


FULL-LENGTH ORIGINAL RESEARCH

Serum sodium levels and related treatment-emergent adverse events during eslicarbazepine acetate use in adults with epilepsy

Robert T. Wechsler¹  | Rodney A. Radtke² | Michael Smith³ | David G. Vossler⁴ | Laura Strom⁵ | Eugen Trinka⁶ | Hailong Cheng⁷ | Todd Grinnell⁷ | David Blum⁷ | Mariana Vieira⁸ | Joana Moreira⁸ | Francisco Rocha⁸

¹Idaho Comprehensive Epilepsy Center, Boise, Idaho

²Duke University School of Medicine, Durham, North Carolina

³Rush University Medical Center, Chicago, Illinois

⁴University of Washington, Valley Medical Center, Renton, Washington

⁵University of Colorado Anschutz Medical Campus, Aurora, Colorado

⁶Uniklinikum Salzburg, Christian-Doppler-Klinik, Salzburg, Austria

⁷Sunovion Pharmaceuticals, Inc., Marlborough, Massachusetts

⁸BIAL – Portela & C^a, S.A., Coronado (S. Romão e S. Mamede), Portugal

Correspondence

Robert T. Wechsler, Consultants in Epilepsy & Neurology PLLC, 1499 West Hays Street, Boise, ID 83702.
Email: rtw@idahoepilepsy.com

Funding information

BIAL – Portela & C^a, S.A., Coronado (S. Romão e S. Mamede), Portugal; Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts

Abstract

Objective: To examine the frequency of hyponatremia and potentially related symptoms in clinical trials of eslicarbazepine acetate (ESL) in adults with focal- (partial-) onset seizures.

Methods: This post hoc, exploratory analysis included data from three controlled phase 3 trials of adjunctive ESL (400–1200 mg once daily), two phase 3 trials of ESL monotherapy (1200–1600 mg once daily), and their open-label extension studies. Exploratory endpoints included clinical laboratory measurements of serum sodium concentrations ($[Na^+]$), incidences of hyponatremia-related treatment-emergent adverse events (TEAEs), and incidences of TEAEs that are potential symptoms of hyponatremia.

Results: The controlled trials of adjunctive ESL and ESL monotherapy included 1447 (placebo, $n = 426$; ESL, $n = 1021$) and 365 (ESL, $n = 365$) patients, respectively; 639 and 274 patients continued onto uncontrolled, open-label extensions. In the controlled and uncontrolled trials $\leq 3.3\%$ of patients taking ESL had a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L, $< 9\%$ had a > 10 mEq/L decrease in $[Na^+]$ from baseline, $< 6\%$ had a hyponatremia-related TEAE, and $< 2\%$ discontinued the controlled trials due to a hyponatremia-related TEAE. Hyponatremia appeared to be more frequent in the monotherapy (vs adjunctive therapy) trials; in the controlled trials of adjunctive ESL and ESL monotherapy, incidence generally increased with increasing ESL dose. The majority of patients with an investigator-reported TEAE of “hyponatremia” or “blood sodium decreased” did not have a corresponding laboratory $[Na^+]$ measurement ≤ 125 mEq/L. Some symptoms potentially related to hyponatremia (including nausea and vomiting) were more frequent in patients with a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L.

Significance: Reductions in serum sodium concentrations and hyponatremia-related TEAEs occurred in a small number of patients taking ESL. Suspected hyponatremia should be confirmed and monitored via $[Na^+]$ measurements.

KEYWORDS

dibenzazepine carboxamides, focal seizures, hyponatremia, safety

1 | INTRODUCTION

Eslicarbazepine acetate (ESL) is a once-daily (QD), oral antiepileptic drug (AED) for the treatment of focal- (partial-) onset seizures in patients 4 years of age or older.¹ ESL is a member of the dibenzazepine carboxamide class of putative voltage-gated sodium channel blocking AEDs, which also includes carbamazepine (CBZ) and oxcarbazepine (OXC).

Hyponatremia (ie, low blood sodium) may occur with the use of dibenzazepine carboxamide AEDs,²⁻⁹ selective serotonin reuptake inhibitors (SSRIs),¹⁰ thiazide diuretics,¹¹ or tricyclic antidepressants.¹² The risk of developing hyponatremia with dibenzazepine carboxamides may be greater with increased fluid intake, older age, AED polypharmacy, or concurrent use of sodium-wasting medications.^{2,12,13}

Minimum serum sodium concentrations ($[Na^+]$) of 125 mEq/L or less are generally considered to be clinically concerning.^{12,14} Nevertheless, AED-induced hyponatremia (which is typically subacute to chronic) is usually asymptomatic, even with $[Na^+] \leq 125$ mEq/L; symptoms rarely occur until levels drop below 120 mEq/L.^{2,12,15} It is therefore important to evaluate whether patients with confirmed reductions in $[Na^+]$, or investigator-reported adverse events (AEs) of suspected hyponatremia, also experienced hyponatremia-related side effects. Furthermore, common symptoms of hyponatremia (eg, nausea, vomiting, headache, confusion, restlessness, and seizures) are similar to AEs frequently reported with AED use. Therefore, in the current article, we evaluated whether the occurrence of these AEs was associated with low $[Na^+]$ in clinical trials of ESL.

The main goal of this post hoc exploratory analysis was to examine the frequency of hyponatremia in five controlled phase 3 trials of ESL and their open-label extensions (OLEs). In addition, we sought to determine whether any of the potential symptoms of hyponatremia (eg, somnolence, headache, nausea, or vomiting) were related to low $[Na^+]$ in these trials.

2 | METHODS

2.1 | Study design

Data from five controlled phase 3 trials of ESL, as well as their OLEs, were analyzed.

2.1.1 | Trials of adjunctive ESL

Data from three randomized, double-blind, placebo-controlled “controlled” trials of ESL were analyzed: BIA-2093-301 (NCT00957684), -302 (NCT00957047), and -304 (NCT00988429). The study designs and primary results of these trials have been previously reported in full.¹⁶⁻¹⁸

Key Points

- In controlled and uncontrolled phase 3 trials, $\leq 3.3\%$ of patients taking ESL had a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L
- Of patients taking ESL as actual monotherapy during the open label extension, 8.8% had a >10 mEq/L decrease in $[Na^+]$ from baseline
- Of patients taking ESL, $>66\%$ had minimum post-dose $[Na^+]$ measurements >135 mEq/L, that is, no evidence of hyponatremia
- In controlled trials of ESL monotherapy, 5.8% of patients had a hyponatremia-related TEAE; 1.6% discontinued due to a hyponatremia TEAE
- Some symptoms of hyponatremia (eg, nausea and vomiting) were more frequent in patients with low $[Na^+]$ measurements

Briefly, patients were 18 years of age or older (Studies 301 and 302) or 16 years of age or older (Study 304), with refractory focal-onset seizures, despite stable treatment with ≥ 1 AED (OXC use was an exclusion criterion). Patients were randomized equally to receive placebo or adjunctive ESL 400 mg (Studies 301 and 302 only), 800 mg, or 1200 mg QD. Patients continued to receive stable doses of baseline concomitant AEDs throughout the studies. The controlled studies comprised an 8-week baseline period, followed by a 2-week titration period, and a 12-week maintenance period.

Patients who completed the double-blind treatment phase of Study 301 or 302 (in any treatment group) had the option to continue into an “uncontrolled” OLE. Patients received add-on ESL at a starting dose of 800 mg QD. After 1 month of treatment, the dose could be adjusted (400-1200 mg QD).

2.1.2 | Trials of ESL monotherapy

Data from two randomized, dose-blind, conversion-to-ESL monotherapy “controlled” trials were analyzed: 093-045 (NCT00866775) and -046 (NCT01091662). Both studies used a historical control comparator.¹⁹ The two study designs were identical; the study designs and primary results of the trials have been reported in full.^{5,20,21}

Briefly, patients were 16 to 70 years of age, with refractory focal-onset seizures, despite stable treatment with 1-2 AEDs (OXC was allowed as a baseline AED). Patients were randomized (2:1) to receive ESL 1600 mg or 1200 mg QD. The controlled studies comprised an 8-week baseline period, followed by a 2-week titration period, a 6-week conversion period (baseline AEDs withdrawn), and a 10-week ESL monotherapy period.

Patients who completed at least the first 3 weeks of dose-blind treatment in Study 045 or 046 had the option to continue into an “uncontrolled” OLE (Study 093-050 [NCT00910247]). In Study 050, patients received ESL monotherapy at a starting dose of 1600 mg QD (or 1200 mg QD if the patient had a dose reduction in the preceding study). The dose could be adjusted (800-2400 mg QD) after 1 week. Addition of up to two concomitant AEDs (not OXC) was allowed.

2.2 | Assessments and data collection

We report data for the safety population of the adjunctive ESL studies, and the intent-to-treat (ITT) population of the ESL monotherapy studies. Both populations comprised all patients who received at least one dose of ESL. The “actual ESL monotherapy” population comprised patients who started monotherapy during Study 045/046 and did not require reintroduction of additional AEDs (non-rescue/non-emergency) during Study 050.

Demographic and clinical characteristics were examined. Exploratory endpoints included clinical laboratory measurements of $[Na^+]$ and incidences of hyponatremia-related treatment-emergent AEs (TEAEs) during the controlled (double/dose-blind) and uncontrolled (OLE) study periods of the adjunctive ESL and ESL monotherapy clinical trials.

In each study, TEAEs were defined as AEs that occurred between the time of the first dose of study medication (or the date of randomization if the date of first dose was missing) and up to 30 days after the last dose of study medication. TEAEs were reported by investigators; supportive $[Na^+]$ measurements were not required to report a hyponatremia-related TEAE. For all studies, AEs were recoded according to MedDRA version 13.1, prior to summarization.

In Studies 301, 302, and 304, $[Na^+]$ was assessed at screening, baseline, and weeks 1, 8, and 14 (as well as at week 18 in Study 301 and week 2 in Study 304), and after 1, 6, and 12 months of open-label treatment. In Studies 045 and 046, $[Na^+]$ was assessed at screening, baseline, weeks 1, 2, 5, 8, 11, 14, 18, and 19, and after 1, 3, 6, 9, and 12 months of open-label treatment.

Minimum postdose $[Na^+]$ measurements were defined as the lowest $[Na^+]$ measurement at any point during the study; patients were categorized based on their $[Na^+]$ as follows: Group A (marked hyponatremia): ≤ 125 mEq/L; Group B (moderate hyponatremia): >125 to ≤ 130 mEq/L; Group C (mild hyponatremia): >130 to ≤ 135 mEq/L; and Group D (no hyponatremia): >135 mEq/L.

Selected patient factors were listed for all patients with a TEAE of “hyponatremia” or “blood sodium decreased” and/or with a clinically meaningful minimum postdose $[Na^+]$ measurement (≤ 125 mEq/L) during the controlled trials.

In the controlled monotherapy studies, the association between minimum postdose $[Na^+]$ measurement and ESL dose was calculated via Fisher's exact test.

3 | RESULTS

3.1 | Patients

3.1.1 | Trials of adjunctive ESL

The safety population of the controlled trials of adjunctive ESL included 1447 patients (placebo, $n = 426$; ESL 400 mg, $n = 196$; ESL 800 mg, $n = 415$; ESL 1200 mg, $n = 410$); 639 patients continued into the uncontrolled OLEs (Table 1). During the OLE, the median ESL daily dose was 818 mg.

Baseline demographic and clinical characteristics have been reported previously.^{16–18} Mean ages were 38.1 years in the ESL groups and 37.8 years in the placebo group. Patients

TABLE 1 Controlled and uncontrolled study analysis populations

Adjunctive ESL	Placebo	ESL 400 mg	ESL 800 mg	ESL 1200 mg	Flexible ESL dosing
Controlled trials (301, 302, 304) ^a	426	196	415	410	-
Uncontrolled OLEs (301, 302)	-	-	-	-	639
ESL monotherapy	ESL 1200 mg	ESL 1600 mg	Flexible ESL dosing	Flexible ESL dosing: “actual ESL monotherapy”	
Controlled trials (045, 046) ^b	123	242	-	-	
Uncontrolled OLE (050)	-	-	274	140	

Abbreviation: ESL, eslicarbazepine acetate; ITT, intent-to-treat; OLE, open-label extension.

Numbers are patients in each treatment arm of the controlled or uncontrolled studies.

^aSafety population.

^bITT population.

60 years of age or older comprised 3.9% and 4.2% of the ESL and placebo groups, respectively. CBZ (51.3% of patients), lamotrigine (23.9%), valproic acid (21.4%), and levetiracetam (17.2%) were the most frequently used concomitant AEDs in the ESL group. SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, or sertraline) were used by 62 patients (4.4%), and thiazides (chlorothiazide or hydrochlorothiazide) by 15 patients (1.0%). One patient (<1%) was taking both an SSRI and a thiazide.

3.1.2 | Trials of ESL monotherapy

The ITT population of the controlled trials of ESL monotherapy included 365 patients (ESL 1600 mg, $n = 242$; ESL 1200 mg, $n = 123$); 274 patients continued into the uncontrolled OLE (Table 1). The “actual ESL monotherapy” population comprised 140 patients. The median ESL daily dose during the OLE was 1597.3 mg for the full ITT population and 1590.6 mg in the actual monotherapy subgroup.

Baseline demographic and clinical characteristics have been reported previously.^{20,21} Median age was 38.0 years, with 6.0% of patients 60 years of age or older. CBZ (27.4% of patients), levetiracetam (24.9%), valproic acid (19.5%), and lamotrigine (16.4%) were the most frequently used baseline AEDs. SSRIs were used by 33 patients (9.2%) and thiazides by 12 patients (3.3%). One patient (<1%) was taking both an SSRI and a thiazide.

3.2 | Primary results

3.2.1 | Trials of adjunctive ESL

In the controlled clinical trials of adjunctive ESL, a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L was reported in 11/993 patients (1.1%) taking ESL, and none taking placebo; incidence appeared to be related to ESL dose (Table 2). In the uncontrolled OLEs, a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L was reported for 10/636 patients (1.6%). Proportions of patients in Groups A-D (representative of minimum post-dose $[Na^+]$) are reported in Table 3; the minimum postdose $[Na^+]$ measurement was >135 mEq/L for the majority of patients (80.9%) in the controlled trials.

When examining the number of patients taking sodium-wasting medications in Groups A-D, concomitant use of thiazides did not appear to be associated with $[Na^+]$ measurement category, whereas concomitant SSRI use appeared to be slightly more frequent in patients with lower $[Na^+]$ (Table 4). Reductions from baseline in $[Na^+]$ were comparable between patients who were or were not taking an SSRI at baseline (+SSRI: -2.6 standard deviation [SD] 4.1 mEq/L; -SSRI: -2.4 , SD 3.6 mEq/L). One of the 11 patients with a minimum

postdose $[Na^+]$ measurement ≤ 125 mEq/L in the controlled trials was taking an SSRI. A single patient was taking both an SSRI and a thiazide; this patient was in Group B (minimum postdose $[Na^+] > 125$ to ≤ 130 mEq/L).

In the controlled trials, a >10 mEq/L decrease in $[Na^+]$ from baseline was reported for 51/993 patients (5.1%) taking ESL and 3/421 patients (0.7%) taking placebo, with incidence increasing with ESL dose (Table 2). In the uncontrolled OLEs, a >10 mEq/L decrease in $[Na^+]$ from baseline was reported for 30/636 patients (4.7%). In the controlled trials, mean $[Na^+]$ decreased by between 0.1 and 0.8 mEq/L across doses between baseline and end of study in patients taking ESL, but did not decrease in those taking placebo (Table 2); $[Na^+]$ did not decrease between baseline and end of study in the uncontrolled OLEs.

Incidences of investigator-reported hyponatremia-related TEAEs, that is, “blood sodium decreased” and “hyponatremia,” are reported in Table 5. In the controlled trials, hyponatremia-related TEAEs were reported for 25 patients (2.4%) taking ESL, and one (0.2%) taking placebo. The incidence of hyponatremia-related TEAEs appeared to increase with increasing ESL dose. In the uncontrolled OLEs, hyponatremia-related TEAEs were reported for 15 patients (2.3%). In the controlled trials, 179 patients (17.5%) taking ESL had a TEAE leading to discontinuation; five of these patients (0.5% of all patients taking ESL) discontinued due to a hyponatremia-related TEAE.

Overall, hyponatremia (either a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L or an investigator-reported hyponatremia-related TEAE) occurred in a total of 31 patients during the controlled studies of adjunctive ESL (Table S1). Hyponatremia-related TEAEs were reported for 2/58 patients age 60 years or older; they were aged 71 and 65 years and taking ESL 800 mg. Two patients with hyponatremia were taking an SSRI and one a thiazide; 19/31 were taking concomitant CBZ. Three patients with hyponatremia had a $\geq 50\%$ increase in seizure frequency, and 9/31 patients (29%) were responders (had a $\geq 50\%$ decrease in seizure frequency).

Incidences of TEAEs according to minimum postdose $[Na^+]$ are shown in Table 6. Somnolence (36.4% vs 13.9%), headache (18.2% vs 12.6%), nausea (36.4% vs 10.6%), vomiting (18.2% vs 7.0%), convulsion (10.0% vs 0.2%), and partial seizures with secondary generalization (10.0% vs 0.3%) occurred more frequently ($>5\%$ difference) in Group A (marked hyponatremia) than in Group D (no hyponatremia), and dizziness (9.1% vs 20.7%) less frequently in Group A than in Group D. It is important to note that Group A contained only a small number of patients ($n = 11$). TEAEs occurring more frequently in Group B (moderate hyponatremia) than in Group D (no hyponatremia) were dizziness (42.0% vs 20.7%), nausea (18.0% vs 10.6%), blurred vision (10.0% vs 4.2%), and diplopia (30.0% vs 7.6%).

TABLE 2 Proportions of patients with a minimum post-dose [Na⁺] measurement ≤125 mEq/L or > 10 mEq/L decrease in [Na⁺] from baseline, and changes from baseline in [Na⁺]

	ESL monotherapy ^b												
	Adjunctive ESL ^a						OLE						
	Double-blind period			OLE			Dose-blind period			OLE			
	ESL 400 mg n = 196	ESL 800 mg n = 415	ESL 1200 mg n = 410	ESL 1600 mg n = 242	ESL 1200 mg n = 123	ESL 1600 mg n = 242	ESL 1200 mg n = 121	ESL 1600 mg n = 238	Total ESL n = 1021	Flexible ESL dosing n = 639	Total ESL n = 365	Flexible ESL dosing n = 274	“Actual monotherapy” patients n = 140
Patients with [Na ⁺] ≤125 mEq/L, n (%)	n = 421 0 (0.5)	n = 401 4 (1.0)	n = 398 6 (1.5)	n = 238 7 (2.9)	n = 993 11 (1.1)	n = 993 10 (1.6)	n = 261 ^c 4 (1.5)	n = 136 2 (1.5)					
Patients with > 10 mEq/L decrease in [Na ⁺] from baseline, n (%)	n = 421 3 (0.7)	n = 401 19 (4.7)	n = 398 26 (6.5)	n = 226 20 (8.4)	n = 993 51 (5.1)	n = 993 30 (4.7)	n = 193 23 (8.8)	n = 98 12 (8.8)					
Mean (SD) change in [Na ⁺]; baseline (or OL baseline) to end of study, mEq/L	n = 421 0.1 (2.7)	n = 401 -0.1 (2.8)	n = 398 -0.7 (3.6)	n = 226 -1.2 (3.5)	n = 993 -0.6 (3.4)	n = 993 0.6 (3.9)	n = 193 -1.4 (4.0)	n = 98 -1.3 (4.4)					

Abbreviation: ESL, eslicarbazepine acetate; ITT, intent-to-treat; [Na⁺], serum sodium concentration; OL, open-label; OLE, open-label extension; SD, standard deviation.

Percentages are calculated based on the number of patients with ≥1 post-baseline assessment for a given parameter.

^aSafety population.

^bITT population.

^cPatients who had normal [Na⁺] values (ie, >135 mEq/L) at baseline.

TABLE 3 Proportion of patients taking ESL in each minimum postdose [Na⁺] category

	Adjunctive ESL ^a		ESL monotherapy ^b	
	Double-blind period	OLE	Dose-blind period	OLE
	Total ESL n = 993 ^c	Total ESL n = 636	Total ESL n = 359 ^c	Total ESL n = 261 ^d
Patients in minimum post-dose [Na ⁺] group, n (%)				
Group A: ≤125 mEq/L	11 (1.1)	10 (1.6)	12 (3.3)	4 (1.5)
Group B: >125 to ≤130 mEq/L	50 (5.0)	31 (4.9)	25 (7.0)	22 (8.4)
Group C: >130 to ≤135 mEq/L	129 (13.0)	75 (11.8)	82 (22.8)	48 (18.4)
Group D: >135 mEq/L	803 (80.9)	520 (81.8)	240 (66.9)	187 (71.6)

Abbreviation: ESL, eslicarbazepine acetate; ITT, intent-to-treat; [Na⁺], serum sodium concentration; OLE, open-label extension.

^aSafety population.

^bITT population.

^cNumber of patients with ≥1 post-baseline assessment of [Na⁺].

^dPatients who had normal [Na⁺] values (ie, >135 mEq/L) at baseline.

3.2.2 | Trials of ESL monotherapy

In the controlled clinical trials of ESL monotherapy, a minimum postdose [Na⁺] measurement ≤125 mEq/L was reported for 12/359 patients (3.3%); incidence did not appear to be related to ESL dose (Table 2). A minimum postdose [Na⁺] measurement ≤125 mEq/L was reported for 4/261 patients (1.5%) in the uncontrolled OLE, and in 2/136 patients (1.5%) in the “actual monotherapy” subgroup of the OLE (Table 2). Proportions of patients in Groups A-D (representative of minimum post-dose [Na⁺]) are reported in Table 3; in the controlled trials, there was no significant association between the two ESL dose groups (1600 mg and 1200 mg) and the proportions of patients in Groups A-D ($P = 0.46$), with 66.9% of patients being in Group D (minimum postdose [Na⁺] measurement >135 mEq/L, ie, no hyponatremia).

Concomitant use of sodium-wasting medications was most frequent in Group A (minimum postdose [Na⁺] measurement ≤125 mEq/L), followed by Group C, Group B, and then Group D (minimum postdose [Na⁺] measurement >135 mEq/L; Table 4). Reductions from baseline in [Na⁺] were numerically greater in patients who were taking an SSRI at baseline than in those who were not (+SSRI: −5.5, SD 4.8 mEq/L; −SSRI: −3.5, SD 3.9 mEq/L). One-third of the 12 patients with a minimum postdose [Na⁺] measurement ≤125 mEq/L were taking an SSRI or thiazide (SSRI only, n = 3; SSRI + thiazide, n = 1); at baseline, all four patients' [Na⁺] measurements were >135 mEq/L (no hyponatremia).

A >10 mEq/L decrease in [Na⁺] from baseline was reported for 28/359 patients (7.8%) in the controlled trials, 23/261 patients (8.8%) in the uncontrolled OLE, and 12/136

patients (8.8%) in the “actual monotherapy” subgroup of the OLE (Table 2). Median decrease in [Na⁺] was 1 mEq/L after 2 weeks of treatment with ESL. Mean [Na⁺] decreased (by 1.1-1.2 mEq/L) between baseline and end of study in the controlled trials and by 1.4 mEq/L in their uncontrolled OLE (Table 2).

Incidences of investigator-reported hyponatremia-related TEAEs, that is, “blood sodium decreased” and “hyponatremia,” are reported in Table 5. In the controlled trials, hyponatremia-related TEAEs were reported for 21 patients (5.8%) and incidence appeared to be related to ESL dose. In the uncontrolled OLE, hyponatremia-related TEAEs were reported for 15 patients (5.5%). In the controlled trials, 47 patients (12.9%) had a TEAE that led to discontinuation; 6 of these patients (1.6% of all patients taking ESL) discontinued due to a hyponatremia-related TEAE.

Overall, hyponatremia (either a minimum post-dose [Na⁺] measurement ≤125 mEq/L or an investigator-reported hyponatremia-related TEAE) occurred in a total of 24 patients during the controlled studies (Table S1). Four of these patients were age ≥60 years (64, 66, 67, and 68 years; of a total of 22 patients aged ≥60 years in the trials of ESL monotherapy); all four patients were taking ESL 1600 mg and had baseline [Na⁺] measurements >135 mEq/L, and two of four were taking an SSRI or thiazide at baseline. Overall, 6 of 24 patients with hyponatremia were taking an SSRI, one of 24 a thiazide, and six of 24 CBZ or OXC at baseline. Eight of the 24 patients with hyponatremia (33.3%) were responders (had a ≥50% decrease in seizure frequency), whereas three had a ≥50% increase in seizure frequency.

TEAE incidences according to minimum postdose [Na⁺] are shown in Table 6. Dizziness (25.0% vs 19.2%), nausea

TABLE 4 Concomitant sodium-wasting medication use in each minimum post-dose [Na⁺] category, for patients treated with ESL in the controlled clinical trials

Adjunctive ESL		ESL monotherapy						
Patients taking a sodium-wasting medication in Groups A-D, n (%)		SSRI use ^a	Thiazide use ^b	SSRI ^a + thiazide use ^b	Patients taking a sodium-wasting medication in Groups A-D, n (%)	SSRI use ^a	Thiazide use ^b	SSRI ^a + thiazide use ^b
Group A: ≤125 mEq/L n = 11		1 (9.1)	0	0	Group A: ≤125 mEq/L n = 12	4 (33.3)	1 (8.3)	1 (8.3)
Group B: >125 to ≤130 mEq/L n = 50		4 (8.0)	2 (4.0)	1 (2.0)	Group B: >125 to ≤130 mEq/L n = 25	2 (8.0)	1 (4.0)	0
Group C: >130 to ≤135 mEq/L n = 129		8 (6.2)	4 (3.1)	0	Group C: >130 to ≤135 mEq/L n = 82	10 (12.2)	2 (2.4)	0
Group D: >135 mEq/L n = 803		36 (4.5)	4 (0.5)	0	Group D: >135 mEq/L n = 240	17 (7.1)	8 (3.3)	0

Abbreviation: ESL, eslicarbazepine acetate; [Na⁺], serum sodium concentration; SSRI, selective serotonin reuptake inhibitor.

Percentages are calculated based on the total number of patients in Group A-D.

^aCitalopram, escitalopram, fluoxetine, paroxetine, or sertraline.

^bChlorothiazide or hydrochlorothiazide.

TABLE 5 Incidences of investigator-reported hyponatremia-related TEAEs

	Adjunctive ESL ^a		ESL monotherapy ^b						
	Double-blind period		OLE		Dose-blind period		OLE		
	ESL 400 mg n = 426	ESL 800 mg n = 415	ESL 1200 mg n = 410	Total ESL n = 1021	ESL 1200 mg n = 123	ESL 1600 mg n = 242	Total ESL n = 365	Flexible ESL dosing n = 274	
Any hyponatremia-related TEAE ^c , n (%)	1 (0.2)	2 (1.0)	9 (2.2)	14 (3.4)	25 (2.4)	4 (3.3)	17 (7.0)	21 (5.8)	15 (5.5)
“Blood sodium decreased”, n (%)	0	1 (0.5)	2 (0.5)	5 (1.2)	8 (0.8)	0	6 (2.5)	6 (1.6)	4 (1.5)
“Hyponatremia”, n (%)	1 (0.2)	1 (0.5)	7 (1.7)	9 (2.2)	17 (1.7)	4 (3.3)	11 (4.5)	15 (4.1)	11 (4.0)

Abbreviation: ESL, eslicarbazepine acetate; ITT, intent-to-treat; OLE, open-label extension; TEAE, treatment-emergent adverse event.

^aSafety population.

^bITT population.

^c“Blood sodium decreased” or “hyponatremia”.

TABLE 6 Incidences of frequently reported TEAEs in each minimum post-dose [Na⁺] category, for patients taking ESL in the controlled studies

TEAEs, n (%)	Minimum post-dose [Na ⁺] category							
	Adjunctive ESL ^b				ESL monotherapy ^c			
	Group A ≤125 mEq/L n = 11 ^d	Group B >125-≤130 mEq/L n = 50 ^d	Group C >130-≤135 mEq/L n = 129 ^d	Group D >135 mEq/L n = 803 ^d	Group A ≤125 mEq/L n = 12 ^d	Group B >125-≤130 mEq/L n = 25 ^d	Group C >130-≤135 mEq/L n = 82 ^d	Group D >135 mEq/L n = 240 ^d
Any TEAE	8 (72.7)	37 (74.0)	69 (53.5)	366 (45.6)	12 (100.0)	20 (80.0)	68 (82.9)	187 (77.9)
Dizziness	1 (9.1)	21 (42.0)	35 (27.1)	166 (20.7)	3 (25.0)	7 (28.0)	23 (28.0)	46 (19.2)
Somnolence	4 (36.4)	7 (14.0)	17 (13.2)	112 (13.9)	1 (8.3)	2 (8.0)	8 (9.8)	31 (12.9)
Headache	2 (18.2)	8 (16.0)	22 (17.1)	101 (12.6)	1 (8.3)	6 (24.0)	23 (28.0)	53 (22.1)
Nausea	4 (36.4)	9 (18.0)	19 (14.7)	85 (10.6)	3 (25.0)	3 (12.0)	11 (13.4)	22 (9.2)
Vomiting	2 (18.2)	4 (8.0)	10 (7.8)	56 (7.0)	4 (33.3)	2 (8.0)	7 (8.5)	10 (4.2)
Fatigue	1 (9.1)	2 (4.0)	9 (7.0)	40 (5.0)	4 (33.3)	3 (12.0)	7 (8.5)	29 (12.1)
Blurred vision	1 (9.1)	5 (10.0)	11 (8.5)	34 (4.2)	4 (33.3)	2 (8.0)	6 (7.3)	11 (4.6)
Diplopia	1 (9.1)	15 (30.0)	19 (14.7)	61 (7.6)	0	0	0	0
Nasopharyngitis	0	0	0	0	2 (16.7)	4 (16.0)	5 (6.1)	23 (9.6)
Back pain	0	0	0	0	0	1 (4.0)	8 (9.8)	16 (6.7)
Seizure TEAEs								
Complex partial seizures	0	0	2 (1.9)	5 (0.8)	1 (8.3)	1 (4.0)	1 (1.2)	12 (5.0)
Convulsion	1 (10.0)	0	1 (1.0)	1 (0.2)	0	0	0	0
Partial seizures	0	1 (2.2)	1 (1.0)	3 (0.5)	0	0	0	0
Partial seizures with secondary generalization	1 (10.0)	0	0	2 (0.3)	0	2 (8.0)	2 (2.4)	8 (3.3)
Simple partial seizures	0	0	0	1 (0.2)	0	1 (4.0)	1 (1.2)	3 (1.3)

Abbreviation: ESL, eslicarbazepine acetate; ITT, intent-to-treat; [Na⁺], serum sodium concentration; TEAE, treatment-emergent adverse event.^aIncidence ≥5% in the total ESL group (pooled data), or seizure TEAEs with an incidence ≥2% in any minimum post-dose sodium category; seizures are TEAEs of special interest as a common symptom of hyponatremia.^bSafety population.^cITT population.^dNumber of patients with ≥1 post-baseline assessment of [Na⁺].^en values for adjunctive ESL: Group A (≤125 mEq/L), n = 10; Group B (>125-≤130 mEq/L), n = 45; Group C (>130-≤135 mEq/L), n = 105; Group D (>135 mEq/L), n = 639.

(25.0% vs 9.2%), vomiting (33.3% vs 4.2%), fatigue (33.3% vs 12.1%), blurred vision (33.3% vs 4.6%), and nasopharyngitis (16.7% vs 9.6%) occurred more frequently (>5% difference) in Group A (marked hyponatremia) than in Group D (no hyponatremia), and headache (8.3% vs 22.1%) occurred less frequently in Group A than Group D. However, Group A contained only a small number of patients ($n = 12$). TEAEs occurring more frequently in Group B (moderate hyponatremia) than in Group D (no hyponatremia) were dizziness (28.0% vs 19.2%) and nasopharyngitis (16.0% vs 9.6%).

3.2.3 | Consistency between investigator-reported TEAEs of hyponatremia and clinical laboratory analyses

In the controlled studies of adjunctive ESL and ESL monotherapy, 15 patients had both an investigator-reported hyponatremia-related TEAE and a clinically meaningful minimum postdose $[Na^+]$ measurement (≤ 125 mEq/L) from clinical laboratory analyses (Table S1); the majority of patients (32/47; 68%) with an investigator-reported hyponatremia-related TEAE did not have a corresponding minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L. Albeit, 21 patients had minimum postdose $[Na^+]$ measurements in Group B (moderate hyponatremia) and 10 in Group C (mild hyponatremia). In addition, hyponatremia-related TEAEs were not reported for approximately one-third (8/23) of the patients with a minimum postdose $[Na^+]$ measurement ≤ 125 mEq/L.

4 | DISCUSSION

This analysis of serum sodium measurements and investigator-reported TEAEs in the large number of patients in phase 3 controlled and uncontrolled trials of ESL provides an understanding of the relationship between hyponatremia, ESL dose, concomitant medications, and potential symptoms of hyponatremia. Considering the small number of patients who were identified as experiencing hyponatremia in these trials of ESL, and the somewhat homogenous nature of patients recruited for these clinical trials, these results should be interpreted with caution.

The data suggest that use of ESL (as either adjunctive therapy or monotherapy) may be associated with hyponatremia. In the controlled and uncontrolled trials of both adjunctive ESL and ESL monotherapy, 1.1%-3.3% of patients taking ESL (but none taking placebo) had a minimum post-dose $[Na^+]$ measurement (≤ 125 mEq/L) at some point during treatment. There is no comparative standard for patients in the monotherapy and uncontrolled trials because there was no placebo group. In addition, a decrease in $[Na^+]$ of >10 mEq/L from baseline was reported for 5% of patients taking adjunctive ESL, and for 8%-9% of patients taking ESL

monotherapy. However, the majority of patients (adjunctive ESL, $>80\%$; ESL monotherapy, $>66\%$) had minimum postdose $[Na^+] >135$ mEq/L and therefore no laboratory evidence of hyponatremia. Incidence of investigator-reported hyponatremia-related TEAEs was 5.8% with ESL monotherapy and 2.4% with adjunctive ESL. Incidence of hyponatremia-related TEAEs leading to discontinuation was 1.6% with ESL monotherapy and 0.5% with adjunctive ESL.

The patients in the current analysis had a long history of treatment-resistant epilepsy. In a study of newly diagnosed epilepsy patients receiving ESL as their first AED monotherapy in a flexible dosing study, hyponatremia possibly related to study drug was reported in 2.5% of patients; none discontinued due to hyponatremia.²² Use of other AEDs (dibenzazepine carboxamide AEDs in particular) has also been associated with the occurrence of hyponatremia. For example, a retrospective study of data from 1252 patients treated at tertiary epilepsy referral clinics found that hyponatremia ($[Na^+] <135$ mEq/L) occurred in 57% of patients taking OXC and 32% of patients taking CBZ.²³ Another analysis of 560 adult inpatients at a single center found that hyponatremia occurred in 16% of patients taking CBZ, 43% of patients taking OXC, and 33% of patients taking ESL.²⁴ A separate analysis of 1782 patients attending a tertiary epilepsy center found that hyponatremia ($[Na^+] \leq 134$ mEq/L) occurred in 26% of patients taking CBZ and 46% of those taking OXC.⁶ Furthermore, a recent register-based case-control study of Swedish patients found that odds ratios for hospitalization due to hyponatremia with newly initiated AEDs (compared with controls) were 9.63 for CBZ, 4.83 for phenytoin, 4.96 for valproate, 1.67 for lamotrigine, 9.76 for levetiracetam, and 1.61 for gabapentin.²⁵

Of interest, the majority of patients (32/47; 68%) with an investigator-reported hyponatremia-related TEAE did not have a corresponding $[Na^+]$ measurement ≤ 125 mEq/L, suggesting that it might be useful to measure $[Na^+]$ in patients with suspected hyponatremia. Symptoms assumed to be indicative of hyponatremia may have been unrelated to $[Na^+]$, but perhaps related to other effects of ESL. It is also possible that symptomatic hyponatremia may have occurred as a result of reductions in $[Na^+]$ that did not drop below 125 mEq/L, but perhaps to below 135 mEq/L in patients with higher pretreatment sodium levels. Unfortunately, sodium measurements were not taken systematically when hyponatremia-related TEAEs were reported in these trials.

AED-induced hyponatremia is often asymptomatic,^{2,12,15} so we also analyzed TEAE incidence in patients grouped according to minimum postdose $[Na^+]$ level. Symptoms typically associated with hyponatremia (including somnolence, headache, nausea, vomiting, convulsion, and partial seizures with secondary generalization) were reported more frequently in patients with the lowest minimum postdose $[Na^+]$ levels (Group A) than in patients with no postdose $[Na^+]$

measurements below 135 mEq/L (Group D) in the adjunctive trials. Similarly, dizziness, nausea, blurred vision, and diplopia were more frequent in patients with a moderate reduction in minimum postdose $[\text{Na}^+]$ level (Group B) compared with Group D. In the monotherapy trials, dizziness, nausea, vomiting, fatigue, blurred vision, and nasopharyngitis were more frequent in Group A than in Group D, and dizziness and nasopharyngitis were more frequent in patients in Group B vs Group D. Overall, somnolence, headache, nausea, and vomiting, all of which can be symptoms of acute hyponatremia,²⁶ were generally more frequent in patients with low $[\text{Na}^+]$ in these trials of ESL, suggesting that $[\text{Na}^+] \leq 125$ mEq/L, and even ≤ 130 mEq/L, may sometimes be symptomatic.

The occurrence of minimum postdose $[\text{Na}^+] \leq 125$ mEq/L or >10 mEq/L decreases in $[\text{Na}^+]$ from baseline, as well as hyponatremia-related TEAEs and TEAEs leading to discontinuation, appeared to be more frequent in the trials of ESL monotherapy vs adjunctive therapy. The differences between these trials could be due to the higher ESL doses used in the monotherapy trials (1200 and 1600 mg vs 400, 800, and 1200 mg QD). Indeed, incidences of hyponatremia-related TEAEs and >10 mEq/L decreases in $[\text{Na}^+]$ from baseline appeared to be related to ESL dose, and incidences were similar between the 1200 mg dose groups of both trial types. The relationship between ESL dose and occurrence of a minimum postdose $[\text{Na}^+]$ measurement ≤ 125 mEq/L, however, was less clear-cut. Incidence increased with dose in the adjunctive trials, but in the monotherapy trials, incidence was higher with ESL 1200 mg vs 1600 mg; incidences in both monotherapy dose groups were higher than in the adjunctive trials. Differences in patients' medical history, such as severity of epilepsy and past medication exposures, between the two study designs also could explain the higher incidence of hyponatremia with ESL monotherapy than with adjunctive therapy. One possible explanation is that approximately 50% of patients in the adjunctive trials were taking CBZ at baseline and thus may have been less susceptible to hyponatremia related to the use of dibenzazepine carboxamide AEDs (as patients who had previously experienced symptomatic hyponatremia on CBZ would probably have been discontinued and consequently perceived less suitable for enrollment in trials of ESL). By comparison, only 27.4% of patients were taking CBZ at baseline in the monotherapy trials. Therefore, it may be that the monotherapy trials included a larger proportion of patients who were naive to dibenzazepine exposure, and thus a greater proportion that was potentially prone to hyponatremia. Another possible factor is that 13% of patients in the monotherapy trials were taking a concomitant sodium-wasting medication, whereas only 5% of patients in the adjunctive trials were using this type of medication. The higher use of concomitant sodium-wasting medications in the monotherapy trials may have increased the likelihood of hyponatremia occurring in these patients.

These possible explanations for the higher rate of hyponatremia in the monotherapy trials than in the adjunctive trials are similar to those identified during postmarketing surveillance of ESL, where most hyponatremia cases were associated with high ESL doses (>1200 mg), dosing errors (eg, no uptitration and not following the administration guidelines), concomitant medications, and/or comorbidities.²⁷

Use of SSRIs and thiazides has been associated previously with the development of hyponatremia.^{10,11} In these controlled trials of ESL, thiazides did not appear to be associated with the occurrence of low $[\text{Na}^+]$ (≤ 125 mEq/L). SSRIs, however, were used more frequently in patients with low (vs higher) $[\text{Na}^+]$ measurements, suggesting that they may have contributed to the development of hyponatremia (although $<10\%$ of patients used these medications, limiting the reliability of this analysis). Indeed, in the monotherapy studies, greater reductions from baseline in $[\text{Na}^+]$ occurred in patients who were taking an SSRI at baseline compared with those who were not. A potential limitation of these analyses is that patients in these studies were on stable treatment with thiazides or SSRIs and had not already discontinued due to symptomatic hyponatremia, and therefore it may be that they represent a subset of patients who are less susceptible to thiazide- or SSRI-induced hyponatremia. Furthermore, factors not investigated here (eg, comorbidities or use of other concomitant medications) may have contributed to the reports of hyponatremia in these trials. In addition, differences between baseline medications may have rendered patients differentially sensitive to hyponatremia.

To gain further understanding of the types of patients who had hyponatremia during the ESL trials, we examined patient age, concomitant use of CBZ, OXC, and sodium-wasting medications, and seizure frequency in all patients who experienced hyponatremia (patients with a hyponatremia-related TEAE or a $[\text{Na}^+]$ measurement ≤ 125 mEq/L). First, despite the general acceptance that older patients are at particular risk of hyponatremia,²⁸ we found that only 6 of 55 patients with hyponatremia in the controlled trials were 60 years of age or older (of a total of 80 patients aged ≥ 60 years). In addition, only 3 of 31 patients (10%) with hyponatremia in the adjunctive trials were also taking a sodium-wasting medication, compared with 7 of 24 (29%) patients with hyponatremia in the monotherapy trials, suggesting that (in the monotherapy trials at least) concomitant use of SSRIs or thiazides may have been associated with the onset of hyponatremia. Furthermore, the proportions of patients with hyponatremia using CBZ or OXC were comparable to the proportions of patients in the full patient population using these AEDs, suggesting that use of multiple dibenzazepine carboxamide AEDs did not increase the risk of hyponatremia. This could be subject to selection bias, as only patients who had tolerated a dibenzazepine carboxamide AED would have entered the ESL clinical trials.

It is of note that the threshold for clinically significant hyponatremia is not clear-cut, and that different thresholds are used in different settings. For example, publications have defined hyponatremia as $[Na^+] < 125$ mEq/L (in line with this analysis),^{27,29} ≤ 132 mEq/L,³⁰ ≤ 134 mEq/L (with severe hyponatremia defined as ≤ 128 mEq/L),^{6,31} < 135 mEq/L,³² and < 137 mEq/L.³³ Therefore, comparisons of hyponatremia rates across studies should be interpreted with caution.

In summary, this analysis of data from 1812 patients in controlled and uncontrolled trials of ESL demonstrates that marked reductions in $[Na^+]$ and hyponatremia-related TEAEs occurred in a small number of patients taking ESL. Suspected hyponatremia should be confirmed by $[Na^+]$ measurements. Some clinicians may find it useful to document and monitor $[Na^+]$ levels during treatment with ESL, particularly in patients with symptoms typically associated with hyponatremia (eg, nausea, vomiting, malaise, headache, lethargy, confusion, irritability, muscle weakness/spasms, obtundation, increased seizure frequency or severity), or those receiving other medications known to affect $[Na^+]$.

ACKNOWLEDGMENTS

The authors wish to thank Dr M. McNulty for her valuable contributions when developing the poster presentation related to this work. Studies 304, 045, 046, and 050, as well as the analyses reported in this publication, were funded by Sunovion Pharmaceuticals Inc., Marlborough, MA. Studies 301, 302 (and their OLEs), and 304 were funded by BIAL – Portela & C^a, S.A., Coronado (S. Romão e S. Mamede), Portugal. Medical writing support was provided by Mallory Gough, PhD, of FireKite, an Ashfield company, part of UDG Healthcare plc, and was funded by Sunovion Pharmaceuticals Inc.

DISCLOSURE OF CONFLICTS OF INTEREST

R.W. has been a clinical trial investigator for Eisai, Sunovion Pharmaceuticals Inc., Biogen, Pfizer, Lundbeck, UCB, SK Life Science, Aquestive, Engage, Upsher-Smith, and Greenwich; received advisory board and/or consultancy honoraria to Consultants in Epilepsy & Neurology, Professional Limited Liability Company (PLLC) from UCB Pharma, Eisai, Upsher-Smith, Engage, Sunovion Pharmaceuticals Inc., Lundbeck, Greenwich, and Brain Sentinel; received speakers bureau honoraria to Consultants in Epilepsy & Neurology, PLLC from LivaNova, Sunovion Pharmaceuticals Inc., UCB Pharma, Greenwich, and Eisai; serves as Medical Director of the Epilepsy Center at St. Luke's Health System in Boise, Idaho; has pay-for-call arrangements with St. Luke's Health System in Boise, Idaho; is a member of the Epilepsy Studies Consortium, a Board Member of the National Association of Epilepsy Centers, a

member of the Executive Committee of the Consortium of Private Epilepsy Centers, and Board President of the Epilepsy Foundation of Idaho. R.A.R. has received consultancy fees from UCB, Sunovion Pharmaceuticals Inc., and Supernus. M.S. has received consultancy fees from SK Life Science and CW Pharmaceuticals. D.G.V. has received Advisory Board or Committee honoraria from SK Life Science, and received honoraria from Sunovion Pharmaceuticals Inc., UCB Pharma, and Greenwich Pharmaceuticals. L.S. has no conflicts of interest to declare. E.T. has received honoraria from UCB, Eisai, GW Pharmaceuticals, LivaNova, Novartis, Ever Pharma, Newbridge, Biogen, and Sunovion Pharmaceuticals Inc.; received consultancy fees from Eisai, GW Pharmaceuticals, Liva Nova, Biogen, and Ever Pharma; and received grants or funds from Biogen, Novartis, UCB, and Bayer. H.C., T.G., and D.B. are employees of Sunovion Pharmaceuticals Inc. M.V., J.M., and F.R. are employees of Bial - Portela & C^a, S.A. 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.

DATA ACCESSIBILITY

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.

ORCID

Robert T. Wechsler  <https://orcid.org/0000-0002-3146-986X>

REFERENCES

1. Sunovion Pharmaceuticals Inc. Aptiom[®] (Eslicarbazepine Acetate), Full Prescribing Information, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022416s009lbl.pdf. Accessed February, 2019.
2. Sachdeo RC, Wasserstein A, Mesenbrink PJ, D'Souza J. Effects of oxcarbazepine on sodium concentration and water handling. *Ann Neurol*. 2002;51:613–20.
3. Berghuis B, De Haan GJ, Van Den Broek MP, Sander JW, Lindhout D, Koeleman BP. Epidemiology, pathophysiology and putative genetic basis of carbamazepine- and oxcarbazepine-induced hyponatremia. *Eur J Neurol*. 2016;23:1393–9.
4. Gandhi S, McArthur E, Mamdani MM, Hackam DG, McLachlan RS, Weir MA, et al. Antiepileptic drugs and hyponatremia in older adults: two population-based cohort studies. *Epilepsia*. 2016;57:2067–79.
5. Sperling MR, French J, Jacobson MP, Pazdera L, Gough M, Cheng H, et al. Conversion to eslicarbazepine acetate monotherapy: a pooled analysis of 2 phase III studies. *Neurology*. 2016;86:1095–102.

6. Berghuis B, Van Der Palen J, De Haan GJ, Lindhout D, Koeleman BPC, Sander JW, et al. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. *Epilepsia*. 2017;58:1227–33.
7. Biton V, Rogin JB, Krauss G, Abou-Khalil B, Rocha JF, Moreira J, et al. Adjunctive eslicarbazepine acetate: a pooled analysis of three phase III trials. *Epilepsy Behav*. 2017;72:127–34.
8. Lu X, Wang X. Hyponatremia induced by antiepileptic drugs in patients with epilepsy. *Expert Opin Drug Saf*. 2017;16:77–87.
9. Villanueva V, Holtkamp M, Delanty N, Rodriguez-Uranga J, McMurray R, Santagueda P. Euro-Esli: a European audit of real-world use of eslicarbazepine acetate as a treatment for partial-onset seizures. *J Neurol*. 2017;264:2232–48.
10. Reid S, Barbui C. Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. *BMJ*. 2010;340:c1468.
11. Hix JK, Silver S, Sterns RH. Diuretic-associated hyponatremia. *Semin Nephrol*. 2011;31:553–66.
12. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. *J Clin Neurol*. 2016;12:21–33.
13. Kim YS, Kim DW, Jung KH, Lee ST, Kang BS, Byun JI, et al. Frequency of and risk factors for oxcarbazepine-induced severe and symptomatic hyponatremia. *Seizure*. 2014;23:208–12.
14. Sachdeo R, Karia R. Antiepileptic drugs and hyponatremia. *Neurol Rev*. 2016;24:S1–8.
15. Castilla-Guerra L, Del Carmen Fernandez-Moreno M, Lopez-Chozas JM, Fernández-Bolaños R. Electrolytes disturbances and seizures. *Epilepsia*. 2006;47:1990–8.
16. Elger C, Halasz P, Maia J, Almeida L, Soares-da-Silva P; BIA-2093-301 Investigators Study Group. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia*. 2009;50:454–63.
17. Ben-Menachem E, Gabbai AA, Hufnagel A, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. *Epilepsy Res*. 2010;89:278–85.
18. Sperling MR, Abou-Khalil B, Harvey J, Rogin JB, Biraben A, Galimberti CA, et al. Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: results of a phase III, double-blind, randomized, placebo-controlled trial. *Epilepsia*. 2015;56:244–53.
19. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia*. 2010;51:1936–43.
20. Sperling MR, Harvey J, Grinnell T, Cheng H, Blum D; 045 Study Team. Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a randomized historical-control phase III study based in North America. *Epilepsia*. 2015;56:546–55.
21. Jacobson MP, Pazdera L, Bhatia P, Grinnell T, Cheng H, Blum D; Study 046 Team. Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study. *BMC Neurol*. 2015;15:46.
22. Trinka E, Ben-Menachem E, Kowacs PA, Elger C, Keller B, Löffler K, et al. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: a phase III double-blind, randomized, parallel-group, multicenter study. *Epilepsia*. 2018;59:479–91.
23. Berghuis B, Stapleton C, Sonsma ACM, Hulst J, de Haan GJ, Lindhout D, et al. A genome-wide association study of sodium levels and drug metabolism in an epilepsy cohort treated with carbamazepine and oxcarbazepine. *Epilepsia Open*. 2019;4:102–9.
24. Intravooth T, Staack AM, Juerges K, Stockinger J, Steinhoff BJ. Antiepileptic drugs-induced hyponatremia: review and analysis of 560 hospitalized patients. *Epilepsy Res*. 2018;143:7–10.
25. Falhammar H, Lindh JD, Calissendorff J, Farmand S, Skov J, Nathanson D, et al. Differences in associations of antiepileptic drugs and hospitalization due to hyponatremia: a population-based case-control study. *Seizure*. 2018;59:28–33.
26. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. *Clin Interv Aging*. 2017;12:1957–65.
27. Gama H, Vieira M, Costa R, Graça J, Magalhães LM, Soares-da-Silva P. Safety profile of eslicarbazepine acetate as add-on therapy in adults with refractory focal-onset seizures: from clinical studies to 6 years of post-marketing experience. *Drug Saf*. 2017;40:1231–40.
28. Woodward M, Gonski P, Grossmann M, Obeid J, Scholes R, Topliss DJ. Diagnosis and management of hyponatraemia in the older patient. *Intern Med J*. 2018;48(Suppl. 1):5–12.
29. Shorvon SD, Trinka E, Steinhoff BJ, Holtkamp M, Villanueva V, Peltola J, et al. Eslicarbazepine acetate: its effectiveness as adjunctive therapy in clinical trials and open studies. *J Neurol*. 2017;264:421–31.
30. Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani MM, Hackam DG, et al. Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. *Am J Kidney Dis*. 2017;69:87–96.
31. Gupta DK, Bhoi SK, Kalita J, Misra UK. Hyponatremia following eslicarbazepine therapy. *Seizure*. 2015;29:11–4.
32. Ley M, Principe A, Jimenez-Conde J, Rocamora R. Assessing long-term effects of eslicarbazepine acetate on lipid metabolism profile, sodium values and liver function tests. *Epilepsy Res*. 2015;115:147–52.
33. Svendsen T, Brodtkorb E, Reimers A, Molden E, Sætre E, Johannessen SI, et al. Pharmacokinetic variability, efficacy and tolerability of eslicarbazepine acetate-A national approach to the evaluation of therapeutic drug monitoring data and clinical outcome. *Epilepsy Res*. 2017;129:125–31.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Wechsler RT, Radtke RA, Smith M, et al. Serum sodium levels and related treatment-emergent adverse events during eslicarbazepine acetate use in adults with epilepsy. *Epilepsia*. 2019;60:1341–1352. <https://doi.org/10.1111/epi.16069>