

Eslicarbazepine acetate as adjunctive therapy in clinical practice: ESLADOBA study

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Objective: To assess seizure control and tolerability of eslicarbazepine acetate (ESL) as adjunctive therapy to one baseline antiepileptic drug (AED), in adults with partial-onset seizures (POS) with or without secondary generalization.

Methods: Multicenter, non-interventional, prospective cohort study conducted between March 2012 and September 2014 at 12 neurology departments in Portugal. Adults with POS not controlled with one AED who had initiated ESL as adjunctive treatment were enrolled. Retention rate was defined at the final visit (Vfinal) 6–9 months of follow-up. Proportion of responders, seizure-free, changes in seizure frequency were evaluated using patients' diaries. Clinical Global Impression of Change (CGI-C) and Clinical Global Impression of Severity (CGI-S) were assessed by the neurologist.

Results: Fifty-two patients (48.1% male) were included with mean age 41.5±13.3 years. Mean epilepsy duration was 18.5±14.8 years; mean seizure frequency in the four previous weeks to baseline was 7.5±12.7. At Vfinal, retention rate was 73.0%; responder rate and seizure-free rates were 71.1% and 39.5%, respectively. The median relative reduction in seizure frequency between baseline and Vfinal was 82.2%. A reduction in epilepsy severity (CGI-S) was observed in 42.1%. According to CGI-C, 73.6% patients had their epilepsy "much improved" or "very much improved". Twelve patients (23.1%) had at least one adverse event (AE), two (3.9%) had one serious AE, and five (9.6%) discontinued due to AE.

Conclusions: Eslicarbazepine acetate showed good retention rates, elicited a significant reduction in seizure frequency, and was well tolerated when used in the clinical practice.

KEYWORDS

adjunctive therapy, adults, eslicarbazepine acetate, partial seizures, refractory epilepsy, retention rate

1 | INTRODUCTION

In the last two decades, several new antiepileptic drugs (AEDs) have become available in Europe and United States for the treatment of patients with epilepsy. Nevertheless, the incidence of refractory epilepsy remains high, and 20%–40% of the patients with newly diagnosed epilepsy will become refractory to treatment, with potentially devastating

consequences.¹ Besides the concerns about efficacy, the majority of the currently available AEDs are commonly associated with a risk of adverse events.² Therefore, there is still a need to further develop AEDs that are effective and safe in the treatment of this condition, especially because add-on therapy with newer AEDs is suggested for patients with refractory epilepsy.³

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Eslicarbazepine acetate (ESL) has been approved in Europe and in United States as a once-daily (QD) adjunctive AED in adults with partial-onset seizures (POS), with or without secondary generalization.⁴ Moreover, the Food and Drug Administration recently approved ESL as monotherapy for the treatment of patients with POS.⁵

The efficacy and safety/tolerability of ESL as adjunctive AED have been established in several randomized controlled trials (RCTs).^{2,6-8} In general, the patients enrolled in these studies had long-standing epilepsy (mean duration in three phase III trials was equal to or over 22 years in all treatment groups,⁹ a high seizure frequency in the four prior weeks to screening,^{8,9} and the majority was treated with two concomitant AEDs^{8,9}), indicating that the populations included severe refractory patients.

Despite being crucial to the clinical development of an AED, RCTs are characterized by rigorous inclusion/exclusion criteria, rigid dosing, and titration schedules. Comparatively, in everyday clinical practice, patients' clinical characteristics are more varied and treatment is individualized to each patient's needs.^{10,11} Therefore, "real-world" studies, such as observational studies, can be useful adjuncts to RCTs in order to complement their evidence and to evaluate whether the demonstrated efficacy translates into effective treatment in routine practice.¹²

This non-interventional study (ESLADOBA) aimed to evaluate the effectiveness and tolerability of ESL, as adjunctive therapy to one baseline AED, in the context of real-world treatment practice in Portugal. When compared to the phase III trials,^{2,6-8} this study will potentially allow us to evaluate a less refractory population by focusing on patients exclusively treated with one baseline AED.

2 | METHODS

2.1 | Study design

This multicenter, non-interventional, prospective cohort study was conducted between March 2012 and September 2014 at 12 Portuguese sites (nine public hospitals with specialized epilepsy clinics and three private outpatient clinics). Patients aged 18 years or more with established diagnosis of epilepsy not sufficiently controlled with one AED, who had experienced at least one POS, with or without secondarily generalization, within four prior weeks to study initiation were eligible for treatment with ESL add-on therapy and were enrolled. The decision to introduce ESL was made by the neurologist, prior to and independently of study inclusion, and was based on the local summary of product characteristics (SPC). All patients gave their written consent prior to enrollment. The observation period was up to 9 months from the initiation of ESL add-on therapy. In order to accommodate the dispersion in intervals between clinical appointments, one intermediate visit (Vinterm) was conducted whenever a patient attended the outpatient clinic.

The following variables were collected: demographic data, epilepsy history (including seizure type and frequency), comorbidities, prior and concomitant AEDs, ESL compliance, Clinical Global Impression of Change (CGI-C), Clinical Global Impression of Severity (CGI-S) scores, and adverse events (AEs). In the patient diary, participants recorded the date, the time, and the type of the seizure episodes (1—simple

partial seizure; 2—complex partial seizure; 3—partial seizures with secondary generalization; 4—unclassified seizure; 5—other type of seizure). In addition, the patient recorded the ESL intake on a daily basis.

2.2 | Endpoints

The primary endpoint was the retention rate (RR), defined as the proportion of patients on ESL treatment at the end of follow-up, based on the patient diary records.

The secondary endpoints included the proportion of responders (patients with at least 50% reduction in seizure frequency compared to baseline), proportion of seizure-free patients, and the change in frequency for partial seizures with or without secondary generalization. Seizure frequency at Vinterm and final visit (Vfinal) was standardized for a 4-week period to allow for comparisons with baseline (4 weeks).

The CGI-S is a clinician-rated measure of global psychopathology, which measures severity of mental illness on a 7-point scale, from normal to extremely ill.^{13,14} The CGI-S was evaluated at baseline and at Vfinal. CGI-C is a clinician-reported 7-point scale to measure improvement or worsening of the epilepsy, with lower scores indicating greater improvement (scores range from 1=very much improved to 7=very much worse).^{13,14} The efficacy index is a composite score that reflects the degree of therapeutic effect of ESL treatment, rating it from 1=unchanged to worse to 4=marked, as well as the side effects, classifying them as 1=none to 4=outweighs therapeutic effect.¹⁵

Adverse events occurring during the follow-up period were recorded by the investigator, including the date of occurrence, duration, treatment, outcome, and assessed with regard to causality (not related, unlikely, possible, probable, or definite) and seriousness.

This study was approved by the ethics committee of each participant hospital.

2.3 | Statistical analysis

Quantitative variables were summarized as median, minimum, and maximum and qualitative variables as absolute frequency. Nonparametric Wilcoxon test (W) was used to analyze within-patient paired analysis of CGI-S and seizure frequency between baseline, intermediate, and final assessment, as normality assumption was rejected.

Bivariate analysis was conducted using baseline independent variables (age, gender, presence of comorbidities, previous AED therapy, CGI-S, and seizure frequency at baseline) and the dependent variables (retention rate, responder rate, and proportion of seizure-free patients). Chi-square or Fisher's exact test was used for categorical variables, and *t*-test or Mann-Whitney for numerical variables.

Missing data were not replaced and a valid case approach was assumed, with the exception of the retention rate analysis, in which patients who had no follow-up data available were considered as failures.

All statistical tests were two-tailed considering a significance level of 5% and using 95% confidence intervals (95% CI), when applicable. Statistical analysis was performed using software IBM® SPSS® Statistics 19.0 (IBM Corp, Armonk, New York, USA).

3. | RESULTS

3.1 | Characterization of participants

A total of 52 patients (48.1% males) were enrolled. Although two patients had their final follow-up assessment 23 and 39 days after month 9, they were included in the analysis dataset. The study population baseline characteristics are described in Table 1. Patients' mean age was 41.5±13.3 years (20-75), 7 (13.5%) had more than 60 years old. Mean epilepsy duration was 18.5±14.8 years (range: <1-59 years); mean seizure frequency in the four previous weeks to baseline was 7.5±12.7. The most common types of seizure were complex partial (82.7%), while 34.6% were partial with secondary generalization. Hereditary/congenital and post-traumatic conditions were the most frequent etiology found for epilepsy. The average initial ESL dose was 800 mg/d. The most common concomitant AEDs were valproate (VPA) (28.8%), carbamazepine (CBZ) (26.9%), and levetiracetam (LEV) (21.2%). The majority of the patients (90.4%) had no familial history of epilepsy, and 28.9% had co-existing medical conditions. At study initiation, 25% of the patients were normal (not at all ill) according to CGI-S, and only 7.7% were markedly or severely ill.

3.2 | Retention rate

Retention rate was 86.5% (95% CI, 77.2%-95.7%) at Vinterm (mean time between initial visit (Vinitial) and Vinterm: 3.70 months) and 73.0% (95% CI, 61.0%-85.2%) at the Vfinal (mean time between Vinitial and Vfinal: 7.80 months). Overall, 36 (69.2%) patients complied 100% with the daily intake of ESL. The RR by baseline concomitant AED is shown in Figure 1.

3.3 | Seizure control

Responder rate was 55.8% (95% CI, 41.0%-70.6%) at Vinterm and 71.1% (95% CI, 56.7%-85.5%) at Vfinal.

Responder rate by concomitant baseline AED is shown in Figure 2. Patients on CBZ showed a higher RR at Vfinal (85.7%) compared to patients receiving other AEDs. The responder rate among patients on VPA was 100%.

Overall, the seizure-free rate was 32.6% (95% CI, 18.6%-46.6%) at Vinterm and 39.5% (95% CI, 24.00%-55.04%) at Vfinal (Figure 3). The highest seizure-free rates were found for the secondary generalized seizures (94.7% at Vfinal).

Seizure-free patients had lower frequency of seizures at baseline than non-seizure-free patients ($P=0.052$).

Statistically significant median reductions were observed for total number of POS from baseline to Vinterm and Vfinal ($P=.005$ and $P<.001$, respectively), partial seizures without secondary generalization from baseline to final assessment ($P=.011$), and for all seizures regardless of type from baseline to Vinterm and Vfinal ($P=.005$ and $P<.011$, respectively). Relative changes in median seizure frequency from baseline to Vinterm and Vfinal are presented in Figure 4.

TABLE 1 Study population baseline characteristics

	Total (n=52)
Gender, n (%)	
Male	25 (48.1%)
Female	27 (51.9%)
Age in years, mean (±SD)	41.5 (±13.3)
Duration of epilepsy in years ^a , mean (±SD)	18.5 (±14.8)
n	33
Incidence of seizures by type, n (%)	
Simple partial	8 (15.4%)
Complex partial	43 (82.7%)
Partial with secondary generalized	18 (34.6%)
Not classified	1 (1.9%)
Possible etiology, n (%)	
Idiopathic	10 (19.2%)
Hereditary/Congenital	8 (15.4%)
Skull fracture	7 (13.5%)
Unknown	7 (13.5%)
Brain tumor	5 (9.6%)
Mesial sclerosis	5 (9.6%)
Infectious disease	3 (5.8%)
Cerebrovascular disease	2 (3.8%)
Others	5 (9.5%)
Familial history of epilepsy ^b , n (%)	
Yes	4 (7.7%)
No	47 (90.4%)
Unknown	1 (1.9%)
Medical history other than epilepsy, n (%)	
Yes	15 (28.9%)
No	37 (71.1%)
Concomitant AED to ESL	
Valproate ^c	15 (28.8%)
Carbamazepine	14 (26.9%)
Levetiracetam	11 (21.2%)
Lamotrigine	4 (7.7%)
Zonisamide	2 (3.8%)
Phenytoin	2 (3.8%)
Clobazam	2 (3.8%)
Pregabalin	1 (1.9%)
Clonazepam	1 (1.9%)
Severity of illness (CGI-S), n (%)	
1-Normal, not at all ill	13 (25.0%)
2-Borderline ill	12 (23.1%)
3-Mildly ill	10 (19.2%)
4-Moderately ill	13 (25.0%)
5-Markedly ill	3 (5.8%)
6-Severity ill	1 (1.9%)
7-Among the most extremely ill patients	0 (0.0%)

SD, standard deviation; AED, antiepileptic drug; ESL, eslicarbazepine acetate; CGI-S, Clinical Global Impression of Severity.

^aTime since diagnosis.

^bOnly first-degree relatives.

^cValproic acid/sodium valproate/association.

3.4 | Adverse events

All 52 patients were eligible for safety analysis (Table 2). Overall, 23 AEs were reported during the study, of which 19 (82.6%) were possibly, probably, or definitely related to the study treatment. Twelve (23.1%) patients had at least one AE, ten patients (19.2%) had at least one AE related to study treatment, and eight had multiple AEs. Three serious adverse events were reported (pneumonia-sepsis, polyarthralgia, and cutaneous rash). Pneumonia-sepsis was unlikely to be related to the study treatment, whereas polyarthralgia and cutaneous rash were possibly related. Five patients (9.6%) were withdrawn from the study due to AEs (one due to alopecia, burning sensation in eye, and vaginal burning; one due to cutaneous eruption; one due to aggravation of seizures, anxiety, and depressive symptoms; one due to polyarthralgia and cutaneous rash; and one due to generalized erythematopapulous cutaneous eruption).

3.5 | CGI-S score at Vfinal and change from baseline

At Vfinal, 36.8% of patients were classified as normal regarding the severity of illness evaluated by CGI-S and 55.3% were borderline or mildly ill. Only about 8% of the patients were moderately or markedly ill. Compared to baseline, 42.1% of the patients reached a less severe disease level, whereas 13.2% attained a more severe level of epilepsy. In 45% of the patients, CGI-S remained stable.

Although the *P*-value is in the borderline of significance (*P*=.066), no statistical differences were found in CGI-S between baseline and Vfinal.

CGI-S score at baseline was found to be statistically associated with the seizure-free rate (*P*=.011) and RR (*P*=.024).

3.6 | CGI-C and efficacy index scores

According to CGI-C, 73.6% of the patients had their epilepsy "much improved" or "very much improved" at Vfinal. There were no cases where epilepsy was considered worse. In addition, the therapeutic effect of ESL was classified by physicians as "marked" or "moderate" for 42.1% and 36.8% of patients, respectively. No side effects were reported by physicians for 78.9% of patients, and for 18.4%, the side effects "did not significantly interfere with patients' functioning".

4 | DISCUSSION

The efficacy and safety/tolerability of ESL as adjunctive therapy were previously established in several clinical trials.^{2,6-8} This study was designed to evaluate the effectiveness of ESL in the real-world setting, with a more heterogeneous population in terms of treatment experiences and comorbidities. Considering the observational nature of the present study and the natural dispersion in the interval between the

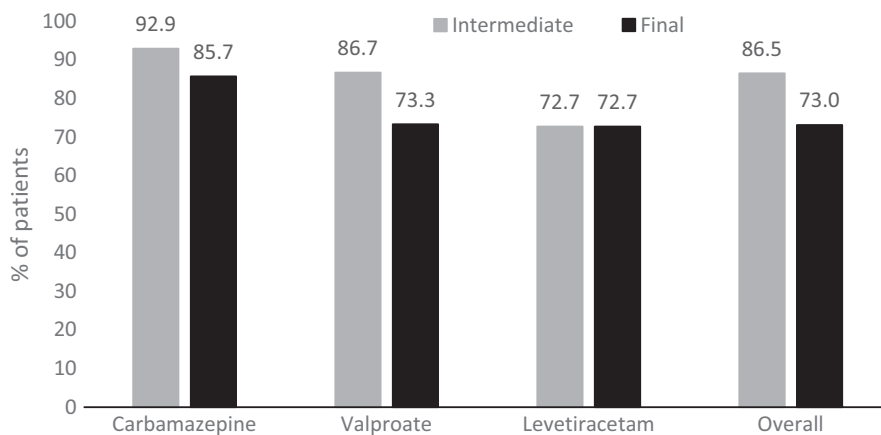


FIGURE 1 Retention rate (proportion of patients on ESL treatment) by AED at intermediate and final assessment

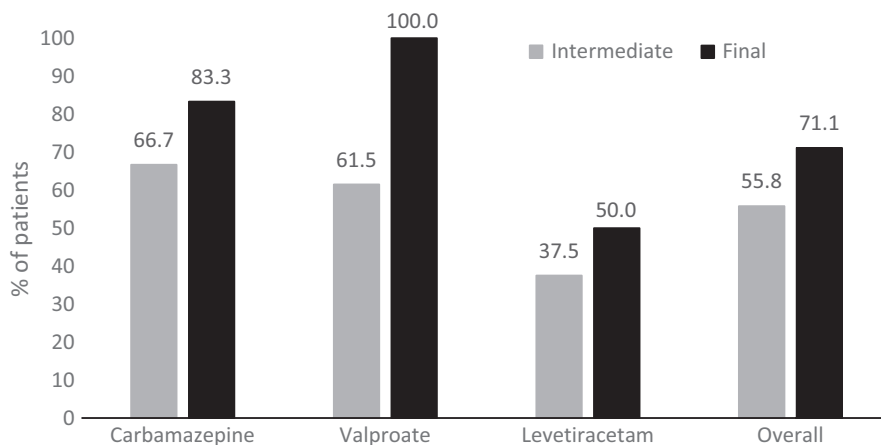


FIGURE 2 Responder rate (proportion of patients with at least 50% reduction in seizure frequency) by AED at intermediate and final assessment

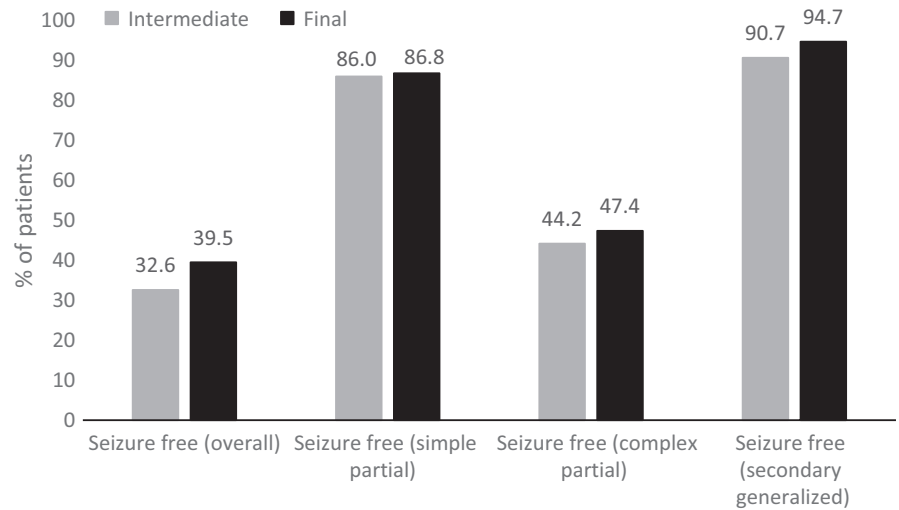


FIGURE 3 Seizure-free rates at intermediate and final assessment

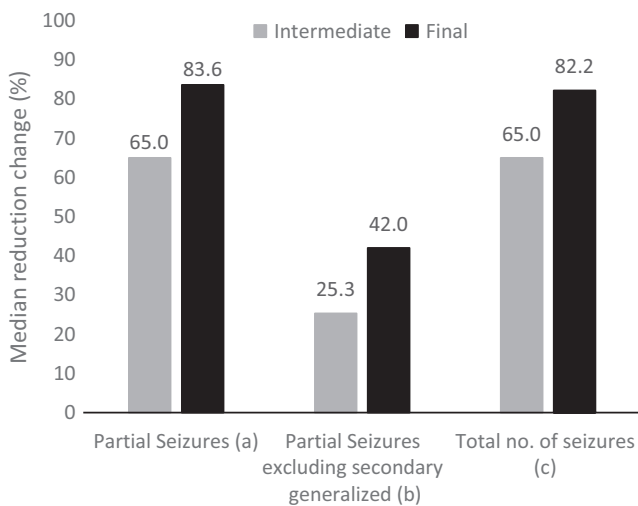


FIGURE 4 Relative changes in median seizure frequency from baseline to intermediate and final assessment. (A) Simple, complex, and secondary generalized seizures. (B) Simple and complex seizures. (C) Simple, complex, secondary generalized, not classified, and other types of seizures

clinical appointments, V_{final} was not performed at a fixed time point, occurring on average of 7.8 months after enrollment. Therefore, the 6-month period reported in previously published studies on ESL adjunctive therapy, whether clinical trials or observational designs, was used for comparison purposes.

The primary endpoint of the study was RR, which is of utmost importance in the analysis of long-term AED treatments as it reflects the complex interactions between efficacy and tolerability.¹⁶ This study showed RR of 73.0% at the V_{final} . At 6 months, higher RR was found in a similar non-interventional prospective study (EPOS)¹⁷ (82.2%), in a 1-year retrospective study¹⁸ (80.1%), and in a 2-year retrospective study¹⁶ (82.9%). The lower RR obtained in this study may be due to an underestimation, as a worst scenario was used by classifying those patients that did not perform the final assessment as failures.

We observed a responder rate of 71.1% at V_{final} . The proportion of responders is lower than the one reported in EPOS study,¹⁷ in which

TABLE 2 Summary of incidence and the number of adverse events

	Total (n=52)
Incidence of adverse events, n (%)	12 (23.1%)
Incidence of adverse events related ^a to study treatment, n (%)	10 (19.2%)
Incidence of serious adverse events, n (%)	2 (3.9%)
Incidence of serious adverse events related ^a to study treatment, n (%)	1 (1.9%)
Incidence of adverse events leading to withdrawal, n (%)	5 (9.6%)
Total no. of adverse events	23
Total no. of adverse events related ^a to study treatment	19
Total no. of serious adverse events	3
Total no. of serious adverse events related ^a to study treatment	2

^aAdverse events related to study treatment includes possible, probable and definitely related events. The most frequent adverse events (MedDRA PT) related to study treatment were rash (n=3), toxicity to various agents (n=2), anxiety (n=2), seizure (n=2). The two serious adverse events (MedDRA PT) considered at least possible related to study treatment were arthralgia and rash. MedDRA PT, Medical Dictionary for Regulatory Activities preferred term.

81.8% of patients presented a reduction in seizure frequency of at least 50% at 6 months. These results might be explained by the fact that EPOS population seemed to be less refractory in comparison to our study, as suggested by a shorter mean time since epilepsy diagnosis (12.3 ± 12.1 years in EPOS¹⁹ vs 18.5 ± 14.8 years in this study). On the other hand, the responder rate attained in this study is significantly higher than the ones reported in the 1-year and 2-year retrospective studies^{16,18} at 6 months (57.9% and 25.7%, respectively). Two main reasons might be responsible for these differences. First, the responder rate observed in the ESLADoba study may be overestimated, as it only considered patients who completed the study (responder rate was calculated not considering the patients who were dropped-out from the study, n=14). Second, the patients included in the two

retrospective studies were more refractory than the ESLADOBA population, as reflected by longer times since epilepsy diagnosis (median of 19.0 years in Villanueva et al.¹⁸ vs median of 16.0 years in this study; mean of 26.8±13.1 years in Correia et al.¹⁶ vs mean of 18.5±14.8 years in this study) and the number of baseline AEDs used (patients used up to five and six AEDs at baseline in Correia et al.¹⁶ and Villanueva et al.,¹⁸ respectively, vs only one baseline AED in this study). Higher RR was observed when ESL was combined with CBZ (85.7%), VPA (73.3%), and LEV (72.7%), demonstrating that ESL was well retained in all combinations. These results are consistent with the ones reported in a subanalysis of EPOS study by baseline AED,¹¹ where VPA and LEV were also associated with high RR (88.5% and 81.9%, respectively), showing that ESL can effectively be used with all AEDs administered in this study.

Valproate and carbamazepine were the concomitant AEDs associated with the highest response rates at Vfinal (100% and 83.3%, respectively). These results are in accordance with EPOS study,¹⁷ in which VPA and CBZ were also the concomitant AEDs presenting the greatest percentage of responders.

Seizure-free rate at Vfinal was 39.5%, considerably higher than the ones reported at 6 months in Correia et al.¹⁶ (9.2%) and in Villanueva et al.¹⁸ (28.0%). These data are in accordance with the differences in the populations across the studies. A similar seizure-free rate was observed in EPOS study¹⁷ (39.2%). The relative reduction in median seizure frequency at Vfinal (82.2%) was also considerably higher than in the study of Correia et al.,¹⁶ with 50.0% at 6 months. Additionally, secondary generalized seizures were associated with the highest seizure-free rate (94.7%) at Vfinal, followed by simple partial seizures (86.8%). Complex partial seizures led to significantly lower seizure-free rates (47.4%). Similar results were reported in EPOS study,¹⁹ where the proportion of seizure-free patients was also higher for secondary generalized seizures (78.6%) and lower for complex partial seizures (46.8%).

Post-authorization studies confirmed that ESL was well tolerated in a real-world setting.^{20,21} The overall rate of AEs in our study was 23.1%. Compared to other studies that use ESL as adjunctive therapy, this rate is lower than the ones reported in EPOS study (26.0%),¹⁷ Correia et al. (42.1%),¹⁶ and that obtained in a pooled analysis of three phase III trials (62.7% and 67.5% in the ESL 800 mg and 1.200 mg groups, respectively).⁹ Most of the frequent AEs reported in our study (Table 2) were also different from the ones published on phase III clinical trials.²⁰

In previous experience with ESL, the incidence of psychiatric AEs (a frequent complaint in patients with epilepsy) was low, which is in accordance with our study.²⁰

The observational nature of our study could provide an explanation for the considerably lower rates and different profile of AEs, observed in comparison to the phase III trials. Phase III Clinical trials are conducted in a more "controlled" environment, often leading to an overreporting of safety outcomes (somnolence, dizziness, between others), which might be not reported in observational studies.²⁰⁻²²

The possible role of patients' age and therapy duration in the developing AEs was not performed and discussed due to the low number of AEs reported. Additionally, 9.6% of the patients discontinued ESL

due to AEs, which is lower than the percentages reported in EPOS (11.4%),¹⁷ in Villanueva et al. (13.4%),¹⁸ and in Correia et al. (21.1%) studies,¹⁶ and in the integrated analysis of pooled data from the phase III clinical trials (approximately 14.0%).⁹ Compared to our study, there were differences in the follow up period, patients' characteristics and sample size, which might explain the different results. Of notice, with the exception of EPOS study, all compared studies allowed more than one concomitant AED, in addition to ESL, which may increase the propensity for AEs.

Although not statistically significant due to limited sample size, favorable CGI-S scores were obtained as 42.1% of patients reached a less severe epilepsy level. CGI-S is a holistic, clinician-rated measure that comprise not only epilepsy severity, but also physical and psychopathological impact of seizures on the patient life. The statistically association between CGI-S score at baseline and seizure free rate ($P=0.011$) and RR ($P=0.024$) showed how this non-objective scale could be an important measure of the good ESL efficacy/tolerability profile in the clinical assessment. Moreover, CGI-C scores suggested a marked global improvement in epilepsy compared to baseline, with 73.6% of the patients considering their condition as "much improved" or "very much improved". Finally, the efficacy index score suggested a therapeutic effect of ESL on adjunctive therapy given the fact that 42.1% of patients were classified by physicians as "marked". The low incidence of AEs was corroborated by the efficacy index score, with 79.8% of patients being classified as having no side effects.

This study has limitations which advise caution when interpreting the results. First, as it was an observational study, the control for confounders is limited in comparison with the rigid setting of clinical trials. Additionally, visits were not made at fixed time points across patients, and therefore, seizure frequency was calculated on events occurring within different time intervals. Nevertheless, seizure frequency at Vinterm and Vfinal was standardized for a 4-week period to allow for comparisons with baseline frequency. Secondly, seizure frequency and seizure-free rate were collected using patients' diaries potentially leading to less accurate data. Moreover, it only reflects patients who completed the Vinterm and Vfinal (discontinuations were not considered). Finally, due to low numbers, the confidence intervals were considerably wide leading to lack of power to detect statistically significant associations between patients' characteristics and study main endpoints, and limiting the use of multivariable models.

5 | CONCLUSIONS

Attending clinical practice of ESL showed good retention rates and elicited a significant reduction in seizure frequency in patients with partial-onset seizures not sufficiently controlled with monotherapy. Our study is in accordance with other observational studies showing favorable tolerability and an efficient seizure control of ESL in adjunctive treatment in this setting. Further research with larger sample sizes is recommended to validate these results.

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CONFLICT OF INTEREST

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