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Incidence of Seizure Exacerbation and Seizures Reported as Adverse Events during Adjunctive Treatment with Eslicarbazepine Acetate: A Pooled Analysis of Three Phase III Controlled Trials

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FULL-LENGTH ORIGINAL RESEARCH

Incidence of seizure exacerbation and seizures reported as adverse events during adjunctive treatment with eslicarbazepine acetate: A pooled analysis of three Phase III controlled trials

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Summary

Objective: **To investigate whether adjunctive eslicarbazepine acetate (ESL) could lead to exacerbation of seizures in some patients.**

Methods: **Post-hoc analysis of data pooled from three Phase III trials of adjunctive ESL (studies 301, 302, and 304) for refractory partial-onset seizures (POS). Following an 8-week baseline period, patients were randomized to receive placebo or ESL 400, 800, or 1,200 mg once daily (2-week titration, 12-week maintenance, 2–4 week tapering-off periods). Patient seizure diary data and seizure treatment-emergent adverse event (TEAE) reports were pooled for analysis.**

Results: **The modified intent-to-treat and safety populations comprised 1,410 patients and 1,447 patients, respectively. *Titration period*: Compared with placebo (32/21%), significantly smaller proportions of patients taking ESL 800 mg (20/15%) and 1,200 mg (22/12%) had a ≥25/≥50% increase in standardized seizure frequency (SSF) from baseline; there was no significant difference between placebo and ESL 400 mg. *Maintenance period*: Compared with placebo (20%), significantly smaller proportions of patients taking ESL (400 mg, 12%; 800 mg, 12%; 1,200 mg, 14%) had an increase in SSF ≥25%. When evaluating ≥50% increases in SSF, only ESL 800 mg (7%) was significantly different from placebo (12%). Some patients had no secondarily generalized tonic-clonic (sGTC) seizures during baseline but had ≥1 sGTC seizure during maintenance treatment (placebo, 11%; ESL 400 mg, 5%; 800 mg, 10%; 1,200 mg, 5%). Fewer patients had a ≥25% increase in sGTC seizure frequency with ESL (400 mg, 11%; 800 mg, 9%; 1,200 mg, 14%) versus placebo (19%). The incidence of seizures reported as TEAEs was low in all treatment groups; incidences were generally lower with ESL versus placebo. *Tapering-off period*: Similar proportions of patients taking ESL and placebo had a ≥25/≥50% increase in SSF. Seizure TEAE incidence was numerically higher with ESL versus placebo.**

Significance: **Treatment with adjunctive ESL does not appear to aggravate POS or sGTC seizures.**

KEY WORDS: **Epilepsy, Focal seizures, Safety, Seizure aggravation, Seizure worsening.**

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Key Points

- Seizure-related TEAEs and ≥25% and ≥50% increases in seizure frequency from baseline were evaluated in Phase III trials of adjunctive ESL
- Treatment with adjunctive ESL did not appear to increase the frequency of partial-onset seizures
- Treatment with adjunctive ESL did not appear to increase the frequency of secondarily generalized tonic-clonic seizures

Seizure aggravation by antiepileptic drugs (AEDs) is the worsening of seizure frequency or severity, or of the type of seizure, in response to administration of an AED.[1] The paradoxical ability of AEDs to increase seizure activity has been recognized for many years, particularly in patients with generalized-onset seizure disorders.[2] It has been suggested that the issue of paradoxical exacerbations will become more common as the number of available AEDs increases.[3] The dibenzazepine carboxamide AEDs, carbamazepine and oxcarbazepine, have been reported to precipitate or exacerbate seizures, most notably absence, atonic, or myoclonic seizures in patients with generalized epilepsies.[2,4–6] Phenytoin and vigabatrin have also been implicated in worsening of generalized seizures, and gabapentin has been associated with precipitation of myoclonic jerks.[2] Most reports of seizure exacerbation concern generalized epilepsies with little published objective or quantitative evidence regarding focal seizures.[7–9]

Eslicarbazepine acetate (ESL) is a member of the dibenzazepine carboxamide family of AEDs and is approved as adjunctive treatment for partial-onset seizures (POS) in the U.S.A., Europe, and Canada and as monotherapy for POS in the U.S.A. and Europe. ESL is rapidly and extensively metabolized to eslicarbazepine,[10] which is thought to act primarily by preferentially stabilizing the inactivated state of voltage-gated sodium channels.[11,12] The efficacy and tolerability of adjunctive ESL in patients with refractory POS have been evaluated in four randomized, placebo-controlled trials (BIA-2093-301, -302, -303, and -304).[13–16] The results of study 303 were consistent with those of the other studies but were not included in the current analysis because study 303 was deemed by a sponsor audit not to be in accordance with Good Clinical Practice (GCP) standards.

To investigate whether adjunctive ESL (a dibenzazepine carboxamide AED) could lead to exacerbation of seizures in some patients, we conducted a post-hoc analysis of seizure diary data pooled from studies 301, 302, and 304 to determine the proportions of patients with increases in seizure frequency between the baseline and treatment periods of the three trials. We also evaluated the incidences of seizures reported as treatment-emergent adverse events (TEAEs) during the maintenance period and the tapering-off period (studies 301 and 304 only; study 302 did not include a tapering-off period). These analyses provide new information about the potential for worsening of focal seizure frequency following initiation of a new dibenzazepine carboxamide AED, a drug class that has previously been shown to exacerbate some types of generalized seizures.

Materials and Methods

Study design

The multinational, randomized, double-blind, placebo-controlled trials (301 [NCT00957684], 302 [NCT00957047], and 304 [NCT00988429]; registered at ClinicalTrials.gov) were conducted between July 2004 and January 2012. The design of each study (including inclusion and exclusion criteria) has previously been reported in full.[13,14,16] Briefly, patients were aged ≥16 years (study 304) or ≥18 years (studies 301 and 302), with at least a 12-month history of simple or complex POS, with or without secondary generalization, continuing to have seizures while receiving stable doses of 1–2 AEDs (studies 301 and 304) or 1–3 AEDs (study 302). Patients with primarily generalized epilepsies were excluded. A key eligibility criterion was the occurrence of ≥4 POS during each of the two 4-week periods during baseline, with no seizure-free period >21 consecutive days (studies 301 and 302) or ≥8 POS during baseline, with ≥3 seizures in each 4-week period and no seizure-free period >28 consecutive days (study 304).

All three studies included an 8-week baseline period, a 2-week ESL titration period (titration schedules differed slightly between studies), and a 12-week ESL maintenance period. After the baseline period, eligible patients were randomized equally to receive placebo, ESL 400 mg (studies 301 and 302 only), 800 mg, or 1,200 mg tablets once daily; patients continued to receive stable dosages of baseline concomitant AEDs, but concomitant oxcarbazepine (OXC) was prohibited because of similarities in metabolites between OXC and ESL. In studies 301 and 302, the 12-week maintenance period was followed by a 2-week tapering-off period, during which the dose of ESL was reduced by 400 mg each week. In study 302, ESL dosing was discontinued abruptly at the end of the 12-week maintenance period.

Analysis population

Patient-level data from studies 301, 302, and 304 were pooled. Following an audit conducted by the study sponsor, a modified intent-to-treat (mITT) population was used in this analysis, comprising all patients who received ≥1 dose of study medication and had ≥1 post-baseline seizure frequency assessment, excluding 20 patients from two sites in study 301 (owing to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-GCP deficiencies).

Seizure diary data

Information obtained from seizure diary entries was used to determine the frequency of occurrence of seizures during the study. The primary efficacy endpoint was standardized seizure frequency (SSF) during the 12-week maintenance period, calculated as the number of seizures per 4 weeks (28 days). The method for calculating seizure frequency for patients from studies 301 and 302 was slightly revised from that used to calculate seizure frequency in the original publications for the individual studies.[13,14] Both studies used event-based diaries, and in the original analyses, it was assumed that patients would not have had a further seizure after their last reported event. Consequently, for each patient, the end of the maintenance period was deemed to be the end of the study period. This uncertainty was eliminated from the current analysis by using the date of the last returned diary card as the end of the study period. Study 304 utilized daily-entry diaries.

Seizures reported as treatment-emergent adverse events

The occurrence of TEAEs was analyzed for the "safety" population (all patients who received at least one dose of study medication). AEs were classed as treatment-emergent if their onset was on or after the date of the first dose of study drug (or was unknown or partially known). AEs were recorded and assessed by the investigators, and additional AEs were identified from audits of investigator records and case report forms, and from review of subject narratives and serious adverse event reports.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1, and patients with any seizures reported as TEAEs (seizure TEAEs) were identified using the higher-level group term "seizures" (including subtypes). Individual patients were counted only once if they had more than one TEAE at a particular level of summarization. Incidences of seizure TEAEs were calculated for patients who entered the maintenance period and those who entered the tapering-off period (studies 301 and 304 only; study 302 did not include a tapering-off period). TEAEs reported more than once (in the same patient) during a treatment period were counted only once, but TEAEs reported during both the titration and maintenance periods were counted separately and contributed to the incidence calculated for both periods.

Statistical analysis

Descriptive statistics (number of patients; percentage of patients; means and standard deviations) for selected baseline clinical and demographic characteristics were calculated for the different treatment groups. The incidence of seizure TEAEs was calculated as the number and percentage of patients, for those who entered the maintenance period or the tapering-off period (overall, and by preferred term).

Proportions of patients with an increase in SSF of ≥25% or ≥50% from baseline were calculated during the different treatment periods. The proportions of patients with an increase in SSF were compared between the placebo group and each of the ESL dose groups using the Cochran–Mantel–Haenszel test.

Potential exacerbation of secondarily generalized tonic-clonic (sGTC) seizures was examined by evaluating the proportion of patients with sGTC seizures during baseline versus the maintenance period. The proportion of patients that did not have a sGTC seizure during baseline but did have this seizure type during the maintenance period (for patients with data on worst seizure type during both the baseline and maintenance periods) was also calculated. The relative change (%) from baseline in SSF among patients who had sGTC seizures during baseline was also calculated for each treatment group.

Results

Demographic and baseline clinical characteristics

The characteristics of the pooled study population have been reported previously.[17] Patients were between 16 and 75 years old (median 37–38 years) and mainly from Europe and North or Latin America. The majority (78–95%) were Caucasian, males and females were equally represented, and demographic data were generally balanced between treatment groups. The mITT population comprised 1,410 patients, and the safety population comprised 1,447 patients.

The mean duration of epilepsy in the different treatment groups was approximately 20 years (Table 1). At baseline, most patients were taking one or two AEDs, the most frequently used being carbamazepine (CBZ), lamotrigine, valproic acid, and levetiracetam (≥15% of patients overall; Table 1). Mean SSF during baseline was between 13 and 16 per 28 days (Table 1), and the most common seizure type apparent during the baseline period was complex partial seizures (70–80% of patients; Table 2). Simple partial seizures were noted in approximately 50% of patients, with "partial evolving to secondarily generalized seizures" in approximately 33–37% (Table 2). The most frequently identified seizure etiologies were: idiopathic; cranial trauma/injury, infectious diseases (Shorvon's 2011 classification guidelines group these etiologies into a single category: "symptomatic epilepsy with predominantly acquired causation"[18]); and congenital/hereditary (or, using the 2011 guidelines, "symptomatic epilepsy with predominantly genetic causation"[18]) (Table 2).

Incidence of exacerbation of seizures

Titration period

One parameter used to assess exacerbation of seizures during the titration period was the proportion of patients with ≥25% increase in SSF compared with the baseline period. According to this measure, compared with the

Table 1. Baseline clinical characteristics (safety population)[a]

	Placebo n = 426	ESL 400 mg n = 196	ESL 800 mg n = 415	ESL 1,200 mg n = 410
Duration of epilepsy, y, mean (SD)	21.6 (13.9)[b]	21.9 (12.0)[c]	21.9 (12.8)[d]	20.8 (12.6)[e]
Baseline SSF, per 28 days, mean (SD)	14.8 (18.0)[b]	13.1 (15.3)[f]	16.0 (26.8)[g]	15.3 (17.9)[h]
Baseline AEDs, n (%)				
1	116 (27.3)[i]	63 (32.1)	107 (26.0)[j]	117 (28.6)[k]
2	297 (69.9)[i]	127 (64.8)	292 (70.9)[j]	280 (68.5)[k]
3	12 (2.8)[i]	6 (3.1)	13 (3.2)[j]	12 (2.9)[k]
AEDs used during baseline,[l] n (%)				
Carbamazepine	198 (46.5)	116 (59.2)	204 (49.2)	204 (49.8)
Lamotrigine	108 (25.4)	46 (23.5)	93 (22.4)	105 (25.6)
Valproic acid	95 (22.3)	37 (18.9)	95 (22.9)	86 (21.0)
Levetiracetam	89 (20.9)	23 (11.7)	80 (19.3)	73 (17.8)

AED, antiepileptic drug; ESL, eslicarbazepine acetate; SD, standard deviation; SSF, standardized seizure frequency.
[a]All randomized patients who received at least one dose of study drug.
[b]mITT population: n = 418.
[c]mITT population: n = 188.
[d]mITT population: n = 407.
[e]mITT population: n = 395.
[f]mITT population: n = 189.
[g]mITT population: n = 408.
[h]mITT population: n = 394.
[i]n = 425.
[j]n = 412.
[k]n = 409.
[l]Used by >15% of patients.

Table 2. Seizure etiology[a] and seizure type during the baseline period (mITT population)

	Placebo n = 418	ESL 400 mg n = 189	ESL 800 mg n = 408	ESL 1,200 mg n = 395	Total n = 992
Possible seizure etiology[b], n (%)					
Idiopathic	90 (21.5)	28 (14.8)	66 (16.3)	83 (21.1)	177 (17.9)
Cranial trauma/injury	62 (14.8)	36 (19.0)	57 (14.0)	45 (11.4)	138 (14.0)
Infectious diseases	29 (6.9)	26 (13.8)	37 (9.1)	38 (9.6)	101 (10.2)
Congenital/hereditary disorders	31 (7.4)	20 (10.6)	39 (9.6)	36 (9.1)	95 (9.6)
Cerebrovascular disease	9 (2.2)	3 (1.6)	14 (3.4)	16 (4.1)	33 (3.3)
Brain tumors	12 (2.9)	3 (1.6)	14 (3.4)	9 (2.3)	26 (2.6)
Systemic/toxic/metabolic disorders	6 (1.4)	3 (1.6)	4 (1.0)	6 (1.5)	13 (1.3)
Other/unknown	179 (42.8)	75 (39.7)	176 (43.3)	165 (41.9)	416 (42.1)
Seizures during baseline, n (%)					
Simple partial	197 (47.1)	88 (46.6)	204 (50.0)	201 (50.9)	493 (49.7)
Complex partial	325 (77.8)	133 (70.4)	320 (78.4)	317 (80.3)	770 (77.6)
Partial evolving to secondarily generalized	149 (35.6)	64 (33.9)	133 (32.6)	147 (37.2)	344 (34.7)
Unclassified	38 (9.1)	18 (9.5)	34 (8.3)	30 (7.6)	82 (8.3)

ESL, eslicarbazepine acetate; mITT, modified intent-to-treat.
[a]According to the 1981 classification of epileptic seizures guidelines.[19]
[b]Seizure etiology categories were specified by study investigators.

placebo group (32%), significantly smaller proportions of patients in the groups randomized to ESL 800 mg (20%) and ESL 1,200 mg (22%) had an increase in seizure frequency ($p \leq 0.001$ and $p \leq 0.01$ vs. placebo, respectively; Fig. 1). The proportion of patients with an increase in SSF was not significantly different between the group randomized to ESL 400 mg (25%) and placebo.

Proportions of patients with ≥50% increase in SSF (compared with the baseline period) were also calculated for the titration period. As with the previous parameter, compared with the placebo group (21%), significantly smaller proportions of patients randomized to ESL 800 mg (15%; $p \leq 0.05$) and 1,200 mg (12%; $p \leq 0.001$) had an increase in SSF. The proportion of patients with an increase in SSF

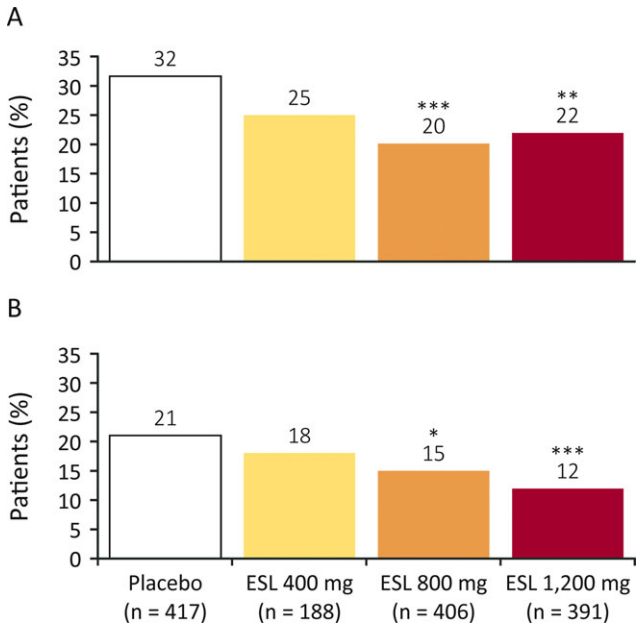

Figure 1.
Proportions of patients† with (A) ≥25% increase and (B) ≥50% increase in seizure frequency (titration period). *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus placebo. †Data are proportions of patients with increases in seizure frequency between the baseline period and the titration period (mITT population). ESL, eslicarbazepine acetate; mITT, modified intent-to-treat.
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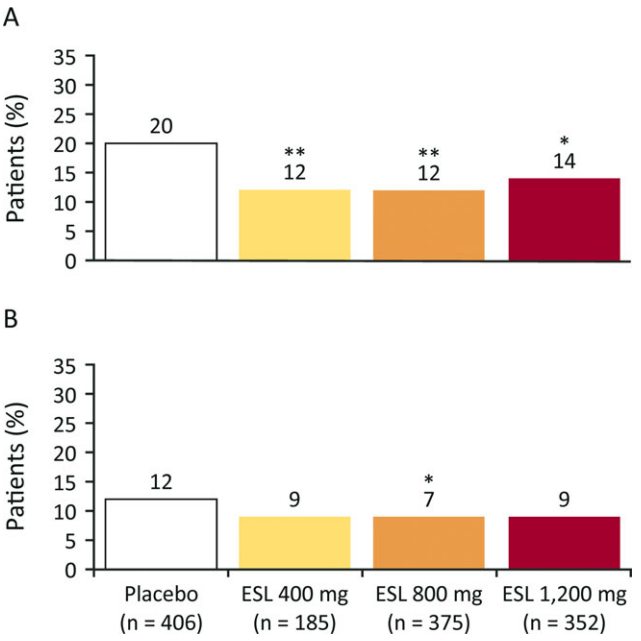

Figure 2.
Proportions of patients† with (A) ≥25% increase in seizure frequency (maintenance period) and (B) ≥50% increase in seizure frequency (maintenance period). *p ≤ 0.05; **p ≤ 0.01 versus placebo. †Data are proportions of patients with increases in seizure frequency between the baseline period and the maintenance period (mITT population). ESL, eslicarbazepine acetate; mITT, modified intent-to-treat.
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was not significantly different between those randomized to ESL 400 mg (18%) versus placebo.

Maintenance period

Seizure diary information during the maintenance period was available for 1,318 of the 1,410 patients in the mITT population. Exacerbation of seizures during this period was first evaluated by the proportion of patients with ≥25% increase in SSF compared with the baseline period. Compared with the placebo group (20%), significantly smaller proportions of patients in each of the three ESL treatment groups (12%, p ≤ 0.01; 12%, p ≤ 0.01; and 14%, p ≤ 0.05; respectively) had an increase in SSF ≥25% (Fig. 2).

When exacerbation of seizures during the maintenance period was evaluated by the proportion of patients with ≥50% increase in SSF compared with the baseline period, significantly fewer patients in the ESL 800 mg group (7%; p ≤ 0.05) had an increase in SSF compared with placebo (12%). There was no significant difference between the proportion of patients with an increase in SSF in the ESL 400 mg (9%) or 1,200 mg (9%) groups versus placebo.

Tapering-off period (study 301 only)

The proportions of patients with a ≥25% increase in seizure frequency between the baseline period and the tapering-off period were similar between the ESL and placebo treatment groups (Fig. 3). At most, there was a six percentage point difference in the proportion of patients with this magnitude of worsening of seizures between the placebo group (17%) and the ESL 800 mg group (23%).

The proportions of patients with a ≥50% increase in seizure frequency between the baseline and tapering-off periods were also similar between the placebo (11%) and ESL treatment groups (ESL 400 mg, 7%; ESL 800 mg, 15%; ESL 1,200 mg, 10%).

There was no clear evidence of a relationship between the dose of ESL and the proportion of patients with an increase in seizure frequency during any of the treatment periods examined.

Secondarily generalized tonic-clonic seizures

Potential exacerbation of the sGTC seizure type was also examined. Analysis of data for patients with no missing data for worst seizure type (both during the baseline and maintenance periods) showed that 462 patients had a sGTC seizure during baseline and that 826 did not. Of those who did have a sGTC seizure during baseline, 70–76% (placebo, 76%; ESL 400 mg, 70%; ESL 800 mg, 72%; ESL 1,200 mg, 71%) also had a sGTC seizure during the maintenance period. Of those patients who did not have a sGTC seizure during baseline, 5–11% experienced this seizure type during maintenance treatment, potentially indicating exacerbation of this seizure type; slightly more of these patients had a

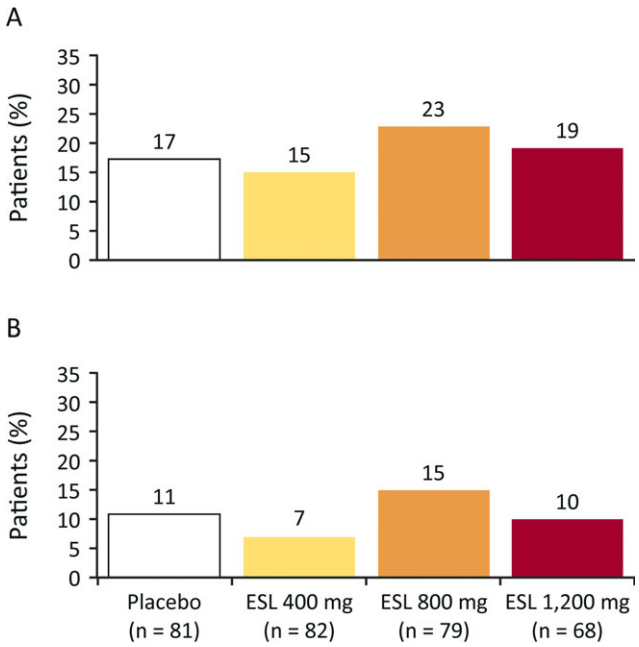

Figure 3.
Proportions of patients† with (A) ≥25% increase in seizure frequency (tapering-off period) and (B) ≥50% increase in seizure frequency (tapering-off period). †Data are proportions of patients with increases in seizure frequency between the baseline period and the titration period (study 301 mITT population only). ESL, eslicarbazepine acetate; mITT, modified intent-to-treat.
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sGTC seizure in the placebo (11%) group than in the ESL 400 mg (5%), ESL 800 mg (10%), and ESL 1,200 mg (5%) groups.

Exacerbation of this seizure type was also evaluated by looking at the proportion of patients with a ≥25% increase in sGTC seizures from baseline during the maintenance period, for all patients who had a sGTC seizure during baseline. Numerically fewer patients had a ≥25% increase in sGTC seizure frequency with ESL (ESL 400 mg, 11%; ESL 800 mg, 9%; ESL 1,200 mg, 14%) than with placebo treatment (19%).

Seizure TEAEs

Incidences of seizure TEAEs were calculated for the patients who entered the maintenance period (placebo group, n = 410; ESL groups, n = 939) and for those who entered the tapering-off period (studies 301 and 304 only; placebo group, n = 93; ESL groups, n = 269).

Maintenance period

The incidences of seizure TEAEs during the maintenance period were low in all treatment groups, but incidences in the ESL treatment groups were generally lower than in the placebo group (Table 3A).

Tapering-off period (studies 301 and 304)

The overall incidence of seizure TEAEs among patients taking ESL was not different between the tapering-off period (2.2%; Table 3B) and the maintenance period (2.2%; Table 3A). However, the tapering-off period (2–4 weeks) was shorter than the maintenance period (12 weeks). The incidence of seizure TEAEs during the tapering-off period was numerically higher in the ESL groups, compared with the placebo group.

Discussion

Information from seizure diaries and reports of seizure TEAEs indicated that, compared with placebo, a smaller

Table 3. Incidence of seizure TEAEs during (A) the ESL maintenance period and (B) the tapering-off period

		ESL			
	Placebo	400 mg	800 mg	1,200 mg	Total
A					
Entered maintenance period, n	410	192	383	364	939
Seizure TEAEs, n (%)	13 (3.2)	4 (2.1)	10 (2.6)	7 (1.9)	21 (2.2)
Partial seizure, n (%)	7 (1.7)	3 (1.6)	7 (1.8)	6 (1.6)	16 (1.7)
Partial seizure with secondary generalization, n (%)	1 (0.2)	0	3 (0.8)	0	3 (0.3)
Convulsion, n (%)	0	1 (0.5)	0	0	1 (0.1)
Epilepsy, n (%)	2 (0.5)	0	0	1 (0.3)	1 (0.1)
Simple partial seizure, n (%)	1 (0.2)	0	1 (0.3)	0	1 (0.1)
Status epilepticus, n (%)	2 (0.5)	0	0	0	0
B					
Entered tapering-off period, n	93	93	92	84	269
Seizure TEAEs, n (%)	0	4 (4.3)	1 (1.1)	1 (1.2)	6 (2.2)
Partial seizure, n (%)	0	3 (3.2)	1 (1.1)	0	4 (1.5)
Complex partial seizure, n (%)	0	1 (1.1)	0	1 (1.2)	2 (0.7)

Data shown are number and percentage of patients with seizure TEAEs, among those who entered the maintenance period or tapering-off period, respectively (overall, and by preferred term).
For Table 3B, data were available for studies 301 and 304 only (study 302 did not include a tapering-off period).
ESL, eslicarbazepine acetate; TEAE, treatment-emergent adverse event.

proportion of patients taking ESL (in addition to their existing AEDs) had an increase in SSF during both the titration and maintenance periods. This analysis suggests that use of adjunctive ESL is not associated with systematic exacerbation of POS (i.e., worsening of seizure frequency or severity relative to placebo). In addition, compared with placebo, a smaller proportion of patients taking ESL had an increase in sGTC seizure frequency, suggesting that use of adjunctive ESL is not associated with systematic exacerbation of this seizure subtype. As specified by the study protocols, the analysis population included only patients with partial seizures; no patients had primary generalized epilepsies (such as myoclonic or absence seizures). Therefore, it is not possible to determine whether ESL might exacerbate these seizure types. Many reports of seizure worsening with AEDs, including with sodium channel blockers, have involved generalized seizure types such as absence and myoclonus.[20–22]

Increases in SSF ≥25% and ≥50% from baseline were reported in the current article. In our clinical studies, SSF varied from month to month by ≥25%. Therefore, increases in SSF ≥50% may be considered more indicative of clinically relevant exacerbations in seizure frequency.

Across all treatment groups, the proportion of patients with ≥25/≥50% increase in SSF was greater during the titration period than during the maintenance period. For the ESL groups, this may be explained by lower eslicarbazepine exposure during the titration period than during the maintenance period, owing to patients spending at least part of their time in the titration period at a dose lower than their respective target dose. The reason for the difference in the proportion of the placebo group with an exacerbation during the titration period (32%) compared with the maintenance period (20%) is unclear but may be due to typical month-to-month variability in seizure frequency, given the short 2-week titration evaluation period compared with the longer (12-week) maintenance evaluation period. When examining potential exacerbation of the sGTC seizure type, 5–11% of patients who did not have a sGTC during baseline did have a seizure of this type during maintenance treatment with placebo or ESL. This apparent exacerbation of sGTC seizures may be due, at least in part, to underrepresentation of this seizure type (which is reported less frequently than POS) during the 8-week baseline period. The proportion of patients experiencing sGTCs may be greater during the 12-week maintenance period than during the baseline period primarily because of the longer duration of the former. The proportions of patients with ≥25/≥50% increase in seizure frequency during the tapering-off period were, in general, not markedly different from the proportions during the maintenance period, i.e., there was no evidence for a rebound in seizure frequency during the tapering-off period (although the data for the tapering-off period were from study 301 only).

The numbers of patients with seizure TEAEs during treatment with ESL were low. During the maintenance period, fewer than 4% of patients in any treatment group had a seizure TEAE of any description. During the tapering-off period, reports of seizure TEAEs were more frequent in the ESL groups (1–4%) than in the placebo group (no reports). Given that adjunctive ESL treatment has been shown to reduce the frequency of POS,[13,14,16] an increase in seizure events on discontinuation of ESL is perhaps expected.

A potential limitation of the current analysis is that statistical comparisons between the placebo and ESL groups were not prespecified; therefore, the incidence of TEAEs was evaluated using descriptive statistics only. Because this post-hoc analysis retrospectively analyzed data pooled from three large studies, the data should be interpreted as exploratory in nature. However, the large sample size generated by pooling the data provided greater sensitivity to detect uncommon safety events of special interest for patients with epilepsy.

To obtain evidence on rates of exacerbation of POS during AED treatment, Somerville (2002) conducted a meta-analysis of increases in seizure frequency during randomized placebo-controlled trials of adjunctive AED therapy in patients with uncontrolled partial seizures.[9] The results indicated that many patients with partial seizures experience an increase in seizures when a new AED is added to their therapy, but that this occurs no more often than with placebo. This conclusion is supported by the current analysis, which was based on data pooled from three randomized placebo-controlled trials of adjunctive ESL. Somerville (2002) concluded that the exacerbations observed during this type of clinical trial often result from spontaneous fluctuations in seizure frequency.[9] French (2002) agreed that such worsening is common in patients with uncontrolled refractory seizures and highlighted that, in clinical practice, it may be prudent to allow time for observation before deciding to abandon a recently initiated AED.[23]

Somerville (2009) pointed out that seizure aggravation by AEDs is frequently overestimated by doctors, and especially by patients.[1] An increase or decrease in dosage, a switch to a generic formulation, or the introduction of a new drug may all be blamed for deterioration when none may actually be the cause. In fact, seizure frequency fluctuates widely in many patients, apparently spontaneously, but this has often been overlooked in published reports of seizure aggravation by AEDs.[1]

French (2002) pointed out that most reports on clinical trials of AEDs do not include data on seizure worsening, even though the information is readily available.[23] However, in two pivotal lamotrigine trials, worsening of seizures was reported; 3–18% of patients had increases in seizure frequency, with no notable difference between the placebo and lamotrigine treatment groups.[24] Information on seizure worsening was also included in a report of a trial of levetiracetam, where worsening of seizures (>25% increase) was more frequent for patients taking placebo (26%) than for those taking levetiracetam (14%; $p < 0.001$).[25] There

was also no evidence for exacerbation of myoclonic or absence seizures with perampanel treatment for tonic-clonic seizures in idiopathic generalized epilepsy.[26] Furthermore, in a post-hoc analysis of a subset of patients with juvenile myoclonic epilepsy, seizure worsening was more frequent in placebo-treated patients (45%) than in topiramate-treated (18%) patients,[27] and no children/adolescents experienced worsening of the intensity or frequency of myoclonus with use of lamotrigine for primary generalized tonic-clonic seizures.[28]

In line with reports from clinical trials of other AEDs, in the current analysis, treatment with adjunctive ESL does not appear to aggravate POS or sGTC seizures.

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Supporting Information

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

Appendix 1. Coinvestigators.