapy (N-127) and conversion to eslicarbazepine acetate monotherapy (N-308).

Table 2
Seizure freedom rate by duration, post hoc analysis.

Seizure freedom rate	Overall (N = 433)	First-line ESL monotherapy (N = 126)	Conversion to ESL monotherapy (N = 307)
0–12 months (N = 419)	229/419 (54.7%)	67/119 (56.3%)	162/300 (54.0%)
0–24 months (N = 315)	156/315 (49.5%)	47/85 (55.3%)	109/230 (47.4%)
0–>24 months (N = 238)	111/238 (46.6%)	28/59 (47.5%)	83/179 (46.4%)
Entire follow-up period (N = 433)	218/433 (50.3%)	71/126 (56.3%)	147/307 (47.9%)

ESL, eslicarbazepine acetate.

adverse events (1100.0 mg) than in those without (845.4 mg; U = 233.0, $P = 0.008$).

Cognitive side effects were reported by 17 patients (3.9%) over the entire follow-up period (2.4% of first-line monotherapy and 4.5% of conversion to monotherapy patients). Only one patient discontinued because of cognitive side effects. There was no difference in mean final dose of ESL between patients with (922.3 mg) and without (929.4 mg) cognitive side effects (U = 3482.5, $P = 0.893$).

3.6. Exploratory analyses

3.6.1. Patients converting from carbamazepine and oxcarbazepine

Sixty-seven patients switched from carbamazepine to ESL monotherapy, and 25 switched from oxcarbazepine. The most common reason was lack of efficacy, followed by poor tolerability (see Supplemental Information B for further details).

The median dose of carbamazepine before switching was 600 mg, to a median dose of 800 mg ESL on the first day, most commonly titrated by 400 mg every 2 weeks. In contrast, the switch to oxcarbazepine most commonly occurred overnight (from a median of 900 mg oxcarbazepine to 800 mg ESL), with 60% achieving target dose on day 1. Seizure control and tolerability were consistent with the overall population (see Supplemental Information B for further details).

3.6.2. Patients aged ≥65 years

Ninety-one patients (21.0%) were aged ≥65 years, and duration of epilepsy was significantly shorter (6.4 years) than patients aged <65 years (9.4 years, U = 10,187.5; $P = 0.003$, Mann–Whitney U test). Mean seizure frequency was 0.99/month, and median number of prior AEDs was one. The first day mean dosage was significantly lower in patients aged ≥65 years (606 mg; median: 400 mg, range: 400–1200 mg) than aged <65 years (711.4 mg; median: 800 mg. range: 400–1600 mg; U = 12,477.0; $P = 0.001$) and at last visit (850.5, median: 800 mg; range: 400–1600 mg *vs* 941.7; median: 800; range: 400–2000 mg; U = 13,252.5; $P = 0.015$). The most common titration schedule was 400 mg every 2 weeks (48.4%; 44/91).

At the last available visit, 69.2% of patients aged ≥65 years (63/91) were free of seizures. Seizure-free rates were not significantly different between the age groups at any time point, except for 3 months (75.4% of patients aged ≥65 years *vs* 62.7% of those <65 years; $\chi^2 = 3.87$; $P = 0.049$).

The overall side-effect rates were not different between the age groups: 28.6% (26/91) of patients aged ≥65 years and 28.0% (96/343) of those <65 years. However, more older patients had hyponatremia (13/91, 14.3%) than younger patients (7/343, 2%; $\chi^2 = 24.53$; $P < 0.001$). In the 13 older patients with hyponatremia, mean sodium levels were 126.8 mEq/l (median: 128.0; range: 113–134 mEq/l); 7 patients had levels <130 (7.6%), and 2 had levels <120 mEq/l (2.1%). Four patients were taking >800 mg/day of ESL and 9 ≤800 mg/day. After hyponatremia, the most common side effect was somnolence (n = 3, 3.3%) and cognitive side effects were seen in 3 patients (all memory disturbance, 3.3%; Supplemental Table S6). During follow-up, 8 older patients (8.8%) discontinued eslicarbazepine monotherapy because of side effects, and 17 patients aged <65 years (5.0%).

3.6.3. Prior psychiatric comorbidity

A current or prior psychiatric comorbidity was reported by 116/419 patients (27.7%), most commonly anxiety (14.6%) and depression (12.4%; Table 5). There were no statistically significant differences in age, epilepsy duration, baseline number of seizures/month, and number of prior AEDs between patients with and without psychiatric comorbidity (Supplemental Information C).

The mean dose of ESL was statistically higher in patients with psychiatric comorbidity than without on the first day (727.6 *vs* 668.0; U = 15,230.5; $P = 0.020$) and at the last available visit (963.8 *vs* 910.9 mg; U = 15,574.5; $P = 0.048$). The most common titration schedule was 400 mg every 2 weeks.

Seizure-free rates were similar between groups: at the last available visit, 64.3% of patients with psychiatric comorbidities were seizure-free (74/115) and 67.9% of patients without psychiatric comorbidity (205/302). Side effects were more frequent in patients with psychiatric comorbidity (36.2%, 42/116) than without (76/303, 25.1%; $\chi^2 = 5.13$, $P = 0.023$). Dizziness was most common (6.0%, 7/116), hyponatremia was reported in 4 patients (3.4%), and 5 patients discontinued ESL monotherapy because of side effects (4.3%). Psychiatric side effects were more common in patients with psychiatric comorbidity (12/116, 10.3%) than without (7/303, 2.3%; $\chi^2 = 12.51$; $P < 0.001$), but there was no difference in discontinuation because of psychiatric side effects (1 patient in each group; 0.9% *vs* 0.3%).

3.6.4. Learning disability

Thirty-three patients had a learning disability or intellectual impairment (33/377, 8.8%); there were no statistically significant differences

Table 3
Seizure frequency change.

	Overall (N = 435)	First-line ESL monotherapy (N = 127)	Conversion to ESL monotherapy (N = 308)
Baseline: evaluable population	N = 425	N = 122	N = 303
Mean seizure frequency (IQR)	1.63 (0.1–1.3)	2.12 (0.3–1.3)	1.44 (0.1–1.3)
12 months: evaluable population	N = 420	N = 121	N = 299
Mean seizure frequency (IQR)	0.45 (0–0.2)	0.46 (0–0.3)	0.45 (0–0.2)
24 months: evaluable population	N = 314	N = 85	N = 229
Mean seizure frequency (IQR)	0.46 (0–0.2)	0.28 (0–0.2)	0.53 (0–0.2)
Final visit: evaluable population	N = 432	N = 126	N = 306
Mean seizure frequency (IQR)	0.40 (0–0.2)	0.27 (0–0.2)	0.45 (0–0.2)
[Fr and *P vs* baseline]	(284.42, $P < 0.001$)	[144.83, $P < 0.001$]	(184.84, $P < 0.001$)
Mean % change from baseline to final visit (median)	75.5% (100%)	87.3% (100%)	68.8% (100%)

ESL, eslicarbazepine acetate; IQR, interquartile range; Fr, Friedman statistic.

Table 4
Side effects occurring during the entire exposure to eslicarbazepine monotherapy.

	Overall (N = 435)	First-line ESL monotherapy (N = 127)	Conversion to ESL monotherapy (N = 308)
≥1 side effect, n (%)	122 (28.0%)	37 (29.1%)	85 (27.6%)
Mild	70 (16.1%)	19 (15.0%)	51 (16.6%)
Moderate	30 (6.9%)	11 (8.7%)	19 (6.2%)
Severe	8 (1.8%)	2 (1.6%)	6 (1.9%)
Unclassified	14 (3.2%)	5 (3.9%)	9 (2.9%)
Leading to discontinuation, n (%)	25 (5.7%)	8 (6.3%)	17 (5.5%)
Individual side effects in > 1 patient, n (%)[a]			
Hyponatremia (< 135 mEq/l)	20 (4.6%)	6 (4.7%)	14 (4.5%)
Dizziness	20 (4.6%)	5 (3.9%)	15 (4.9%)
Somnolence	19 (4.4%)	8 (6.3%)	11 (3.6%)
Memory disturbance	16 (3.7%)	3 (2.4%)	13 (4.2%)
Headache	12 (2.8%)	2 (1.6)	10 (3.2%)
Anxiety	7 (1.6%)	2 (1.6%)	5 (1.6%)
Depression	7 (1.6%)	4 (3.1%)	3 (1.0%)
Irritability	7 (1.6%)	2 (1.6%)	5 (1.6%)
Insomnia	7 (1.6%)	0	7 (2.3%)
GI disturbance[b]	7 (1.6%)	2 (1.6%)	5 (1.6%)
Liver enzymes increase	6 (1.4%)	2 (1.6%)	4 (1.3%)
Cholesterol increase	5 (1.1%)	2 (1.6%)	3 (1.0%)
Fatigue	3 (0.7%)	2 (1.6%)	1 (0.3%)
Sexual dysfunction	3 (0.7%)	1 (0.8%)	2 (0.6%)
Nausea/vomiting	2 (0.5%)	2 (1.6%)	0

ESL, eslicarbazepine acetate; TSH, thyroid-stimulating hormone.
[a] Other side effects were reported in 1 patient each: skin lesion; ataxia; weight increase; paresthesia; blurred vision, confusion; TSH increase; folic acid decrease; triglyceride increase.
[b] Excluding nausea/vomiting.

in age, epilepsy duration, baseline number of seizures/month, and number of prior AEDs between patients with and without learning disability (Supplemental Information D).

The mean dose of ESL in those with and without learning disability was similar at initiation (678.8 *vs* 724.2) but lower at last visit (848.5 *vs* 946.9; U = 4497.0, $P = 0.034$). The most common titration schedule was 400 mg every 2 weeks (39.4%).

Seizure-free rates at the last available visit were similar in patients with (69.7%, 23/33) and without (63.2%, 216/342) learning disability. Side-effect rates were similar in patients with (33.3%, 11/33) and without (29.7%, 102/344) learning disability. Dizziness occurred in 12.1% of patients (4/33) with learning disability (*vs* 4.4%, 15/344 without); rates of hyponatremia (6.1%, 5.2%), other side effects, and discontinuation due to side effects (9.1%, 6.4%) were similar. No psychiatric side effects were reported in the group with learning disability, and 2 patients reported cognitive side effects (6.1%).

4. Discussion

In a large population of 435 patients treated with ESL monotherapy, we showed high retention rates (79.1% at last visit) and high rates of seizure freedom during long-term treatment — 63.2% at 1 year, 65.1% at 2 years, and 50.3% maintaining seizure freedom over the entire follow-up period. Eslicarbazepine monotherapy was tolerated well, with a side-effect rate of 28%, and side effects led to discontinuation in 5.7%.

The seizure-free rates we report here are similar to those in shorter studies with ESL monotherapy: 71.1% of 388 patients were seizure-free for ≥6 months in a randomized controlled trial reported by Trinka et al. [16]; 77.4% of 229 patients were seizure-free at 1 year in an observational study reported by Holtkamp et al. [21]; and 66.1% of 59 patients were seizure-free at 1 year in a study by Toledano et al. [22]. Our study adds value by showing that these outcomes are sustained to 2 years and beyond.

Our results are also similar compared with other AEDs. Seizure-free rates at 1 year were 60.2% in 98 patients taking first-line lacosamide monotherapy and 52.5% in 341 patients converting to lacosamide monotherapy [24]. In the Keppra vs Older Monotherapy in Epilepsy Trial (KOMET) study, 53.9% of 841 patients with newly diagnosed epilepsy were seizure-free for the 12 months since randomization to levetiracetam [25]. This is comparable with our rate of 56.3% from 0 to 12 months in the 126 patients with first-line eslicarbazepine monotherapy (Table 2).

The retention rate among our monotherapy patients (88.0% at 1 year, 81.9% at 2 years) is high, as reported with ESL use in early add-on (82.2% at 6 months [20]; 92.9% at 1 year [19]) and in monotherapy (90% after 1 year by Toledano et al. [22] and 71% at 6 months by Trinka et al. [16]). The retention rate for lamotrigine in the Standard and New Antiepileptic Drugs (SANAD) monotherapy trial was somewhat lower — 77% at 1 year and 65% at 2 years [26].

Tolerability of ESL was good, and the most common side effects were as expected (hyponatremia, dizziness, and somnolence). Side effectsled to discontinuation in 5.7% of patients over the entire follow-up (4.4% over 1 year). Toledano et al. reported that 15.3% of patients discontinued because of side effects, over 1 year of treatment with ESL (most common side effects leading to discontinuation being dizziness, somnolence, and hyponatremia) [22].

Considering side effects of special interest, few patients reported psychiatric side effects (4.4%) even in those with a prior psychiatric comorbidity, and few discontinued as a result (0.9%). This reaffirms the benign psychiatric profile previously reported by Jalihal et al. — in a small group of 26 patients with psychiatric or behavioral side effects with levetiracetam, good psychiatric outcome was reported after switching to ESL [27].

With respect to hyponatremia, 1.6% of patient discontinued because of low sodium, and 4.6% had sodium levels <135 mEq/l. This is in line with pooled rates across four eslicarbazepine clinical trials: levels < 135 mEq/l were reported in 4.8% of patients taking 800 mg and 6.6% with 1200 mg [28]. In a pooled analysis of patients converting to ESL monotherapy in two randomized controlled trials, hyponatremia led to discontinuation in 1.4% of patients over the 18-week treatment period [29].

Table 5
Types of prior and current psychiatric comorbidity.

Type of psychiatric comorbidity	Overall (N = 419)	First-line ESL monotherapy (N = 124)	Conversion to ESL monotherapy (N = 216)
Psychiatric comorbidity, n (%)	116 (27.7%)	37 (29.8%)	79 (26.8%)
Anxiety	61 (14.6%)	19 (15.3%)	42 (14.2%)
Depression	52 (12.4%)	23 (15.8%)	29 (9.8%)
Personality disorder	9 (2.1%)	1 (0.8%)	8 (2.7%)
Psychosis	6 (1.4%)	2 (1.6%)	5 (2.1%)
Hyperactivity	1 (0.2%)	0	1 (0.3%)
Other	9 (2.1%)	1 (0.8%)	8 (2.7%)

ESL, eslicarbazepine acetate.

The median daily dose of ESL was 800 mg at all time points in our overall population, consistent with the European monotherapy trial [16], in which the majority of patients (67.6%) remained at 800 mg. We found that the most common titration schedule was an increase of 400 mg every 2 weeks (42.3% overall). Most other patients either achieved target dose on the first day (21.4%) or were titrated by 400 mg every week (29.9%).This differs from the suggested 400-mg weekly increase in the European clinical trial, emphasizing the importance of an individual approach in clinical practice.

In our patients switching from carbamazepine, the carbamazepine to ESL dose ratio was 1:1.5, slightly higher than the 1:1.3 previously suggested [30]. The oxcarbazepine to ESL ratio in our patients was 1.1:1, slightly different from the 1:1 suggested by Peltola et al. [30]. Patients switching from carbamazepine or oxcarbazepine because of poor tolerability tolerated eslicarbazepine well, which is consistent with previous studies [19].

Patients aged ≥65 years benefitted from ESL monotherapy — 65.9% remaining seizure-free at last available visit. In a population of patients aged ≥65 years whose seizures are more refractory (72 people with focal seizures despite treatment with 1–2 AEDs), 11 (15.5%) were seizure-free and 39 (54.9%) were responders with adjunctive ESL [31]. Rates of hyponatremia were higher than in our study (9.7% had levels <130 mEq/l *vs* 3.4% in our patients), and discontinuations because of side effects were more common in their population (22.2%) than ours (8.8%), which illustrates the tolerability advantages of monotherapy.

In our 32 patients with learning disability, ESL monotherapy was effective (69.7% seizure-free at last visit), and there were no psychiatric side effects and only 2 cognitive side effects in this group. This is consistent with the lack of significant effects on cognition and behavior in a recent of adjunctive ESL in 123 pediatric patients with refractory focal-onset seizures (FOS) [32].

An observational study like this has limitations, and our data must be interpreted carefully in light of the observational, nonblinded, and uncontrolled nature of the study. Our population also included 105 patients previously included in a study of ESL use, with shorter follow-up [19]. The main strengths of this study are that a large population of patients with ESL monotherapy had a long-term follow-up confirming previous outcomes reported over a shorted time frame.

In conclusions, our patients with focal seizures who started ESL monotherapy as first-line treatment, or converted to it, had high retention and seizure-free rates, and good tolerability up to 2 years.

Declaration of Competing Interest

V Villanueva has participated in advisory boards and industry-sponsored symposia for Eisai, UCB, Bial, Esteve, Novartis, GW pharmaceuticals.

Andreu Massot-Tarrús has received honoraria for speaking engagements and advisory boards from Bial, Eisai and UCB Pharma, and research support from Eisai and UCB. M Toledo has received honoraria from BIALlaboratories, EISAI Inc., Sanofi and ESTEVE, and obtained grants from BIAL Laboratories, UCB Pharma, and ESTEVE.

JJ Rodriguez-Uranga has participated in advisory boards for UCB, Eisai, Bial, and Pfizer.

JÁ Mauri has participated in advisory boards and industry-sponsored symposia for Eisai, UCB Pharma, Bial, GSK, and Esteve.

JJ Poza has participated in advisory boards and pharmaceutical-industry-sponsored symposia for Eisai, Bial, UCB, Esteve, Shire, GSK, and Pfizer.

M Bonet has participated in industry-sponsored symposia for UCB, Bial, and Eisai.

MD Castro-Vilanova has participated in advisory boards for UCB and in industry-sponsored symposia for UCB, Bial, Eisai, and Esteve.

FJ López-González has participated in advisory boards and industry-sponsored symposia for UCB, Bial, Eisai, Sanofi, Esteve, Livanova; Novartis, Exeltis.

X Rodríguez-Osorio has participated in advisory boards for UCB Pharma and Esteve and industry-sponsored symposia for Eisai, UCB Pharma, Bial, GSK, and Esteve.

J Ojeda has acted as a paid consultant to Eisai and UCB, and has received speakers' honoraria from Bial, Eisai, Pfizer, GSK, and UCB Pharma. He has received research funding from Alter, and travel support from Bial, Kern Pharma, Eisai, and UCB.

M Garcés has participated in industry-sponsored symposia for Eisai, UCB Pharma, and Bial.

P Bermejo, J Montoya, ML Galiano, V Bertol, J Ruiz-Giménez, D Tortosa-Conesa, P Giner, P Esteve, JJ Baiges, BM Alvarez, P Quiroga-Subirana, and K Hampel have no conflicts of interests to declare.

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Appendix A. Supplementary data

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