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Long-term safety and efficacy following conversion to eslicarbazepine acetate monotherapy in adults with focal seizures

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ABSTRACT

Objective: To assess the long-term safety and efficacy of eslicarbazepine acetate (ESL) monotherapy in adults with focal seizures (FS).

Methods: Study 050 was a long-term, multicenter, open-label (OL) safety extension of two conversion-to-ESL monotherapy studies in adults with refractory FS. After participating in Study 045 or 046, patients started on ESL 1600 mg once daily (QD) (or 1200 mg if they previously had a dose reduction), and could adjust the dose 400 mg/week to a dose between 800–2400 mg QD. Patients could add up to two additional antiepileptic drugs (AEDs). This post-hoc analysis focuses on the actual monotherapy subgroup, which included patients in Studies 045/046/050 who did not add additional AEDs. Study endpoints included treatment retention time, time on ESL monotherapy, change in standardized seizure frequency (SSF), change in quality of life (QoL) in epilepsy (QOLIE-31) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores, and incidence of treatment-emergent adverse events (TEAEs); serious adverse events (SAEs), TEAEs leading to discontinuation, and TEAEs related to allergic reaction, hyponatremia and thyroid function were also evaluated.

Results: There were 274 patients in the Study 050 full intent-to-treat (ITT) population and 140 patients in the actual monotherapy subgroup. Median treatment retention time and time on ESL monotherapy were both > 5 years. Median reduction in SSF from baseline was 66.4% in the full ITT population and 78.3% in the actual monotherapy subgroup; responder (≥ 50% reduction in SSF) rates were 62.4% and 74.3%, respectively. QOLIE-31 scores increased from baseline in the full ITT population and the actual monotherapy subgroup (4.1- and 7.5-point increases, respectively). MADRS scores decreased from baseline in both the full ITT population and the actual monotherapy subgroup (0.7- and 2.9-point decreases, respectively). TEAEs occurred in 85.4% of patients in the full ITT population and 81.4% of patients in the actual monotherapy subgroup. Incidences of SAEs and TEAEs leading to discontinuation, as well as dizziness, depression, fall, partial seizures with secondary generalization, and complex partial seizures, were higher in the full ITT population than in the actual monotherapy subgroup. Allergic reactions, hyponatremia, and hypothyroidism were infrequent, particularly in the actual monotherapy subgroup.

Conclusions: The results of this post-hoc analysis suggest that long-term treatment with ESL was effective and well tolerated, both as a monotherapy and in combination with other AEDs for FS. QoL and tolerability appeared to be better, and incidence of depression lower, in the patient population taking ESL as a monotherapy, compared with the population that included patients taking ESL as an adjunctive therapy.

Abbreviations: AED, antiepileptic drug; AEs, adverse events; CBZ, carbamazepine; CI, confidence interval; ESL, eslicarbazepine acetate; FS, focal seizures; HR, hazard ratio; ITT, intent-to-treat; LEV, levetiracetam; LTG, lamotrigine; MADRS, Montgomery–Åsberg Depression Rating Scale; MedDRA, Medical Dictionary for Regulatory Activities; OL, open-label; OLE, open-label extension; OXC, oxcarbazepine; QD, once daily; QoL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SAE, serious adverse event; SD, standard deviation; SSF, standardized seizure frequency; SUDEP, sudden unexpected death in epilepsy; TEAE, treatment-emergent adverse event; VPA, valproic acid

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1. Introduction

Eslicarbazepine acetate (ESL) is a once-daily oral antiepileptic drug (AED) approved for the treatment of focal (partial-onset) seizures (FS) in patients aged 4 years and older. Double-blind, fixed duration clinical trials of adjunctive ESL and ESL monotherapy have demonstrated that ESL is an effective and well tolerated treatment for FS (Ben-Menachem et al., 2010; Biton et al., 2017; Elger et al., 2009; Jacobson et al., 2015; Sperling et al., 2015a, 2015b, 2016; Trinka et al., 2018). In addition, 1-year open-label extensions (OLEs) of the adjunctive studies showed that the efficacy and safety of adjunctive ESL was maintained over the longer term (Halasz et al., 2010; Hufnagel et al., 2013). Data for the long-term efficacy and safety of ESL taken as a monotherapy are limited.

Here we report long-term safety and efficacy outcomes in adults with FS who participated in Study 050, an OLE of two conversion-to-ESL monotherapy studies (Studies 045 and 046) (Jacobson et al., 2015; Sperling et al., 2016). We evaluate data from the entire study, which included patients who chose to add up to two concomitant AEDs during the course of the OLE, but also conduct a post-hoc analysis to specifically focus on the subgroup of patients who were taking ESL as a monotherapy throughout the OLE. We evaluated treatment retention, time on monotherapy, seizure outcomes and overall safety and tolerability, and also assessed changes in quality of life (QoL) (as measured by the Quality of Life in Epilepsy Inventory-31 [QOLIE-31]), depression (as measured by the Montgomery–Åsberg Depression Rating Scale [MADRS]), and other aspects of safety that are of particular interest for AEDs in general, and for dibenzazepine carboxamide AEDs (i.e., oxcarbazepine [OXC] and carbamazepine [CBZ]) in particular, including allergic reaction, hyponatremia, and thyroid function. We also evaluated the risk of certain adverse events (AEs) in patients taking ESL as a monotherapy, relative to the risk in the population that included patients taking ESL concomitantly with other AEDs.

2. Methods

2.1. Study design

Study 093 − 050 (ClinicalTrials.gov identifier: NCT00910247) was a long-term, multicenter, open-label (OL) safety extension of Studies 093 − 045 (NCT00866775) (Sperling et al., 2015b) and 093 − 046 (NCT01091662) (Jacobson et al., 2015). The designs of Studies 045 and 046 were identical; they were 18-week, dose-blind, randomized, Phase III, conversion-to-monotherapy studies that assessed the effects of ESL 1600 mg and 1200 mg once daily (QD) in patients with FS versus a historical control (as described by French et al., 2010) (French et al., 2010).

Patients aged 16–70 years with FS not well controlled by one or two AEDs (≥4 seizures per 28 days) were randomized (2:1) to receive ESL 1600 mg or 1200 mg QD for 16 weeks (after a 2-week titration period) in Study 045/046. Patient eligibility criteria, as well as individual and pooled analyses of data from Studies 045 and 046 have been reported previously (Jacobson et al., 2015; Sperling et al., 2015b, 2016).

In order for patients to participate in Study 050, they were required to have completed at least the first 3 weeks of the 18-week dose-blind period of Study 045/046, and then to enter Study 050 immediately following completion, discontinuation (for reasons other than safety) or exit from the prior study. The initial duration of Study 050 was 1 year (the 1-year OLE). Patients subsequently had the option to continue treatment into the post-1-year OLE until the patient discontinued the study, the study drug became clinically available in the patient's locale, or until the sponsor terminated the ESL clinical development program.

When entering Study 050, patients received a starting dose of ESL 1600 mg QD (or 1200 mg QD if they had a dose reduction during Study 045/046) for 1 week. Patients then had the option (at the discretion of the investigator) to adjust the ESL dose in increments of 400 mg/week to optimize clinical outcomes. The minimum and maximum allowed ESL doses were 800 mg and 2400 mg QD, respectively. Patients with a clinically significant increase in seizure frequency, duration, or severity, or who did not respond to, or tolerate, an increase in ESL dose, were permitted to add an additional AED. A maximum of two additional AEDs (excluding OXC) were allowed. Patients discontinued treatment if they required ESL doses outside the 800–2400 mg QD range or addition of more than two adjunctive AEDs, if serum sodium levels dropped to ≤125 mEq/L, or if a hypersensitivity reaction considered related to ESL occurred. Rescue medication was permitted no more than once every 28 days.

The study was designed, conducted, and monitored in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and relevant national, state, and local laws. The study protocol was approved by the relevant independent ethics committees/institutional review boards, and all patients provided written informed consent.

2.2. Study objectives and endpoints

The primary objective of Study 050 was to evaluate the long-term safety and tolerability of ESL (800–2400 mg QD) in patients with FS. Secondary objectives included evaluation of the maintenance of therapeutic effects, health-related QoL, and depressive symptoms with long-term ESL treatment.

Efficacy endpoints included treatment retention time (time to ESL discontinuation due to lack of efficacy or AEs); time on ESL monotherapy (after the AED conversion period in Study 045/046); reduction in standardized seizure frequency (seizures per 28 days; SSF) from baseline; responder rate (proportion of patients with a ≥50% reduction from baseline in SSF); proportion of seizure-free patients; and change in QOLIE-31 and MADRS scores from baseline.

Safety analyses included incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, and deaths; and proportion of patients with sodium levels ≤125 mEq/L, and > 10 mEq/L reductions from baseline.

2.3. Assessments

Baseline characteristics and values were evaluated during the baseline period of Study 045/046. Compliance was calculated as a percentage based on the number of tablets taken divided by the number of tablets that should have been taken.

Seizure events were recorded using seizure diaries completed by the patient/caregiver at baseline, Week 1, and Months 1, 3, 6, 9, and 12. Standardized seizure frequency was calculated based on seizure frequency during the OL period (up to 1 year of follow-up or until discontinuation, whichever was earliest). The MADRS was administered by a trained rater at baseline, Months 6 and 12, and every 3 months during the post-1-year OLE until study completion/termination. Patients aged ≥18 years at the start of Study 045/046 completed the QOLIE-31 at the same time points.

AEs were recorded at each clinic visit, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1. TEAEs were defined as AEs that occurred on or after the first dose of study drug. SAEs were reported separately; classification of AEs as serious was at the judgment of investigators. Plasma sodium levels were assessed at baseline, Months 1 and 3, and every 3 months for the first 1-year of the OLE.

2.4. Data analysis

Data analyses were conducted for the full intent-to-treat (ITT) population (i.e., patients who had taken ≥1 dose of ESL in Study 050) and the actual monotherapy subgroup (a subset of the full ITT population that included patients who received ESL as a monotherapy during Study

045/046 and Study 050, without the addition of other non-rescue or non-emergency AEDs).

All statistical procedures were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were summarized using descriptive statistics, including number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, summaries included numbers of patients and percentages. Median treatment retention time and median time on monotherapy (with 95% confidence intervals [CIs]) were estimated using the Kaplan-Meier method. A Cox proportional hazards regression model was used to examine the effect of patient factors (region, baseline seizure frequency, number of baseline AEDs, specific baseline AED, age at baseline, duration since epilepsy diagnosis, and ESL dose during Study 045/046) on the time to add AED(s) (non-rescue/non-emergency); the hazard ratio (HR) with 95% CIs and a P-value were estimated for each covariate. Nominal P-values were calculated for the differences in completion rates and TEAE incidences between the actual monotherapy subgroup and patients who added an AED during Study 050, using the chi-square test of independence or Fisher's exact test (for TEAEs occurring in fewer than 5 patients), without correcting for multiplicity.

3. Results

3.1. Patient baseline characteristics and disposition

In total, 274 patients entered Study 050 (full ITT population); 132 (48%) completed Study 050 (Table S1). There were 140 patients (51%) in the actual monotherapy subgroup, and 134 patients (49%) added a non-rescue/non-emergency AED during Study 050.

Demographic and baseline characteristics were generally similar between the full ITT population and the actual monotherapy subgroup (Table 1), with some exceptions. A higher proportion of patients in the actual monotherapy subgroup were from non-USA study centers compared with the full ITT population. In addition, although CBZ, levetiracetam (LEV), and valproic acid (VPA) were the most commonly used baseline AEDs in the actual monotherapy subgroup, baseline use of CBZ, LEV, VPA, lamotrigine (LTG), and OXC was less frequent in the actual monotherapy subgroup than in the full ITT population.

Table 1
Demographics and baseline characteristics.[a]

Characteristic	Actual monotherapy subgroup (n = 140)	Full ITT population (n = 274)
Age (years), median (range)	36 (16–65)	37 (16–67)
Males, n (%)	71 (50.7)	140 (51.1)
Race, n (%)		
Caucasian	118 (84.3)	229 (83.6)
Black/African American	12 (8.6)	22 (8.0)
Other[b]	10 (7.1)	23 (8.4)
Region, n (%)		
USA	58 (41.4)	167 (60.9)
Non-USA	82 (58.6)	107 (39.1)
BMI (kg/m^2), median (range)	25.8 (17.6–65.0)	26.3 (17.6–65.0)
Duration of epilepsy, n (%)		
< 20 years	96 (68.6)	175 (63.9)
≥20 years	44 (31.4)	99 (36.1)
Baseline AEDs,[c] n (%)		
Carbamazepine	35 (12.8)	76 (27.7)
Levetiracetam	30 (10.9)	65 (23.7)
Valproic acid	44 (16.1)	58 (21.2)
Lamotrigine	17 (6.2)	38 (13.9)
Oxcarbazepine	5 (1.8)	18 (6.6)
Number of baseline AEDs, n (%)		
1	108 (77.1)	191 (69.7)
2	32 (22.9)	83 (30.3)

[a] During the baseline period of Study 045/046.
[b] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and Asian races.
[c] Oxcarbazepine, lamotrigine, and AEDs used by ≥15% of patients. AED, antiepileptic drug; BMI, body mass index; ITT, intent-to-treat.

The study completion rate was higher in the actual monotherapy subgroup (54%, n = 76) (Table S1) than in the subgroup of patients who added an AED during Study 050 (42%, n = 56; P = 0.0385).

3.2. Exposure to ESL

In the full ITT population, overall exposure to ESL was 749.3 patient-years; mean daily ESL dose was 1636.1 mg and median duration of exposure was 955 days (˜2.6 years), with 202 patients exposed to ESL for > 1 year and 173 for > 2 years. In the actual ESL monotherapy subgroup, overall exposure to ESL monotherapy was 412.4 patient-years; mean daily ESL dose was 1558.8 mg and median duration of exposure was 1017 days (˜2.8 years), with 104 patients exposed to ESL monotherapy for > 1 year, and 92 for > 2 years. Mean treatment compliance was 96% in both the full ITT population and the actual monotherapy subgroup.

3.3. Efficacy

3.3.1. Treatment retention and time on ESL monotherapy

Of the 255 patients who started the ESL monotherapy period in Study 045/046, a total of 110 patients (43.1%) in the full ITT population discontinued treatment with ESL during Study 050 and 145 (56.9%) were censored (at the last known dose before study withdrawal or end of study). The median treatment retention time was 1939 days (5.3 years; lower bound of the 95% CI = 1429 days [3.9 years]). When excluding 17 patients who were using a concomitant AED during the ESL monotherapy period in Study 045/046, 98/238 patients (41.2%) discontinued ESL monotherapy (i.e., added a non-rescue/non-emergency AED) during Study 050 and 140 (58.8%) were censored (at the last known dose before study withdrawal or end of study). Therefore, the median time on ESL monotherapy was 1975 days (5.4 years; lower bound of the 95% CI = 1179 days [3.2 years]). LEV (used by 44/274 patients, 16.1%), VPA (8.0%), lacosamide (8.0%), CBZ (7.7%), and topiramate (5.8%) were the most frequently used concomitant AEDs (non-rescue, non-emergency) during Study 050.

Patients with a higher baseline seizure frequency (HR = 1.034 [95% CI: 1.010, 1.057], P = 0.0047), taking more baseline AEDs (2 [vs 1] AEDs; HR = 1.878 [95% CI: 1.250, 2.821], P = 0.0024), or taking (vs not taking) OXC at baseline (HR = 2.290 [95% CI: 1.248, 4.203], P = 0.0075) had a significantly higher HR for adding AED(s). Patients from ex-USA (vs USA) sites (HR = 0.235 [95% CI: 0.144, 0.384], P < 0.0001) or taking (vs not taking) VPA at baseline (HR = 0.308 [95% CI: 0.160, 0.593], P = 0.0004) had a significantly lower HR for adding AED(s). Age at baseline, duration since epilepsy diagnosis, ESL dose during Study 045/046 (1600 vs 1200 mg/day), baseline CBZ use, baseline LEV use, and baseline LTG use were not significant factors for addition of AEDs.

3.3.2. Seizure frequency

During the baseline period of Study 045/046, mean (SD) SSF was 9.2 (7.1) in the full ITT population and 7.9 (5.9) in the actual monotherapy subgroup. During the 1-year OL period, mean (SD) SSF decreased to 5.0 (8.7) in the full ITT population, and to 3.0 (4.5) in the actual monotherapy subgroup, representing median reductions in SSF from baseline of 66.4% and 78.3%, respectively. Median reductions from baseline in SSF generally increased successively over time during the 1-year OL period in both the full ITT population (Month 3: 64.8%, Month 6: 69.6%, Month 9: 71.7%, Month 12: 74.2%) and the actual monotherapy subgroup (77.0%, 81.5%, 81.3%, and 84.7%, respectively). The responder rate (proportion of patients with a ≥50% reduction in SSF) during the 1-year OL period was higher in the actual monotherapy subgroup (74.3%) than in the full ITT population

(62.4%). There was no clear trend in responder rate over time in the actual monotherapy subgroup (73.7%, 77.2%, 71.7%, and 74.3%, respectively) or the full ITT population (60.4%, 65.5%, 63.7%, and 69.2%, respectively). Eleven patients remained seizure free between the start of the 10-week monotherapy period of Study 045/046 and the end of the 1-year OL period (full ITT population: 4.0%; actual monotherapy subgroup: 7.1%). Rescue and/or emergency medications were used less frequently in the actual monotherapy subgroup (4.3%) than in the full ITT population (15.7%).

3.3.3. QoL and depression

Mean (SD) overall QOLIE-31 scores at baseline were 59.3 (16.6) in the full ITT population and 58.7 (14.9) in the actual monotherapy subgroup. There was a slight increase in overall QOLIE-31 scores between baseline and the end of the study/early termination visit in both the full ITT population (mean [SD] change from baseline, 4.1 [16.8]) and in the actual monotherapy subgroup (7.5 [16.0]), indicating a slight improvement in overall QoL with ESL treatment.

Mean (SD) overall MADRS scores at baseline were 6.9 (6.8) in the full ITT population and 7.7 (6.7) in the actual monotherapy subgroup. Overall MADRS scores decreased slightly between baseline and the end of the study/early termination visit in both the full ITT population (mean [SD] change from baseline, -0.7 [7.1]) and the actual monotherapy subgroup (-2.9 [6.2]), potentially indicating a slight improvement in depressive symptoms with ESL treatment.

3.4. Safety

3.4.1. TEAEs, SAEs and TEAEs leading to discontinuation

Overall TEAE incidence was similar between the full ITT population and the actual monotherapy subgroup (85.4% and 81.4%, respectively, Table 2). The majority of TEAEs were mild-to-moderate in severity. Incidences of SAEs and TEAEs leading to discontinuation were higher in the full ITT population than in the actual monotherapy subgroup (Table 2). Five deaths occurred during Study 050; causes of death were sudden unexpected death in epilepsy (SUDEP; $n = 2$), metastatic non–small-cell lung cancer ($n = 1$), drowning ($n = 1$), and arteriosclerosis ($n = 1$). All were considered not related or unlikely to be related to ESL. There was one death in the actual monotherapy subgroup (one of the SUDEP cases reported above).

The most frequently reported TEAEs in both the full ITT population and the actual monotherapy subgroup were headache (31.8% and 37.9%, respectively), dizziness (21.9% and 14.3%), and nasopharyngitis (15.3% and 15.7%) (Table 3). TEAEs reported ≥5% more frequently in the full ITT population than in the actual monotherapy subgroup were dizziness (21.9% vs 14.3%, respectively), depression (10.2% vs 5.0%), fall (9.1% vs 2.9%), partial seizures with secondary generalization (7.7% vs 0), and complex partial seizures (7.3% vs 2.1%); headache was ≥5% more frequent in the actual monotherapy subgroup than in the full ITT population (37.9% vs 31.8%, respectively). In a further analysis of these TEAEs, we compared incidences in the actual monotherapy subgroup with those in patients who were exclusively taking ESL concomitantly with other AED (s). Dizziness (P = 0.0006), depression (P = 0.0311), fall (P = 0.0072), partial seizures with secondary generalization (P < 0.0001), and complex partial seizures (P = 0.0114) were significantly more frequent in patients taking ESL as an adjunctive therapy, and headache was significantly more frequent in the actual monotherapy subgroup (P < 0.0001). The most frequent SAEs were partial seizures with secondary generalization and complex partial seizures, both of which were reported more frequently in the full ITT population than in the actual monotherapy subgroup (in fact, no patients in the actual monotherapy subgroup had an SAE of partial seizures with secondary generalization); the most frequent TEAE leading to discontinuation was partial seizures with secondary generalization, which, again, did not occur in the actual monotherapy subgroup (Table 3).

In general, in the actual monotherapy subgroup, incidences of the most frequent TEAEs did not appear to be higher with higher daily ESL doses (Table S2).

Table 2
Incidence of TEAEs, SAEs, and TEAEs leading to discontinuation.

n (%)	Actual monotherapy subgroup (*n* = 140)	Full ITT population (*n* = 274)
Any TEAE	114 (81.4)	234 (85.4)
Any SAE	11 (7.9)	64 (23.4)
Deaths	1 (0.7)	5 (1.8)
Any TEAE leading to discontinuation	3 (2.1)	27 (9.9)

ITT, intent-to-treat; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3
TEAEs,[a] SAEs,[b] and TEAEs leading to discontinuation.[b]

	Actual monotherapy subgroup (*n* = 140)	Full ITT population (*n* = 274)
Any TEAE, *n* (%)	**114 (81.4)**	**234 (85.4)**
Headache	53 (37.9)	87 (31.8)
Dizziness	20 (14.3)	60 (21.9)
Nasopharyngitis	22 (15.7)	42 (15.3)
Nausea	15 (10.7)	34 (12.4)
Fatigue	12 (8.6)	33 (12.0)
Back pain	17 (12.1)	29 (10.6)
Depression	7 (5.0)	28 (10.2)
Influenza	16 (11.4)	25 (9.1)
Insomnia	10 (7.1)	25 (9.1)
Fall	4 (2.9)	25 (9.1)
Diarrhea	13 (9.3)	22 (8.0)
Vomiting	8 (5.7)	21 (7.7)
Partial seizures with secondary generalization	0	21 (7.7)
Complex partial seizures	3 (2.1)	20 (7.3)
Urinary tract infection	6 (4.3)	19 (6.9)
Somnolence	9 (6.4)	17 (6.2)
Anxiety	5 (3.6)	17 (6.2)
Contusion	3 (2.1)	17 (6.2)
Toothache	6 (4.3)	16 (5.8)
Vertigo	9 (6.4)	14 (5.1)
Asthenia	9 (6.4)	14 (5.1)
Cough	5 (3.6)	14 (5.1)
Any SAE, *n* (%)	**11 (7.9)**	**64 (23.4)**
Partial seizures with secondary generalization	0	10 (3.6)
Complex partial seizures	1 (0.7)	5 (1.8)
Non-cardiac chest pain	0	3 (1.1)
Convulsion	0	3 (1.1)
Grand mal convulsion	0	3 (1.1)
Suicidal ideation	0	3 (1.1)
Transient ischemic attack	2 (1.4)	2 (0.7)
Vertigo	1 (0.7)	2 (0.7)
Sudden unexpected death in epilepsy	1 (0.7)	2 (0.7)
Requirement for electroencephalogram	1 (0.7)	2 (0.7)
Simple partial seizures	1 (0.7)	2 (0.7)
Fall	0	2 (0.7)
Status epilepticus	0	2 (0.7)
Any TEAE leading to discontinuation, *n* (%)	**3 (2.1)**	**27 (9.9)**
Partial seizures with secondary generalization	0	3 (1.1)
Fatigue	0	2 (0.7)
Simple partial seizures	0	2 (0.7)

ITT, intent-to-treat; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] Reported for ≥5% of patients.

[b] Reported for ≥2 patients.

3.4.2. Allergic reaction and rash

In the full ITT population, 29 patients (10.6%) had a TEAE within the 'skin and subcutaneous tissue disorders' category. The most frequent of these TEAEs (occurring in > 1% of patients) were rash (n = 9 [3.3%] vs n = 2 [1.4%] in the actual monotherapy subgroup), contact dermatitis (n = 5 [1.8%] vs n = 0) and hyperhidrosis (n = 3 [1.1%] vs n = 0). Three types of 'skin and subcutaneous tissue disorders' were reported in the actual monotherapy subgroup (rash [as reported above]; photosensitivity reaction, n = 1 [0.7%]; skin swelling, n = 1 [0.7%]). There was one 'skin and subcutaneous tissue disorders' SAE (0.4%, skin mass); the patient was not in the actual monotherapy subgroup. No 'skin and subcutaneous tissue disorders' led to treatment discontinuation.

3.4.3. Hyponatremia

In the full ITT population, 261/274 patients (95.3%) had normal sodium levels (i.e., sodium > 135 mEq/L) at baseline. Of these 261 patients, 4 (1.5%) had a post-baseline sodium concentration measurement ≤125 mEq/L, and 23 (8.8%) had a ≥10 mEq/L decrease in sodium concentration from baseline during the 1-year OL period. In the actual monotherapy subgroup, 136/140 (97.1%) patients had normal sodium levels at baseline. Incidences of post-baseline serum sodium measurements ≤125 mEq/L or ≥10 mEq/L decreases in sodium concentration from baseline during the 1-year OL period were the same in the actual monotherapy subgroup as in the full ITT population (1.5% [n = 2 and n = 4] and 8.8% [n = 12 and n = 23], respectively).

3.4.4. Thyroid and parathyroid function

Throughout Study 050, three TEAEs related to thyroid function occurred in more than 1 patient in the full ITT population; hypothyroidism was reported for 4 patients (1.5%), increased blood parathyroid hormone for 3 patients (1.1%), and decreased free thyroxine (T4) for 2 patients (0.7%); in comparison, these three TEAEs were reported by 1 patient each (0.7%) in the actual monotherapy subgroup. There were no thyroid-related SAEs or TEAEs leading to discontinuation.

4. Discussion

The results of this study demonstrate that ESL was effective as a long-term treatment for refractory FS. The improvements in seizure frequency seen during Study 045/046 were maintained throughout Study 050, and no new safety concerns were identified. Long-term use of ESL was generally well tolerated, with the majority of TEAEs being mild-to-moderate in severity.

AED monotherapy is generally preferable to adjunctive AED therapy due to the lower risk of side effects and drug-drug interactions, the simplicity and convenience of taking one versus multiple AEDs, and the cost benefits associated with use of a single AED (Perucca, 2008; Perucca and Tomson, 2011). We therefore analyzed two patient populations in this study; the full ITT population (which included patients who were taking ESL as a monotherapy, as well as those who had added up to two concomitant AEDs throughout the course of Study 050) and the actual monotherapy subgroup (a subset of the full ITT population that included patients who were taking ESL as an AED monotherapy during the monotherapy period of Study 045/046 and throughout Study 050, without adding AEDs). This analysis enabled us to establish the efficacy and safety of ESL over the long term, in patients who were able to maintain treatment with ESL as a monotherapy, as well as in those who chose to, or needed to, add additional AED(s) to manage their FS.

When interpreting the results of this study, it is important to consider the non-randomized nature of the actual monotherapy subgroup. Patients would only be expected to add AED(s) to their treatment regimen if they had a suboptimal response to ESL, and thus patients in the actual monotherapy subgroup would be expected to have had better seizure control than those in the full ITT population.

A significantly higher proportion of patients in the actual monotherapy subgroup (54%) completed Study 050 (vs the subgroup of patients who added AEDs [42%]; P = 0.0385). In the full ITT population, both median treatment retention time and time on ESL monotherapy were > 5 years. Some baseline demographic and clinical characteristics differed slightly between the full ITT population and the actual monotherapy subgroup. For example, there were fewer patients from the USA, and taking baseline CBZ, LEV, VPA, LTG, or OXC in the actual monotherapy subgroup versus the full ITT population.

A noteworthy finding of this study is that patients with a higher seizure frequency at baseline, taking more baseline AEDs (2 vs 1), or taking OXC at baseline had a significantly higher risk of adding non-rescue/non-emergency AEDs. More frequent seizures and more baseline AEDs may represent more treatment-resistant epilepsy so it is not surprising that these patients had a higher risk of adding another AED to their treatment regimen. Patients taking OXC at baseline had uncontrolled seizures despite use of OXC, and thus may have been less likely to respond to treatment with ESL than those taking other baseline AEDs, due to similarities in chemical structure. Further studies would be required to confirm this hypothesis, as the study designs of Study 045/046 are not reflective of clinical practice e.g., there was no randomization to ensure that patients taking high doses of OXC were converted to high doses of ESL. Patients from outside of the USA or those taking VPA at baseline had a significantly lower risk of adding AED(s). Regional differences could be related to differences in patient characteristics and/or in the management of epilepsy. Demographic or disease severity-related factors may have influenced the decision to use VPA at baseline, complicating the interpretation of this finding.

At baseline, patients were required to be experiencing at least 4 seizures per 28 days to participate in Study 045 or 046. During the 1-year OL period of Study 050, the median reduction (%) in SSF from baseline was numerically greater in patients who received actual monotherapy (78%) than in the full ITT population (66%). Similarly, 50% responder rates were higher in the actual monotherapy subgroup (74%) than in the full ITT population (62%). Seizure response was maintained throughout the 1-year OL period. Reductions in seizure frequency during Study 050 were more marked than during Study 045/046, as would be expected for an open-label study of this design, in which patients were given the option to continue treatment with ESL. In Study 045/046, median reductions in SSF from baseline were 43.2% in the ESL 1600 mg group and 35.7% in the ESL 1200 mg group; responder rates were 42.7% and 36.0%, respectively (Sperling et al., 2016). Seizure freedom (between the start of the monotherapy period in Study 045/046 until the end of the 1-year OL period) occurred in 11 patients (full ITT population: 4%; actual monotherapy subgroup: 7%). Rescue and/or emergency medications were used less frequently in the actual monotherapy subgroup than in the full ITT population. It is of note that baseline SSF was slightly higher in the full ITT population than in the actual monotherapy subgroup, perhaps suggesting less severe epilepsy in the actual monotherapy subgroup. As discussed above, the better efficacy in patients who remained on ESL monotherapy is not surprising, as patients who were doing well on ESL would be less likely to add additional AEDs.

Safety outcomes in the actual monotherapy subgroup were generally consistent with those reported in the full ITT population, in the dose-blind periods of the conversion-to-ESL monotherapy trials (i.e., Studies 045 and 046) (Jacobson et al., 2015; Sperling et al., 2015b, 2016) and in a separate clinical trial of ESL monotherapy in patients with newly-diagnosed FS (Trinka et al., 2018). SAEs and TEAEs leading to discontinuation were less frequent in the actual monotherapy subgroup than in the full ITT population, potentially due to the higher drug load in patients taking more than one AED, increasing the risk of adverse reactions (Perucca, 2008). Dizziness, depression, fall, partial seizures with secondary generalization, and complex partial seizures were reported significantly more frequently in patients who were taking ESL concomitantly with other AED(s) than in the actual monotherapy

subgroup (no patients in the actual monotherapy subgroup had a partial seizure with secondary generalization). The difference between the actual monotherapy subgroup and the subgroup taking ESL as an adjunctive therapy could suggest that these TEAEs are related to use of AED polytherapy, or that patients with recurrent seizures (severe enough to initiate adjunctive AED therapy) may be more likely to experience AEs of this nature. AEs did not appear to be more frequent with higher doses of ESL. It is important to note that Study 050 was not designed to compare outcomes between patients who continued to take ESL as a monotherapy and those who added AEDs to their treatment regimen. There was no randomization to assign patients to the monotherapy or adjunctive therapy subgroups, and so comparisons between subgroups are entirely exploratory.

TEAEs related to allergic reaction/rash were reported more frequently in the full ITT population than in the actual monotherapy subgroup, again this was potentially related to use of AED polytherapy increasing the risk of adverse reactions. Hyponatremia is a potential concern for clinicians prescribing dibenzazepine carboxamide AEDs such as ESL. During the 1-year OL period, potentially clinically significant sodium concentrations (≤125 mEq/L) occurred in 4 patients (1.5%) in the full ITT population, and 23 patients (8.8%) had a ≥10 mEq/L decrease in sodium concentration from baseline; rates of potentially clinically significant sodium concentrations/reductions were the same in the actual monotherapy subgroup.

Improvements in QoL and depressive symptoms at the end of the study were slightly greater in patients receiving actual monotherapy than in the full ITT population, with the changes from baseline greater than the minimal clinically significant change identified for QOLIE-31 (5 points) (Borghs et al., 2012) and for MADRS (-1.6 to -1.9 points) in this subgroup (Duru and Fantino, 2008). The slightly greater improvements in QoL and depression in the actual monotherapy subgroup could have been related to the better seizure control in this group, and/or the lower incidence of SAEs and TEAEs leading to discontinuation, compared with the full ITT population.

Limitations of our study include the lack of a control group and the OL nature of the study, which are typical design features for OLE studies. In addition, the designs of the conversion-to-ESL monotherapy studies were suboptimal in nature. Patients were required to adhere to a strict conversion protocol that was not tailored to individual patient needs or circumstances, which may have limited the likelihood of long-term success in the studies. Furthermore, statistical comparisons and Cox proportional hazard regression analyses were carried out retrospectively, and were not corrected for multiplicity.

5. Conclusions

The results of this analysis demonstrate that the efficacy and tolerability of ESL monotherapy for FS (median retention time and median time on monotherapy > 5 years) is generally maintained over the long term, with no new safety concerns arising. Over the 1-year OL period, in the actual monotherapy subgroup, median SSF decreased by 78% from baseline, with 74% of patients classified as responders. Furthermore, consistent with previous research around the merits of AED monotherapy (vs polytherapy), taking ESL as a monotherapy appeared to be associated with better tolerability than taking ESL concomitantly with other AEDs. Slight improvements in QoL and depression also appeared to be sustained over the longer-term in patients who elected to continue therapy in Study 050, particularly in patients who continued to take ESL as a monotherapy. This study extends the findings of previous short- and longer-term, dose/double-blind studies of ESL and suggests that ESL may be a valuable option for the long-term treatment of FS, as a monotherapy or in combination with other AEDs.

Disclosures

S. Chung received honoraria as a speaker for Sunovion Pharmaceuticals Inc. S. R. Sinha received advisory board honoraria from Basilea Inc.; is on the ABRET, ACNS, and ABCN boards of directors; received consulting fees from Cadwell Inc.; and received grants/funds from UCB and Eisai. A. Shah is a member of the ROW Foundation advisory council; received consulting fees from ORAU; and received grants/funds from Sunovion Pharmaceuticals Inc., Eisai, and UCB. J. M. Stern is a member of an advisory council/committee for Sunovion Pharmaceuticals Inc.; and received honoraria from Sunovion Pharmaceuticals Inc. H. Cheng, J. Jung, T. Grinnell, and D. Blum are employees of Sunovion Pharmaceuticals Inc.

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Data sharing statement

Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability please visit https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx and click on Sunovion.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.03.018.

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