

Real-world data on eslicarbazepine acetate as add-on to antiepileptic monotherapy

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Objective – To assess retention, tolerability, and safety, efficacy and effects on quality of life (QoL) of eslicarbazepine acetate (ESL) add-on treatment over 6 months in a real-world adult population with partial-onset seizures. **Methods** – This non-interventional, multicenter, prospective study was performed in eight European countries. Adult patients ($n = 247$) for whom the physician had decided to initiate ESL as add-on to an existing antiepileptic drug (AED) monotherapy were invited to participate. The study comprised three visits: baseline, and after 3 and 6 months. Data on ESL retention, efficacy, tolerability, safety, and QoL were collected. **Results** – After 6 months, the retention rate of ESL was 82.2%, and 81.8% of patients reported a reduction of seizure frequency of at least 50%; 39.2% of patients reported seizure freedom at this time. The mean QOLIE-10 score improved from 2.9 (SD \pm 0.8) at baseline to 2.1 (SD \pm 0.8) after 6 months. 109 adverse events (AEs) were reported in 57 patients (26.0%); the majority were rated as related to ESL by the investigator and led to a discontinuation of ESL in 25 patients (11.4%). Eight patients (3.7%) suffered at least one serious AE. The most frequently reported AEs were dizziness, headache, convulsion, and fatigue. **Conclusions** – This study shows that ESL was well tolerated and efficacious as add-on therapy to one baseline AED. The use of ESL in patients less refractory than those included in previous clinical trials led to higher responder and seizure freedom rates. No new safety issues were observed.

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Introduction

Although the majority of newly diagnosed patients will respond to initial antiepileptic therapy and enter long-term remission, approximately one-third of the patients show treatment refractory epilepsy (1) and require combinatorial antiepileptic drug (AED) regimens. Thus, achieving seizure freedom or significant reduction of seizure frequency, while avoiding drug interactions and toxicity, is a major challenge in the management of epilepsy. The choice of AED combination partners is often difficult due to unacceptable toxicities caused by drug interactions, which in turn lead to dissatisfaction and low treatment compliance (2, 3).

Eslicarbazepine acetate (ESL) is a once-daily anticonvulsant approved as add-on antiepileptic therapy for adults with partial-onset seizures (POS), with or without secondary generalization. Upon oral administration, ESL is extensively converted to eslicarbazepine which modulates the activity of voltage-gated sodium and calcium channels (4, 5). Importantly, in the course of this first-pass metabolism, no epoxide derivatives are produced, thus resulting in a favorable pharmacokinetic profile of ESL (6). The efficacy and safety of ESL add-on treatment for POS have been extensively assessed in the pivotal controlled clinical trials (7–9). However, in everyday clinical practice, patients are more diverse in terms of their clinical characteristics (e.g. disease severity,

comorbidities, adjunct medications) and are often less refractory to AED treatment than patients usually recruited in controlled clinical trials. In this context, non-interventional studies may provide useful additional information regarding clinical efficacy and tolerability under real-life conditions.

This non-interventional study EPOS (Eslicarbazepine acetate in Partial-Onset Seizures) aimed to assess retention rate and dosing regimens of ESL as add-on treatment to frequently prescribed AED monotherapies in a real-life European population. In addition, reported efficacy and tolerability were assessed.

Methods

Patients and study design

This open-label, non-interventional study was performed between April 23, 2012 and March 31, 2014 at 88 sites (mostly general neurologist practices) across Europe (Denmark, France, Germany, Norway, Sweden, UK, Ireland, Czech Republic). The trial was registered in www.clinicaltrials.gov (NCT01830400) and was subject to ethical approval in all countries involved. Initially, it was estimated to include 800 patients in 200 centers in the study. However, due to slow recruiting, this number of patients could not be achieved. Of 247 participating patients, 24 patients from two sites were excluded from the analysis due to poor data quality. Of the remaining 223 patients at 86 sites, 219 had completed informed consent, received at least one dose of ESL and had at least one post-dose safety assessment, and thus were considered evaluable for analysis.

Adult patients with POS, with or without secondary generalization, insufficiently controlled under AED monotherapy were invited to participate in the study if their physician had previously made the decision to prescribe ESL add-on therapy independently of participation and upon providing informed consent. ESL was recommended to be administered within the recommendation of the ESL Summary of Product Characteristics (SmPC) (10). Upon the patient signing informed consent, baseline data on demographics, medical history, previous antiepileptic therapy, adjunct medication, and diseases were collected, and the physicians were to record the planned titration schedule for ESL add-on therapy. The patients' seizure situation at the baseline visit was recorded retrospectively covering the period of 3 months prior to the baseline visit (based on patient dia-

ries, written patient records or detailed interviews); throughout the study, reported efficacy of ESL add-on treatment was assessed over 3-month intervals at the respective study visits after 3 and 6 months based on patient diaries. At these visits, the physicians also documented dosing, adverse events, retention, and treatment satisfaction. At all visits, patients were asked to complete the Quality of Life in Epilepsy Inventory-10 (QOLIE-10) (11). The QOLIE-10 was applied for a subset of sites where it was used in routine clinical practice and was available and validated in local language.

Statistical analysis

Quantitative variables were analyzed by means of basic statistical parameters, qualitative, and ordinal scaled variables were presented as absolute and relative frequency distributions. Relative frequencies were based on the number of available data, that is excluding missing data. No imputation methods of missing values were applied to the data. Additionally, two-sided 95% confidence intervals (CI) were calculated for the retention rates over 3 and over 6 months, respectively. For subgroup analyses, patients were classified according to gender, age (≤ 60 years, >60 years), number of discontinued AED regimens within the last 5 years prior to baseline and most frequently used baseline AEDs (carbamazepine, levetiracetam, lamotrigine, and valproate), and occurrence of adaptations of adjunct AED regimen throughout the study.

All analyses were performed with the SAS[®] package, version 9.2 (SAS Institute, Cray, NC, USA).

Results

Baseline description of patient population

From the 247 enrolled patients, 219 were included in the analysis. The mean duration of study participation was 178.7 days (range 7–301 days). The gender distribution was slightly imbalanced (57.5% male), the median age was 43 years (range 18–83); 18.7% of the patients were older than 60 years, and for 42.5%, concomitant diseases were recorded (mainly vascular, psychiatric, and nervous system disorders). Correspondingly, adjunct intake of medication other than AEDs was documented for 40.6% of the patients. The mean time since the initial diagnosis of epilepsy with POS was 12.3 years for all patients (SD \pm 12.1 years, range 0.0–57.3 years).

The seizure situation over 3 months prior to baseline is shown in Table 1. For only 3 of the 219 analyzed patients, no seizures were reported over the 3 months prior to baseline.

For 165 patients (75.3%), there was a documentation of at least one AED being discontinued during the last 5 years before enrollment into the study; of these, 76 patients (34.7%) had exactly one, 48 patients (21.9%) had two, and 41 patients (18.7%) had three or more discontinued AED regimens documented.

Reasons for prescribing and dosing of ESL as add-on therapy

The main reason for prescribing ESL add-on therapy was the lack of efficacy of AED monotherapy (89.0%), followed by adverse events caused by previous AED treatment (22.8%). For the majority (74.3%) of patients, the planned target dose of ESL was 800 mg/day; a target dose of 400 mg/day was documented for 6.4% and 1200 mg/day or higher was documented for 19.4%. Although ESL was recommended to be applied according to the recommendations of the SmPC (10), target doses higher than 1200 mg/day were documented for eight patients (mainly 1600 mg/day). The majority of patients reached their target dose after one titration step (79.3%), and the median of the duration until target dose was achieved was 14.0 days. Only for 40 patients (18.3%), dose changes after titration were documented, of whom 92.3% required only one dose change.

Adjunct antiepileptic drug medication

All patients were to receive adjunct AED medication licensed for monotherapy of epilepsy at baseline. Five patients had no documentation of such treatment. Levetiracetam ($n = 83$), lamotrigine ($n = 54$), valproate ($n = 30$), and carbamazepine ($n = 14$) were the most commonly reported baseline AEDs. Patients that took other than the

above AEDs ($n = 33$) were subsumed under a 'Various' class and are not shown in this manuscript.

Throughout the duration of the study, for the majority of patients (76.7%), no change of baseline AED medication or its dosing was documented. For the remaining 23.3% of patients, changes of adjunct AEDs were documented, including dose changes, withdrawals, novel prescriptions, and/or combinations thereof; these patients were summarized as one subgroup (with adaptation of adjunct AED) for further analyses.

Retention of ESL add-on therapy

For the total population, the 6-month retention rate of ESL add-on therapy was 82.2% (95%-CI: 76.5–87.0%). The retention rate at 3 months was higher with 89.0% (95%-CI: 84.1–92.9%). The 6-month retention rate showed only slight variations between the four most frequently prescribed baseline AED subgroups; the highest rate was seen in patients taking carbamazepine [100%, 95%-CI: (76.8%, 100.0%)], the lowest was observed in the lamotrigine group [75.9%, 95%-CI: (62.4%, 86.5%)]. The occurrence of adjunct AED adaptation did not significantly affect retention: the 6-month retention was 83.3% [95%-CI: (76.8%, 88.6%)] in patients without any AED adaptation, and 78.4% [95%-CI: (64.7%, 88.7%)] in those for whom an adaptation of adjunct AED medication was documented. The majority (97.2%) of patients, in whom ESL treatment was not discontinued during the study, wished to continue treatment with ESL beyond the study.

Adverse events

Overall, 109 adverse events (AEs) were reported in 57 patients (26.0%), thereof eight patients (3.7%) with at least one serious AE (Table 2). One patient, a 78-year-old male with a history of cardiac myxoma surgery and concomitant intake of antiarrhythmic and antihypertensive medication died during the course of the study. The reporting physician considered the death that occurred suddenly after waking up as not related to ESL treatment. No autopsy was performed. Eighty-four adverse drug reactions (ADRs), defined as an AE with a causal relationship to ESL, were reported in 49 patients (22.4%). For 25 patients (11.4%), an AE was the reason for withdrawal of ESL during the study.

The most frequent AEs with respect to System Organ Class (SOC) were nervous system disorders (31 patients, 14.2%), psychiatric disorders

Table 1 Seizure frequency over 3 months prior to baseline

	Simple partial seizures	Complex partial seizures	Secondary generalized seizures	Total
N (patients)	97	162	113	219
Mean (seizures)	22.8	25.9	2.2	29.3
SD	60.4	103.2	4.7	95.8
Minimum	0	0	0	0
Median	6	7	1	9
Maximum	450	900	47	900

Table 2 List of serious adverse events (SAE) according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term

SAE	Relatedness assessed by the investigator
Convulsion	Possible
Hyponatremia	Probable
Grand mal convulsion	Possible
Grand mal convulsion	Not related
Grand mal convulsion	Not related
Anaplastic oligodendroglioma	Not related
Death	Not related
Dermatitis allergic	Probable
Urticaria	Probable
Vertigo	Probable
Dizziness	Probable
Muscular weakness	Probable
Hypotonia	Probable

(12 patients, 5.5%), and skin and subcutaneous tissue disorders (11 patients, 5.0%). The most frequently reported preferred terms (PTs) of AEs were dizziness (10 patients, 4.6%), headache, convulsion (each 7 patients, 3.2%), and fatigue (6 patients, 2.7%).

Subgroup analysis of adverse events was complicated by small sample size and low number of events, especially for the subgroups of most frequently prescribed AEDs. Hypothesis driven analysis whether adaptations of adjunct AED regimen would result in a differential outcome, failed to show a clear difference: the rate of patients with at least one AE was 24.4% in the group of patients for whom no adaptations were recorded, while it was 31.4% for the group of patients for whom an adaptation was recorded. Also, the rate of serious AE was lower in the group without adaptation of adjunct AED (1.8% vs 9.8%); however, it needs to be stated that the number of events was very low (4 SAE in 3 patients vs 9 SAE in 5 patients), and therefore does not allow to draw definitive conclusions.

Reported efficacy

At the visit after 3 months, 25.9% of the patients reported to be seizure free, and seizure freedom rate at the 6 months visit was 39.2%. The responder rate (number of patients with a reduction of seizure frequency of at least 50% vs baseline over an observation interval of 3 months) was 69.9% at 3 months and 81.8% at 6 months (Fig. 1).

While age did not seem to affect reported efficacy and the responder rate after 3 months did not show an impact of gender, after 6 months male patients showed a higher responder rate than females (87.2% vs 74.4%).

Responder rates further varied considerably with respect to the number of previously discontinued AED regimens, where more previously discontinued AEDs led to a lower responder rate. After 6 months, the highest responder rate was observed for patients with exactly one (responder rate 90.9%), followed by those with two (responder rate 82.2%) and three or more (responder rate 77.4%) previously discontinued AEDs; for patients without documented discontinued AED regimen, the responder rate was 71.1%.

Analysis of responder rates after 6 months depending on the AED regimen at baseline showed similarly high rates in the carbamazepine (92.9%) and valproate (88.5%) groups, followed by patients taking levetiracetam (81.9%) and lamotrigine (69.8%).

Patients, for whom no adaptations of adjunct AED medication were documented, showed a slightly lower seizure freedom rate at 6 months (37.7%) than patients with an AED adaptation (44.2%). Similarly, the responder rate at this time point was also slightly lower in patients without documented adaptation of their adjunct AED regimen (80.6%) than in patients with an adaptation (86.0%).

Quality of life

The Quality of Life in Epilepsy Inventory-10 (QOLIE-10) was completed at baseline by 128 patients, at the 3-month visit by 114 patients and at the 6-month visit by 109 patients. The mean value of the score declined from 2.9 at baseline to 2.4 at 3 months and to 2.1 at the 6-month visit, with lower values representing better QoL (11) (Fig. 2). No major influence on QOLIE-10 scores was observed in subgroup analyses according to gender, age, baseline AED, and number of previously discontinued AED regimens (*not shown*).

Discussion

Eslicarbazepine acetate (ESL), a once-daily anti-convulsant approved for adjunctive therapy of adults with POS has shown a favorable pharmacokinetic profile (6) and good efficacy and tolerability in controlled clinical settings (7–9, 12). The population evaluated in this non-interventional trial showed a relatively low baseline seizure frequency (median of nine seizures in 3 months, Table 1), most likely attributable to the design of the study as early add-on study, in which only patients with monotherapy at baseline were to be included, and with differences in capturing seizure data (more frequent visits in interventional clinical

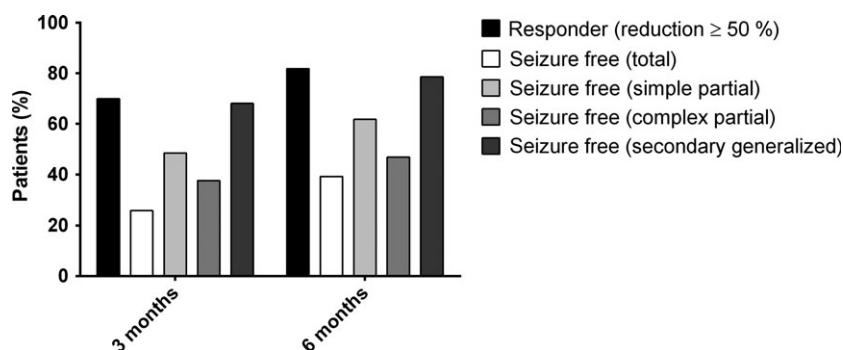


Figure 1. Reported efficacy at 3- and 6-month follow-up visits. Responder rate (\geq 50% reduction of seizure frequency compared to reported seizure frequency over the last 3 months prior to baseline, black bars) and seizure freedom, sorted by seizure type (white bars: total number of seizures; light gray simple partial seizures; medium gray: complex partial seizures; dark gray: secondary generalized seizures). Percentages are calculated based on number of patients with valid data available: at 3 months $n = 212$; at 6 months $n = 189$.

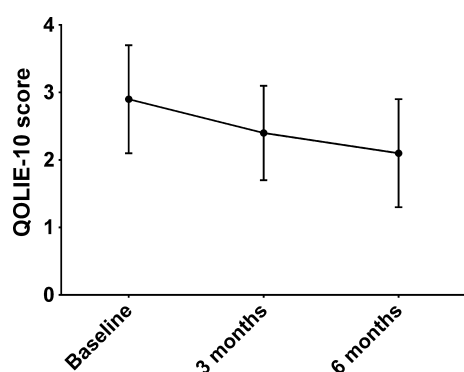


Figure 2. Quality of life assessed by means of the QOLIE-10 questionnaire. Course of QOLIE-10 score throughout the study, with lower values representing better QoL. QOLIE-10 was only completed by a subset of patients (baseline: $n = 128$, 3-month follow-up: $n = 114$, 6-month follow-up: $n = 109$). Mean and SD are depicted.

cal trials) being another possible source of variation. Together with the possibility for an individualized dosing of ESL and adaptations of adjunct AED regimen, these aspects represent the major differences between this real-life observational study, and the pivotal clinical trials with ESL, where much higher baseline seizure frequencies were observed (7–9, 12).

The most frequent ESL target dose was 800 mg/day. Only a minority of patients required dose adaptations after titration. If required, for the vast majority of these patients, one post-titration dose change was sufficient to achieve satisfactory results. These findings suggest that ESL add-on treatment is easy to handle.

For the majority of patients, no changes of adjunct AED medications, or their dosage, were necessary under ESL add-on therapy, thus suggesting good efficacy and tolerability of the add-on treatment and indicative of a clinically unproblematic interaction profile (6). Retention rate has been

recommended as useful outcome measure for clinical trials with AEDs, as it comprises clinical drug effectiveness (efficacy and tolerability aspects) and patient choice (13). Accordingly, the high proportion of patients who retained the treatment for 6 months (82.2%) is likely to reflect patients' and physicians' satisfaction with ESL add-on treatment, with the vast majority of patients stating their intent to continue with ESL add-on treatment beyond the present study. Correspondingly, reported efficacy was good, with almost 40% of the patients reporting at least 3 months of seizure freedom after 6 months and a responder rate at 6 months of 81.8% (Fig. 1). These figures are much higher than in previous clinical trials with ESL where responder rates between 30 and 40% (7–9, 12) were observed, likely attributable to a less severe seizure situation at baseline and potentially less refractory epilepsies in the patients included in the present study. This assumption is strengthened by observations from longer-term trials with other AEDs, which also suggest that outcome measures like retention may vary in dependency of the severity of epilepsy in the population studied (14).

The median of the QOLIE-10 score showed improvement after 3, and further after 6 months, indicating that ESL add-on treatment led to some improvement in health-related quality of life (Fig. 2). Therefore, it may be concluded that for the majority of the present patients, the addition of ESL to an existing monotherapy did not worsen, but rather stabilizes or even improves QoL. This finding in itself is important, as dissatisfaction with AED treatment and poor tolerability of AED regimens are well-known determinants of poor QoL (2, 3).

Subgroup analyses of ESL add-on treatment retention according to baseline AED medication indicate that ESL can be combined with the most

frequently prescribed and currently monotherapy-approved AEDs, as retention rates were higher than 75% for all combinations: carbamazepine (100.0%), levetiracetam (85.5%), valproate (80.0%), and lamotrigine (75.9%). Correspondingly, reported efficacy (responder rate) at 6 months was also high when ESL was combined with the most frequent baseline AEDs: carbamazepine (92.9%), valproate (88.5%), levetiracetam (81.9%), and lamotrigine (69.8%). The apparent differences should be interpreted cautiously, due to the relatively small sample size in some subgroups. The findings of high retention and reported efficacy rates in the *carbamazepine* subgroup are noteworthy, as they appear to correspond to previous findings, where additional efficacy of ESL was observed also in combination with carbamazepine (12). Eslicarbazepine and carbamazepine have been shown to display differential kinetics regarding the inactivation of voltage-gated sodium channels (5), which may be linked to differential clinical efficacy. More recently, both in humans and experimental models of epilepsy, it was demonstrated that eslicarbazepine may overcome a cellular resistance mechanism to carbamazepine (15).

In terms of reported efficacy, responder rate was also affected by the degree of failure of previous AED treatments: the highest responder rate at 6 months was seen in patients with one previously discontinued AED regimen (90.9%), followed by patients with two (82.2%) and those with ≥ 3 previous AED regimens (77.4%), corroborating previous findings (16). In contrast, responder rate in the group of patients without any documentation of previously discontinued AED was lowest at 71.1%. At a first glance, this finding might seem contradictory. However, this group is most likely to be highly heterogeneous in terms of illness severity and treatment refractoriness (17) and could therefore contain a higher proportion of patients in whom early add-on AED therapy was consciously preferred over switching to an alternative monotherapy (e.g. due to knowledge of the underlying pathology or higher seizure density) (18). Indeed, a *post hoc* subgroup analysis of the baseline seizure situation revealed the highest mean numbers of simple and complex partial seizures as well as total seizure number in these patients (over 3 months prior to baseline; *not shown*).

The overall analysis of tolerability was favorable and in line with the known tolerability profile of ESL (10). Fifty-seven patients (26.0%)

suffered from adverse events (AE, $n = 109$). The majority of the AE were considered adverse drug reactions, that is assessed as related to ESL treatment by the physician (84 AE in 49 patients). Of the 13 serious AE (in eight patients) (Table 2), nine were judged as related to ESL treatment by the physicians. One patient died during the study (cause of death unknown), but the physician did not see a causal relationship to ESL treatment. The most frequently reported events were dizziness (4.6%), headache (3.2%), convulsion (3.2%), and fatigue (2.7%); all other events were reported for less than six patients.

Compared to controlled clinical studies, the limitations of the present research are obvious and predetermined by the non-interventional, single-arm character of the trial, which only allows for descriptive analyses. The relatively low numbers especially for subgroups imposes the necessity for careful interpretation of the obtained results. Nonetheless, studies like the present one are of value for the treating physician as they help obtain a realistic picture of the real-life clinical practice, where patient populations are highly variable in terms of disease severity, adjunct medication, and comorbidities.

Taken together, the present study shows a high retention rate as well as promising reported efficacy of ESL add-on treatment in a real-life clinical setting. The treatment was well tolerated by the majority of patients and did not negatively affect health-related quality of life. Subgroup analyses indicate potentially differential effects of AED combination partners on ESL effectiveness. However, due to small sample size, these subgroup findings should be interpreted cautiously.

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