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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

# Efficacy and safety of eslicarbazepine acetate monotherapy in patients converting from carbamazepine

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## Summary

**Objective:** To evaluate the influence of prior use of carbamazepine (CBZ) and other antiepileptic drugs (AEDs) with a putatively similar mechanism of action (inhibition of voltage-gated sodium channels; VGSCs) on seizure outcomes and tolerability when converting to eslicarbazepine acetate (ESL), using data pooled from 2 controlled conversion-to-ESL monotherapy trials (studies: 093-045, 093-046).

**Methods:** Adults with treatment-resistant focal (partial-onset) seizures were randomized 2:1 to ESL 1600 or 1200 mg once daily. The primary efficacy endpoint was study exit (meeting predefined exit criteria related to worsening seizure control) versus an historical control group. Other endpoints included change in seizure frequency, responder rate, and tolerability. Endpoints were analyzed for subgroups of patients who received CBZ (or any VGSC inhibitor [VGSCi]) during baseline versus those who received other AEDs.

**Results:** Of 365 patients in the studies, 332 were evaluable for efficacy. The higher risk of study exit in the subgroups that received CBZ (or any VGSCi) during baseline, versus other AEDs, was not statistically significant (hazard ratios were 1.49 for +CBZ vs −CBZ [$P$ = .10] and 1.27 for +VGSCi vs. −VGSCi [$P$ = .33]). Reductions in seizure frequency and responder rates were lower in patients who converted from CBZ or other VGSCi compared with those who converted from other AEDs. There were no notable differences in overall tolerability between subgroups, but the incidence of some adverse events (eg, dizziness, somnolence, nausea) differed between subgroups and/or between treatment periods.

**Significance:** Baseline use of CBZ or other major putative VGSC inhibitors did not appear to significantly increase the risk of study exit due to worsening seizure control, or to increase the frequency of side effects when converting to ESL monotherapy. However, bigger improvements in efficacy may be possible in patients converting to ESL monotherapy from an AED regimen that does not include a VGSC inhibitor.

**KEYWORDS**
antiepileptic drugs, focal seizures, refractory epilepsy, switching

## 1 | INTRODUCTION

Eslicarbazepine acetate (ESL) is a third-generation member of the dibenzazepine carboxamide class of antiepileptic drugs (AEDs), which also includes carbamazepine (CBZ) and oxcarbazepine (OXC). ESL was approved by the United States Food and Drug Administration (FDA) for monotherapy following successful completion of 2 conversion-to-monotherapy trials with identical protocols (studies 093-045 and -046).[1,2] ESL was subsequently approved by the European Medicines Agency for use as monotherapy in adults with newly diagnosed epilepsy.

Studies 045 and 046 demonstrated that conversion to ESL monotherapy was effective and well tolerated in patients with focal (partial-onset) seizures not adequately controlled by 1 or 2 AEDs.[1,2] Whether or not prior CBZ use influences outcomes following conversion to ESL monotherapy is of interest to practicing clinicians; it is particularly important given that in previous conversion-to-monotherapy studies, the effect of converting from CBZ-containing regimens to other AED monotherapies raised the hazard rate of study exit (due to seizure worsening) by 8%, compared with converting from regimens that did not contain CBZ.[3] In addition, concomitant use of CBZ together with ESL may result in plasma eslicarbazepine concentrations that are 20%-30% less than those observed in patients taking ESL without concomitant enzyme-inducing AEDs.[4] The 2 conversion-to-ESL monotherapy studies in the current analysis permitted enrollment of patients taking CBZ,[1,2] allowing the influence of previous exposure to CBZ to be examined.

Both ESL and CBZ are believed to exert their anticonvulsant/antiepileptic effects, at least in part, through inhibition of voltage-gated sodium channels (VGSCs). Clinicians may therefore question whether differences in seizure control can be expected following conversion from CBZ to ESL monotherapy, and if so, what the magnitude of such differences might be. Notably, recent evidence suggests that there may be differences between ESL and CBZ with regard to their interaction with VGSCs. Both agents have relatively higher affinity for the inactivated state than the resting state of the channel,[5] and so would be expected to reduce high frequency neuronal firing in a use-dependent fashion. However, the kinetics of inactivation may differ between the 2 agents; eslicarbazepine (the primary active metabolite of ESL) does not appear to be involved in fast inactivation of VGSCs but may preferentially enhance their slow inactivation, whereas CBZ alters the fast inactivation of VGSCs but appears to have a lesser effect on their slow inactivation (compared with eslicarbazepine).[6] These differences between the mechanisms of action (MoAs) of the 2 agents suggest that conversion from CBZ to ESL monotherapy may be feasible and that such a conversion could lead to alterations in seizure frequency.

**Key Points**

- When converting to ESL, the risk of study exit due to worsening seizure control was not significantly higher with baseline use of CBZ or other VGSC-inhibiting AEDs
- Improvements in seizure frequency and responder rates were numerically lower in patients converting to ESL from baseline CBZ or other VGSC inhibitors
- ESL was well tolerated regardless of baseline use of CBZ or other VGSC inhibitors; rates of specific treatment-emergent adverse events varied between groups and treatment periods
- Greater improvements in efficacy may be possible in patients converting to ESL monotherapy from an AED regimen that does not include CBZ or other VGSC inhibitors

Combining data from studies 045 and 046 allows a detailed analysis of the efficacy and safety of ESL monotherapy in patients who were or were not taking baseline CBZ. The primary objective of the current analysis was to evaluate whether use of CBZ prior to conversion to ESL monotherapy affected seizure outcomes and the incidence of treatment-emergent adverse events (TEAEs) during and following the conversion, in patients with refractory focal seizures. To further examine the potential influence of prior exposure to an agent with a similar MoA, the efficacy and safety of ESL monotherapy were evaluated in patients who converted from AEDs with a putatively similar MoA (ie, AEDs believed to work primarily via VGSC inhibition), compared with those who converted from regimens that did not include those agents. CBZ, lamotrigine (LTG), OXC, and phenytoin (PHT) were the most frequently used baseline VGSC inhibitors (VGSCi) in the conversion-to-ESL monotherapy trials, and so were included in this analysis.

The findings of the current analysis may provide additional insights on the viability of converting to ESL from AEDs with a putatively similar primary MoA, and/or whether converting patients from CBZ specifically, to ESL, poses unique challenges for the physician.

## 2 | METHODS

### 2.1 | Standard protocol approvals, registration, and patient consent

Data were pooled from 2 phase III conversion-to-monotherapy trials (093-045 [NCT00866775] and 093-046 [NCT01091662], registered at ClinicalTrials.gov) that used

a historical control comparator. The trials were conducted between 2009 and 2013 at sites in the United States, Canada, Bulgaria, Serbia, the Ukraine, and the Czech Republic. Both studies were performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and all relevant national, state, and local laws; study protocols were approved by the relevant independent ethics committees/institutional review boards, and all patients provided informed consent.

## 2.2 | Patients

Eligible patients were aged 16-70 years with treatment-resistant "partial-onset" seizures (classified according to the 1981 version of the International League Against Epilepsy [ILAE] classification of seizures),[7] and were receiving 1-2 AEDs. Note that in the 2017 ILAE classification of seizure types, the term "focal" replaces the 1981 term "partial-onset."[8] Key inclusion and exclusion criteria have been previously published.[1,2] If patients were receiving 2 AEDs at baseline, only one could be a sodium channel inhibitor (defined as CBZ, LTG, OXC, or PHT), and only one could be in the upper dose range (defined as greater than approximately two-thirds of its defined daily dose [the assumed average maintenance dose per day for a drug used for its main indication in adults[9]]).

## 2.3 | Study design

Study designs (Figure S1) and statistical methods (including details of sample size determination) were identical for both studies.[1,2] Briefly, after an 8-week baseline period, eligible patients were randomized 2:1 to receive oral ESL (1600 mg or 1200 mg tablets once daily), and began the 18-week, dose-blind treatment period (2-week ESL titration, 6-week baseline AED taper [concomitant AEDs withdrawn], 10-week ESL monotherapy).

### 2.3.1 | Primary endpoint

The primary efficacy endpoint was the proportion (%) of patients meeting ≥1 of 5 exit criteria (signifying worsening seizure control) over the 16-week study period (between the start of the baseline AED taper period [week 2] and the end of the ESL monotherapy period [week 18]).

### 2.3.2 | Secondary endpoints

Secondary efficacy endpoints included change in standardized seizure frequency (SSF; seizures per 28 days) from baseline, and responder rate (proportion of patients with ≥50% reduction in SSF from baseline), for the 18-week dose-blind treatment period.

### 2.3.3 | Safety and tolerability

Investigator-reported AEs were coded using the Medical Dictionary for Regulatory Activities, version 13.1. TEAEs were defined as any AE that occurred on or after the first dose of study drug; TEAEs leading to discontinuation (DCAEs) were defined as any TEAE that led to discontinuation of the study drug. Treatment-emergent serious AEs (SAEs) were reported separately by the investigators.

## 2.4 | Study populations and statistical analyses

Individual patient data from studies 045 and 046 were pooled, as previously reported,[10] and a post hoc exploratory analysis was conducted. The pooled intent-to-treat (ITT) population for the 2 trials comprised all randomized patients who received ≥1 dose of study drug. The ITT population was used to evaluate patient disposition, overall baseline demographics and characteristics, and safety outcomes. The efficacy population (ie, all ITT patients who entered the baseline AED taper period) was used to evaluate efficacy outcomes.

Endpoints were analyzed for subgroups of patients who were taking baseline AED regimens that included CBZ, and separately for those taking regimens that included any VGSC inhibitor (CBZ, LTG, OXC, or PHT), compared with those who were taking other AEDs during the baseline period. Throughout this article, these subgroups are described by the terms "+CBZ" or "−CBZ," and "+VGSCi" (VGSC inhibitor) or "−VGSCi."

Both studies used an historical control comparator, as proposed by French et al., 2010.[3] The historical control exit rate was determined from the placebo/pseudo-placebo groups of 8 historical conversion-to-monotherapy trials. The lower bound of the 95% prediction interval of the overall exit rate (ie, 65.3% at 112 days) was used as the exit threshold for a single study. Cumulative exit rates and 95% confidence intervals (CIs) at 112 days were estimated using Kaplan-Meier (KM) methodology for each ESL dose group, and according to baseline CBZ/VGSCi use. To examine the potential effects of baseline CBZ and VGSCi use, an analysis of exit rate was conducted using a Cox proportional hazards (PH) regression model, including baseline CBZ/VGSCi use as a covariate. The potential effect of baseline CBZ dose on exit rate was further investigated using a PH regression model with total daily baseline CBZ dose as a covariate.

Statistical summaries and analyses were performed to compare baseline demographic and clinical characteristics,

safety, and efficacy data between subgroups. All statistical procedures were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All statistical tests were 2-sided.

# 3 | RESULTS

## 3.1 | Patients

The ITT population comprised 365 patients (ESL 1600 mg, n = 242; ESL 1200 mg, n = 123) and the efficacy population comprised 332 patients (ESL 1600 mg, n = 218; ESL 1200 mg, n = 114).

Overall, 27% of patients (ITT and efficacy populations) were taking CBZ at baseline. Patient demographics and baseline characteristics were generally well balanced between the +CBZ and −CBZ subgroups (Table 1). In the efficacy population, 81 patients converted to ESL monotherapy from CBZ alone, and 10 patients converted from CBZ taken in combination with another baseline AED; 241 patients did not take CBZ during the baseline period. The +VGSCi ITT subgroup comprised 212 patients (58% of the total; ESL 1600 mg, n = 133; ESL 1200 mg, n = 79), 47% of whom were taking CBZ during the baseline period. The −VGSCi ITT subgroup comprised 153 patients (ESL 1600 mg, n = 109; ESL 1200 mg, n = 44).

Overall, 139 patients (38.1%; ITT population) discontinued the study early (+CBZ, 41%; −CBZ, 37%; reasons for discontinuation are shown in Figure S2). The rate of early discontinuation was 41% for the +CBZ subgroup and 37% for the −CBZ subgroup; except for "met one of five exit criteria" (discussed in the "Primary endpoint" section), there were no clear differences between groups in reasons for early discontinuation. The rates of early discontinuation in the + and −VGSCi subgroups were comparable to those in the + and −CBZ subgroups (+VGSCi, 41%; −VGSCi, 34%). For the +CBZ group, the rate of study discontinuation during the titration period was greater for patients taking ESL 1600 mg (12%) versus 1200 mg (5%), whereas during the baseline AED taper period discontinuation rates were comparable for both dose groups (1600 mg, 20%; 1200 mg, 21%); discontinuation rates during the monotherapy period were lower for patients taking ESL 1600 mg (7%) versus 1200 mg (21%). For the −CBZ group, discontinuation rates during the titration and baseline AED taper periods were comparable between dose groups (titration: 1600 mg 9%, 1200 mg 8%; baseline AED taper: 1600 mg 15%, 1200 mg 18%), whereas discontinuation rates during the monotherapy period were slightly higher for 1200 mg (16%) than for 1600 mg (11%).

## 3.2 | Efficacy

### 3.2.1 | Primary endpoint

The KM-estimated exit rate was higher for patients taking CBZ or VGSCi at baseline than for those who were not, for both ESL doses (Figure 1A). For +CBZ and −CBZ, as well as for +VGSCi and −VGSCi, the upper 95% confidence limits (UCLs) of the exit rates for both ESL doses were lower than the historical control threshold (65.3%[3]). The overall hazard ratios for study exit rate were 1.49 (95% CI 0.93-2.39; $P = .10$) for the +CBZ versus −CBZ groups, and 1.27 (95% CI 0.79-2.04; $P = .33$) for the +VGSCi versus −VGSCi groups, indicating that although the risk of study exit was higher for the +CBZ/VGSCi groups than for the −CBZ/VGSCi groups, baseline use of CBZ or VGSCi had no significant effect on the risk of study exit, for either ESL dose group. In addition, time to study exit was similar between the +CBZ and −CBZ groups. Furthermore, when the few patients taking CBZ in the upper dose range (>1200 mg/day, the maximum recommended maintenance dose for most patients[11]) were excluded from the analysis, the association between total daily CBZ dose (during baseline) and exit rate was not statistically significant ($P = .09$); when patients taking CBZ doses >1200 mg/day were included in the analysis, the association was statistically significant ($P = .04$).

### 3.2.2 | Secondary endpoints

Median reductions (%) in SSF between baseline and the 18-week treatment period (2-week titration, 6-week AED taper, and 10-week monotherapy) were apparent in the +CBZ, −CBZ, +VGSCi and −VGSCi groups (Figure 1B). The magnitude of seizure reduction was lower for patients who converted from CBZ or VGSCi than for those who did not (CBZ: 23.5 and 30.8 percentage-point difference, in the 1600 mg and 1200 mg groups, respectively; VGSCi: 19.8 and 21.8 percentage-point difference, respectively; Figure 1B). Similarly, responder rates (proportion of patients with ≥50% reduction in SSF) during the 18-week treatment period were lower in the +CBZ versus the −CBZ group (ESL 1600 mg, 22.2% vs. 49.4%; 1200 mg, 18.9% vs. 44.2%) and lower in the +VGSCi group versus the −VGSGi group (ESL 1600 mg, 35.0% vs. 52.5%; 1200 mg, 28.8% vs. 48.8%) (Figure 1C). In the +CBZ group, no patients were seizure-free for the 18-week treatment period, whereas 11 patients in the −CBZ group (ESL 1600 mg, 8 [4.9%]; 1200 mg, 3 [3.9%]) became seizure-free. The rate of seizure freedom was similar in the +VGSCi and −VGSCi groups (ESL 1600 mg, 3.4% vs. 4.0%; 1200 mg, 1.4% vs. 4.9%). The proportions of patients with a ≥25% increase in seizure frequency between

**TABLE 1** Baseline demographic and clinical characteristics, by baseline CBZ use (ITT population)

| | +CBZ | | −CBZ | |
|---|---|---|---|---|
| | **ESL 1200 mg (n = 39)** | **ESL 1600 mg (n = 61)** | **ESL 1200 mg (n = 84)** | **ESL 1600 mg (n = 181)** |
| Age, years; median (range) | 33.0 (16-64) | 40.0 (20-67) | 39.0 (16-67) | 38.0 (16-68) |
| Gender, male; n (%) | 23 (59.0) | 30 (49.2) | 39 (46.4) | 83 (45.9) |
| Race, n (%) | | | | |
| White | 33 (84.6) | 52 (85.2) | 73 (86.9) | 149 (82.3) |
| Black or African American | 3 (7.7) | 2 (3.3) | 6 (7.1) | 17 (9.4) |
| Asian | 0 | 1 (1.6) | 1 (1.2) | 3 (1.7) |
| Other | 3 (7.7) | 6 (9.8) | 4 (4.8) | 12 (6.6) |
| Hispanic or Latino ethnicity, n (%) | 6 (15.4) | 9 (14.8) | 9 (10.7) | 16 (8.8) |
| Region, n (%) | | | | |
| USA | 23 (59.0) | 38 (62.3) | 56 (66.7) | 113 (62.4) |
| Non-USA | 16 (41.0) | 23 (37.7) | 28 (33.3) | 68 (37.6) |
| BMI, kg/m$^2$; median (range) | 26.3 (17.6-59.4) | 27.3 (18.4-65.0) | 26.5 (17.4-47.3) | 26.2 (16.9-109.2) |
| Weight, kg; mean (SD) | 83.3 (24.7) | 83.4 (26.0) | 81.5 (22.8) | 80.8 (22.6) |
| Baseline AEDs used by ≥15% patients,[a] n (%) | | | | |
| Carbamazepine | 39 (100.0) | 61 (100.0) | 0 | 0 |
| Lamotrigine | 0 | 0 | 23 (27.4) | 37 (20.4) |
| Levetiracetam | 3 (7.7) | 5 (8.2) | 27 (32.1) | 56 (30.9) |
| Valproic acid | 1 (2.6) | 3 (4.9) | 15 (17.9) | 52 (28.7) |
| Number of AEDs used at baseline,[a] n (%) | | | | |
| 1 | 31 (79.5) | 46 (75.4) | 60 (71.4) | 116 (64.1) |
| 2 | 8 (20.5) | 15 (24.6) | 24 (28.6) | 65 (35.9) |
| SSF; median (range) | 6.5 (2.5-19)[b] | 7.7 (1-29)[c] | 5.5 (1.9-36)[d] | 7.7 (1.9-47)[e] |
| Patients with secondarily generalized seizures present at baseline, n (%) | 13 (33.3) | 15 (24.6) | 23 (27.4) | 55 (30.4) |

AED, antiepileptic drug; BMI, body mass index; CBZ, carbamazepine; ESL, eslicarbazepine acetate; ITT, intent-to-treat; SD, standard deviation; SSF, standardized seizure frequency; USA, United States of America.

Percentages are calculated based on the number of patients with available data in the ITT population in each subgroup.

[a]An AED was considered to be used during the baseline period if it was started at any time prior to the first dose of the study drug and continued into the titration period.

[b]Efficacy population: n = 37.

[c]Efficacy population: n = 54.

[d]Efficacy population: n = 77.

[e]Efficacy population: n = 162.

baseline and the 18-week treatment period were 14.3% in the +CBZ group, 12.9% in the −CBZ group, 15.3% in the +VGSCi group, and 10.7% in the −VGSCi group.

## 3.3 | Safety

During the 18-week dose-blind treatment period, overall TEAE incidence was 75.0% in the +CBZ group and 80.0% in the −CBZ group, and most TEAEs were classified as mild or moderate in severity. Incidences of some individual TEAEs differed between the 2 groups (Table 2, Figure 2); dizziness and somnolence were reported more frequently in the +CBZ group, and nausea, nasopharyngitis, and back pain more frequently in the −CBZ group (Figure 2). The incidences of dizziness, somnolence, nausea, fatigue, and blurred vision were higher during the titration period than during the monotherapy period, in both the +CBZ and −CBZ groups (Table 2). DCAEs occurred in similar proportions of the +CBZ and −CBZ groups (Table 2). No specific TEAE led to treatment discontinuation by >5% of patients, in either dose group. The overall incidence of SAEs was numerically higher in the +CBZ group than in the −CBZ group (Table 2).

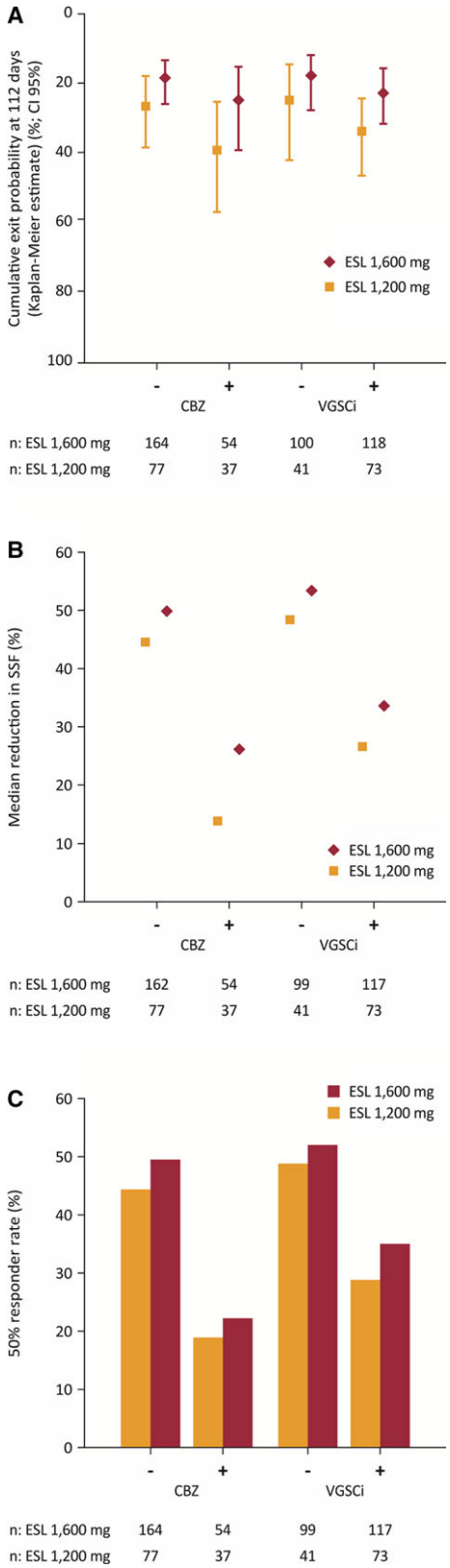


**FIGURE 1** A, Kaplan-Meier estimates of exit rate, B, median reduction in SSF,[a] and C, 50% responder rate,[a] by baseline CBZ use. [a]Between baseline and the 18-week dose-blind treatment period. CBZ, carbamazepine; CI, confidence interval; ESL, eslicarbazepine acetate; SSF, standardized seizure frequency (seizures per 28 days)

The overall incidence of TEAEs during the 18-week treatment period was 80.7% in the +VGSCi subgroup and 75.8% in the −VGSCi subgroup. There were some differences in the incidences of individual TEAEs between the 2 subgroups, and between treatment periods (Table 3). The incidence of dizziness was 8% higher in the +VGSCi subgroup (25.0%) than the −VGSCi subgroup (17.0%), an effect that was dose related (1200 mg, ~6% higher; 1600 mg, ~10% higher); no other incidences differed by >5% between subgroups. DCAEs occurred in 13.7% of patients in the +VGSCi subgroup and 11.8% in the −VGSCi subgroup (Table 3). The incidence of individual DCAEs was <5% in both dose groups. The overall incidence of SAEs was numerically higher in the +VGSCi subgroup (6.1%) than the −VGSCi subgroup (5.2%) (Table 3). In the +VGSCi subgroup, no SAE was reported in >1 patient taking either dose of ESL. In the −VGSCi subgroup, hyponatremia was reported as a SAE in 2 patients (1.8%), both taking ESL 1600 mg once daily. Status epilepticus occurred in 1 patient (ESL 1600 mg, +CBZ/+VGSCi subgroups). Injury (joint injury) occurred in 1 patient (ESL 1200 mg, −CBZ/−VGSCi subgroups) and was classified as potentially related to ESL.

## 4 | DISCUSSION

This analysis shows that in patients with treatment-resistant focal seizures, conversion to ESL from baseline AED regimens including CBZ did not lead to a significantly higher rate of study exit, or more side effects, than conversion from treatment regimens that did not include CBZ. However, it was apparent that the magnitudes of improvement (ie, reduction) in seizure frequency and responder rates with ESL were numerically lower for patients who were taking baseline CBZ than for those who were not. A similar pattern of results was apparent when the data were analyzed according to whether patients were taking any of the 4 specified putative VGSC inhibitors (CBZ, LTG, OXC, or PHT) immediately prior to converting to ESL monotherapy. This suggests that the treatment effects apparently related to prior CBZ use may not have been specific to CBZ, but related to its MoA. Further research is warranted to assess whether MoA should be considered when switching from one AED to another.

The primary endpoint of studies 045 and 046 was the proportion (%) of patients meeting one or more exit criteria signifying worsening seizure control, between the start of the baseline AED taper period and the end of the monotherapy period.[1,2] The hazard ratio for study exit rate for +CBZ vs −CBZ was 1.49 ($P$ = .10); so, although there was a trend toward a higher rate of study exit for +CBZ, difference in exit rates were not statistically significant

**TABLE 2** Overall incidence of TEAEs, incidences of individual TEAEs[a] and SAEs according to use of CBZ at baseline, during each treatment period (ITT population)

| | | +CBZ | | −CBZ | |
|---|---|---|---|---|---|
| **Treatment period** | **TEAE, n (%)** | **ESL 1200 mg** | **ESL 1600 mg** | **ESL 1200 mg** | **ESL 1600 mg** |
| 18-week dose-blind treatment period | *n* | *39* | *61* | *84* | *181* |
| | **Any TEAE** | **24 (61.5)** | **51 (83.6)** | **66 (78.6)** | **146 (80.7)** |
| | Mild | 8 (20.5) | 22 (36.1) | 30 (35.7) | 66 (36.5) |
| | Moderate | 15 (38.5) | 24 (39.3) | 32 (38.1) | 69 (38.1) |
| | Severe | 1 (2.6) | 5 (8.2) | 4 (4.8) | 11 (6.1) |
| | Headache | 6 (15.4) | 15 (24.6) | 19 (22.6) | 43 (23.8) |
| | Dizziness | 8 (20.5) | 19 (31.1) | 16 (19.0) | 36 (19.9) |
| | Nausea | 1 (2.6) | 6 (9.8) | 12 (14.3) | 20 (11.0) |
| | Fatigue | 4 (10.3) | 7 (11.5) | 13 (15.5) | 19 (10.5) |
| | Nasopharyngitis | 3 (7.7) | 2 (3.3) | 8 (9.5) | 21 (11.6) |
| | Somnolence | 5 (12.8) | 13 (21.3) | 4 (4.8) | 20 (11.0) |
| | Back pain | 1 (2.6) | 2 (3.3) | 12 (14.3) | 10 (5.5) |
| | Vomiting | 2 (5.1) | 4 (6.6) | 6 (7.1) | 11 (6.1) |
| | Blurred vision | 2 (5.1) | 5 (8.2) | 5 (6.0) | 11 (6.1) |
| | Diarrhea | 1 (2.6) | 3 (4.9) | 6 (7.1) | 8 (4.4) |
| | Insomnia | 2 (5.1) | 2 (3.3) | 5 (6.0) | 9 (5.0) |
| | Anxiety | 4 (10.3) | 3 (4.9) | 1 (1.2) | 5 (2.8) |
| | Vertigo | 1 (2.6) | 4 (6.6) | 1 (1.2) | 2 (1.1) |
| | Bronchitis | 2 (5.1) | 3 (4.9) | 0 | 1 (0.6) |
| | **Any SAE** | **2 (5.1)** | **6 (9.8)** | **3 (3.6)** | **10 (5.5)** |
| | **Any DCAE** | **1 (2.6)** | **13 (21.3)** | **9 (10.7)** | **24 (13.3)** |
| Titration period | *n* | *39* | *61* | *84* | *181* |
| | **Any TEAE** | **16 (41.0)** | **42 (68.9)** | **49 (58.3)** | **105 (58.0)** |
| | Dizziness | 5 (12.8) | 14 (23.0) | 13 (15.5) | 21 (11.6) |
| | Headache | 2 (5.1) | 9 (14.8) | 6 (7.1) | 23 (12.7) |
| | Fatigue | 3 (7.7) | 4 (6.6) | 9 (10.7) | 14 (7.7) |
| | Nausea | 0 | 4 (6.6) | 6 (7.1) | 11 (6.1) |
| | Somnolence | 3 (7.7) | 12 (19.7) | 4 (4.8) | 11 (6.1) |
| | Blurred vision | 1 (2.6) | 5 (8.2) | 3 (3.6) | 4 (2.2) |
| Taper/conversion period | *n* | *37* | *54* | *77* | *164* |
| | **Any TEAE** | **14 (37.8)** | **31 (57.4)** | **43 (55.8)** | **94 (57.3)** |
| | Headache | 4 (10.8) | 6 (11.1) | 8 (10.4) | 21 (12.8) |
| | Dizziness | 3 (8.1) | 6 (11.1) | 5 (6.5) | 18 (11.0) |
| | Nausea | 1 (2.7) | 2 (3.7) | 2 (2.6) | 11 (6.7) |
| | Fatigue | 2 (5.4) | 3 (5.6) | 2 (2.6) | 5 (3.0) |
| Monotherapy period | *n* | *30* | *42* | *63* | *139* |
| | **Any TEAE** | **13 (43.3)** | **27 (64.3)** | **39 (61.9)** | **80 (57.6)** |
| | Headache | 1 (3.3) | 9 (21.4) | 9 (14.3) | 12 (8.6) |
| | Back pain | 1 (3.3) | 1 (2.4) | 5 (7.9) | 8 (5.8) |
| | Nasopharyngitis | 2 (6.7) | 1 (2.4) | 5 (7.9) | 7 (5.0) |
| | Dizziness | 1 (3.3) | 3 (7.1) | 1 (1.6) | 7 (5.0) |

Bold text represents total numbers/proportions of TEAEs, SAEs and DCAEs; individual TEAEs are not bold. CBZ, carbamazepine; DCAE, TEAE leading to discontinuation; ESL, eslicarbazepine acetate; ITT, intent-to-treat; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Reported for ≥5% of patients in the total group for +CBZ or −CBZ, during the 18-week dose-blind treatment period.

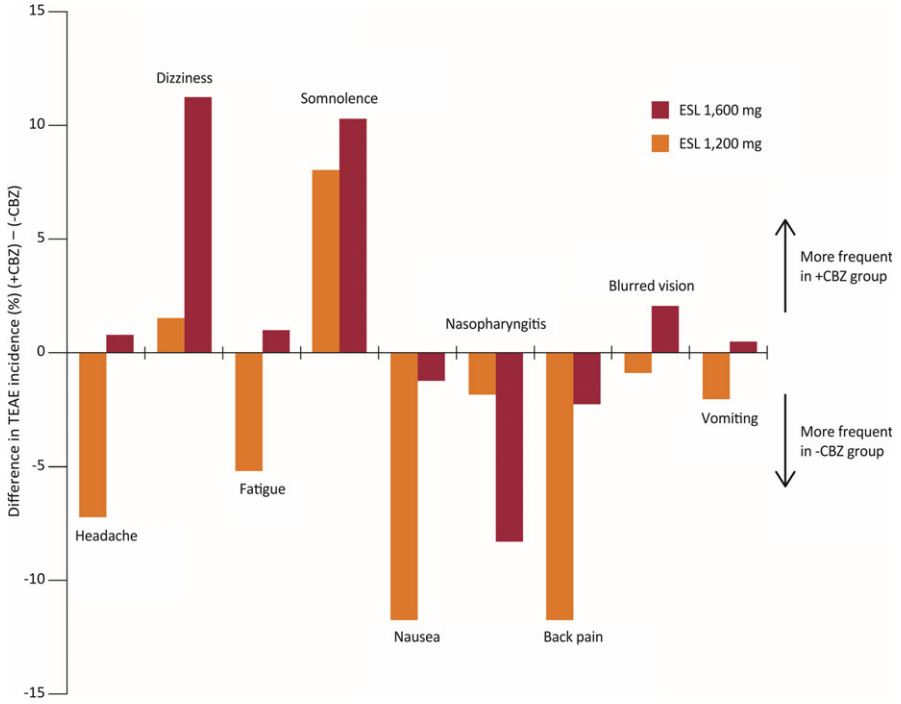


**FIGURE 2** Differences in TEAE[a] incidence[b] between patients who were or were not taking CBZ during the baseline period (ITT population). [a]TEAEs that were most frequently reported in studies 045 and 046. [b]During the 18-week dose-blind treatment period. Differences in TEAE incidence were calculated as follows: [incidence +CBZ (%)] - [incidence −CBZ (%)]. CBZ, carbamazepine; ITT, intent-to-treat; TEAE, treatment-emergent adverse event

between the 2 groups. Baseline use of any VGSC-blocking AED (CBZ, LTG, OXC, or PHT) also had no significant effect on risk of study exit (hazard ratio = 1.27; $P$ = .33). Similarly, a pooled analysis of 8 previously completed conversion-to-AED monotherapy studies (comprising the historical control comparator described by French, et al. 2010) showed that, although baseline CBZ use increased the hazard rate for study exit (by 8%), withdrawal from CBZ did not statistically significantly increase the likelihood of study exit ($P$ = .56).[3] It is of note that in French et al.,[3] the hazard rate for study exit was calculated from pooled data and did not focus on switching between AEDs with the same primary MoA. In the current analysis, when patients taking CBZ in the upper dose range were excluded, total daily CBZ dose did not significantly affect the risk of study exit. However, when patients taking CBZ doses >1200 mg/day were included in the analysis, the association between total daily CBZ dose and exit rate was statistically significant.

A previous pooled analysis of data from studies 045 and 046 showed that patients from the United States were significantly more likely to exit the studies (due to seizure worsening) than patients from countries outside of the United States, potentially due to the U.S. patients having more severe epilepsy at baseline.[10] It is therefore important to note that in the current analysis, the proportion of U.S. and non-U.S. patients was similar between the +CBZ and −CBZ groups.

Concomitant use of CBZ and ESL has been evaluated previously in a pooled analysis of data from 3 phase III trials of adjunctive ESL.[12] This analysis showed that adjunctive ESL (800 and 1200 mg) was effective in reducing seizure frequency in patients with treatment-resistant focal seizures, whether or not they were taking concomitant CBZ; although, improvements in efficacy were somewhat greater in patients who were not taking concomitant CBZ (which may reduce plasma eslicarbazepine concentrations by 20%-30%).[4] In the current analysis, improvements in seizure frequency were apparent, although less marked in the +CBZ group than in the −CBZ group, perhaps owing in part to the fact that the analysis period included 10 weeks when the patients were taking ESL as monotherapy, without CBZ. We speculate that, due to CBZ's potent effect on VGSC inhibition (which targets the key step in the propagation of action potentials during seizures), conversion from CBZ (alone or with other AEDs) might generally decrease the likelihood of further seizure improvements compared with conversion from other baseline AEDs. Improvements in seizure frequency were also less marked in the +VGSCi subgroup than in the −VGSCi subgroup, suggesting that the same may also be true for LTG, OXC, and PHT,

**TABLE 3** Overall incidence of TEAEs, incidences of individual TEAEs[a] and SAEs according to VGSCi[b] use at baseline, during each treatment period (ITT population)

| | | +VGSCi | | −VGSCi | |
|---|---|---|---|---|---|
| **Treatment period** | **TEAE, n (%)** | **ESL 1200 mg** | **ESL 1600 mg** | **ESL 1200 mg** | **ESL 1600 mg** |
| 18-week dose-blind treatment period | *n* | *79* | *133* | *44* | *109* |
| | **Any TEAE** | **58 (73.4)** | **113 (85.0)** | **32 (72.7)** | **84 (77.1)** |
| | Headache | 17 (21.5) | 33 (24.8) | 8 (18.2) | 25 (22.9) |
| | Dizziness | 17 (21.5) | 36 (27.1) | 7 (15.9) | 19 (17.4) |
| | Fatigue | 10 (12.7) | 11 (8.3) | 7 (15.9) | 15 (13.8) |
| | Nausea | 6 (7.6) | 14 (10.5) | 7 (15.9) | 12 (11.0) |
| | Somnolence | 5 (6.3) | 20 (15.0) | 4 (9.1) | 13 (11.9) |
| | Nasopharyngitis | 7 (8.9) | 13 (9.8) | 4 (9.1) | 10 (9.2) |
| | Back pain | 10 (12.7) | 6 (4.5) | 3 (6.8) | 6 (5.5) |
| | Hyponatremia | 2 (2.5) | 5 (3.8) | 2 (4.5) | 6 (5.5) |
| | Insomnia | 4 (5.1) | 7 (5.3) | 3 (6.8) | 4 (3.7) |
| | Blurred vision | 5 (6.3) | 12 (9.0) | 2 (4.5) | 4 (3.7) |
| | Vomiting | 7 (8.9) | 10 (7.5) | 1 (2.3) | 5 (4.6) |
| | Diarrhea | 4 (5.1) | 8 (6.0) | 3 (6.8) | 3 (2.8) |
| | Diplopia | 4 (5.1) | 8 (6.0) | 1 (2.3) | 2 (1.8) |
| | Complex partial seizures | 3 (3.8) | 9 (6.8) | 1 (2.3) | 2 (1.8) |
| | **Any SAE** | **4 (5.1)** | **9 (6.8)** | **1 (2.3)** | **7 (6.4)** |
| | **Any DCAE** | **6 (7.6)** | **23 (17.3)** | **4 (9.1)** | **14 (12.8)** |
| Titration period | *n* | *79* | *133* | *44* | *109* |
| | **Any TEAE** | **39 (49.4)** | **87 (65.4)** | **26 (59.1)** | **60 (55.0)** |
| | Dizziness | 12 (15.2) | 25 (18.8) | 6 (13.6) | 10 (9.2) |
| | Headache | 6 (7.6) | 19 (14.3) | 2 (4.5) | 13 (11.9) |
| | Somnolence | 3 (3.8) | 16 (12.0) | 4 (9.1) | 7 (6.4) |
| | Nausea | 2 (2.5) | 9 (6.8) | 4 (9.1) | 6 (5.5) |
| | Blurred vision | 3 (3.8) | 8 (6.0) | 1 (2.3) | 1 (0.9) |
| Taper/conversion period | *n* | *73* | *118* | *41* | *100* |
| | **Any TEAE** | **38 (52.1)** | **68 (57.6)** | **19 (46.3)** | **57 (57.0)** |
| | Headache | 10 (13.7) | 13 (11.0) | 2 (4.9) | 14 (14.0) |
| | Dizziness | 6 (8.2) | 16 (13.6) | 2 (4.9) | 8 (8.0) |
| | Nausea | 1 (1.4) | 6 (5.1) | 2 (4.9) | 7 (7.0) |
| Monotherapy period | *n* | *61* | *98* | *32* | *83* |
| | **Any TEAE** | **35 (57.4)** | **61 (62.2)** | **17 (53.1)** | **46 (55.4)** |
| | Headache | 4 (6.6) | 14 (14.3) | 6 (18.8) | 7 (8.4) |
| | Nasopharyngitis | 4 (6.6) | 4 (4.1) | 3 (9.4) | 4 (4.8) |
| | Dizziness | 1 (1.6) | 4 (4.1) | 1 (3.1) | 6 (7.2) |
| | Back pain | 5 (8.2) | 4 (4.1) | 1 (3.1) | 5 (6.0) |
| | Complex partial seizures | 2 (3.3) | 6 (6.1) | 0 | 1 (1.2) |

Bold text represents total numbers/proportions of TEAEs, SAEs and DCAEs; individual TEAEs are not bold. CBZ, carbamazepine; DCAE, TEAE leading to discontinuation; ESL, eslicarbazepine acetate; ITT, intent-to-treat; LTG, lamotrigine; OXC, oxcarbazepine; PHT, phenytoin; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VGSCi, voltage-gated sodium channel inhibitor.

[a]Reported for ≥5% of patients in the total group for +VGSCi or −VGSCi, during the 18-week dose-blind treatment period.

[b]CBZ/LTG/OXC.

perhaps to a lesser extent. It is notable that in a clinical setting, dose-limiting toxicity is another potential reason to consider converting from a VGSCi (such as CBZ) to another AED, including to another VGSCi. Therefore, individual patient tolerability is an important consideration.

In addition, it is of note that these clinical studies were not designed to optimize patient outcomes following conversion to ESL and did not consider the type or dose of baseline AEDs, or the factors necessitating the conversion to an alternative therapy. The studies were instead designed to investigate whether seizure worsening would occur following conversion from 1 or 2 AEDs to ESL monotherapy, compared with a historical control comparator, as per FDA requirements at the time of the studies. Patients were required to follow a fixed conversion protocol when transitioning to ESL monotherapy, without consideration of the needs of individual patients. It is possible that patients may have achieved better seizure control if ESL titration and AED taper rates (as well as the final ESL dose) had been tailored for individual patients.

Although the interpretation and extrapolation of data from most, if not all, registration clinical trials to the real-world setting may be restrained by the nature of controlled study designs, this issue is of relevance for this analysis, as all the data from our studies, as well as the French et al analysis of the historical control trials, used a variant of a forced conversion protocol. In the real-world clinical setting, careful management of the method of conversion from CBZ (or other VGSCi) to ESL may result in better outcomes than those reported here.

The overall incidence of TEAEs was comparable between the +CBZ and −CBZ groups; incidences of dizziness and somnolence were >5% higher in the +CBZ group than in the −CBZ group, whereas incidences of nausea, nasopharyngitis, and back pain were >5% higher in the −CBZ group than in the +CBZ group (Figure 2). The reason for these contrasting differences is unknown. The incidence of dizziness was also >5% higher in the +VGSCi subgroup than the −VGSCi subgroup.

Incidences of dizziness, somnolence, nausea, fatigue, and blurred vision were all higher during the titration period than during the monotherapy period (in the + and −CBZ and VGSCi groups), suggesting that new-onset TEAEs are more likely to occur while patients are taking ESL with existing AED regimens, than after conversion to ESL monotherapy. The incidence of TEAEs classed as severe was comparable between the +CBZ and −CBZ groups, whereas the incidence of SAEs was numerically higher in the +CBZ and +VGSCi groups than in the −CBZ and −VGSCi groups, respectively.

In a previous analysis of 3 trials of adjunctive ESL, overall TEAE incidence was slightly lower for the +CBZ versus the −CBZ group, although dizziness, diplopia, vomiting, and nausea were reported more frequently in patients taking ESL and concomitant CBZ than in those not taking concomitant CBZ.[13] Another analysis of the same data showed that overall TEAE incidence was comparable between patients who were or were not concomitantly taking LTG, another VGSC inhibitor (and who were not taking baseline CBZ or PHT); although, in the ESL 1200 mg dose group, incidences of dizziness, diplopia, and vertigo were higher among patients taking concomitant LTG.[14] It is therefore unclear whether the higher incidences of specific TEAEs that occurred when ESL was combined with CBZ/other VGSC inhibitors (compared with other AEDs, during the adjunctive studies and the titration and baseline AED taper periods of the conversion-to-monotherapy studies) was driven by a possible pharmacodynamic interaction due to the common MoA (VGSC inhibition), or there was another unknown reason or epiphenomenon.

A potential limitation of the current analysis is that differences in dose could have had differential effects on tolerability outcomes, which would not be detected here. In addition, although patients were not permitted to use more than 1 VGSC inhibitor during baseline, use of more than 1 baseline AED (with different MoAs) was permitted and could affect outcomes; this was not examined in the current analysis. Another potential limitation is that the +VGSCi subgroup included patients taking CBZ, as well as patients taking other VGSC inhibitors (LTG, OXC, and PHT). It is therefore unclear whether prior use of LTG, OXC, and PHT alone would have reduced the magnitude of seizure improvements with ESL (compared with the −VGSCi group), or if the results were driven primarily by seizure responses in patients who had been taking CBZ. Another limitation is the post hoc nature of the analyses; statistical comparisons of TEAE incidences were not prospectively planned and were therefore described primarily using descriptive statistics.

The results of the current analysis suggest that conversion to ESL from CBZ, or the other VGSCi analyzed here, could be a viable treatment strategy, both for patients who are seeking better tolerability and for those requiring improved seizure control from the conversion. Although, further studies would be required to examine long-term tolerability with ESL versus CBZ. Patients who converted to ESL from CBZ were not significantly more likely to exit the study (due to seizure worsening) than patients who converted to ESL from AED regimens that did not include CBZ. In fact, ~20% of patients who converted to ESL from CBZ actually achieved a clinically meaningful response (a ≥50% reduction in seizure frequency) following the conversion. The overall frequency of side effects was similar between the +CBZ and −CBZ groups. Comparable

outcomes were observed when converting to ESL from CBZ, LTG, OXC, or PHT; therefore, the above recommendations and considerations will likely be relevant when converting to ESL from any baseline VGSC inhibitor.

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## CONFLICT OF INTEREST

LP received financial support for research from Sunovion Pharmaceuticals Inc. and is an employee of Vestra Clinics. MRS received financial support for research from Sunovion Pharmaceuticals Inc., UCB Pharma, SK Life Sciences, Eisai, Acorda, Upsher-Smith, Medtronics, Brain Sentinel, Visualase, GSK, Pfizer, Marinus, and Neurelis; consulting fees for development of CME programs for Medscape; and consulting fees paid to Thomas Jefferson University for investigational protocol development for Medtronics. JHH received financial support for research, speakers' bureau fees and consultant fees from Sunovion Pharmaceuticals Inc. MCS received financial support as a trial investigator for Sunovion Pharmaceuticals Inc. LAS received financial support for research from Sunovion Pharmaceuticals Inc. DB, TG, and HC are employees of Sunovion Pharmaceuticals Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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