

# Eslicarbazepine acetate in post-stroke epilepsy: Clinical practice evidence from Euro-Esli

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## Abstract

**Objectives:** To assess the effectiveness and safety/tolerability of eslicarbazepine acetate (ESL) in patients included in the Euro-Esli study who had focal seizures associated with post-stroke epilepsy (PSE).

**Materials and Methods:** Euro-Esli was a pooled analysis of 14 European clinical practice studies. Effectiveness assessments (evaluated after 3, 6 and 12 months of ESL treatment and at final follow-up ["last visit"]) included rates of response ( $\geq 50\%$  seizure frequency reduction), seizure freedom (no seizures since at least the prior visit) and retention. Safety/tolerability was assessed throughout ESL treatment by evaluating adverse events (AEs) and discontinuation due to AEs. A *post hoc* analysis was conducted of patients with PSE versus patients without PSE ("non-PSE").

**Results:** Of 1656 patients included in the analysis, 76 (4.6%) had PSE and 1580 (95.4%) had non-PSE. Compared with non-PSE patients, PSE patients were significantly older, had significantly shorter epilepsy duration, significantly lower total baseline seizure frequency, and were treated with significantly fewer prior and concomitant antiepileptic drugs ( $P < .001$  for all). At the last visit, the responder rate was significantly higher in PSE versus non-PSE patients (72.9% vs 60.6%;  $P = .040$ ), as was the seizure freedom rate (48.6% vs 31.7%;  $P = .003$ ). After 12 months, retention was significantly higher in PSE versus non-PSE patients (87.8% vs 77.4%;  $P = .035$ ). The incidence of AEs was similar for PSE versus non-PSE patients (36.0% vs 35.8%;  $P = .966$ ).

**Conclusions:** These findings suggest that ESL may be an effective and well-tolerated treatment option for patients with focal seizures due to PSE.

## KEYWORDS

Epilepsy, eslicarbazepine acetate, seizures, stroke

## 1 | INTRODUCTION

Stroke is a common cause of epilepsy, accounting for 11% of all epilepsy cases and 55% of newly diagnosed seizures in the elderly population.<sup>1</sup> Moreover, the relationship between stroke and epilepsy appears

to be bidirectional, since middle-aged and elderly patients with newly diagnosed epilepsy have a twofold to threefold increased risk of stroke within approximately 2 years of epilepsy onset.<sup>2,3</sup> Post-stroke seizures usually have a focal seizure semiology, with approximately one third of cases presenting with focal to bilateral tonic-clonic seizures.<sup>4</sup>

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Post-stroke epilepsy (PSE)—defined as two or more unprovoked epileptic seizures occurring at least 1 week after the stroke—is thought to occur in at least 4–6% of the stroke population.<sup>5</sup> Factors associated with a higher risk of PSE include the presence of cortical lesions, a haemorrhagic component, early seizures and younger age at stroke onset.<sup>6</sup> PSE may be associated with unfavourable outcomes and increased mortality, and the European Stroke Organisation has therefore published evidence-based guidelines on the management of PSE.<sup>7</sup> Since observational studies have demonstrated a high risk of seizure recurrence (70%) after one post-stroke unprovoked seizure, the European Stroke Organisation guidelines recommend that antiepileptic drug (AED) treatment after one unprovoked seizure should be considered.<sup>7</sup> However, evidence for the effectiveness and safety/tolerability of AEDs in the PSE setting is currently limited.<sup>1,7,8</sup> Moreover, psychiatric comorbidities, particularly depression, are frequent in patients with epilepsy and in those who have suffered a stroke,<sup>9,10</sup> but information on AED treatment in patients with PSE who have psychiatric comorbidities is also lacking at present.

Eslicarbazepine acetate (ESL) is a once-daily AED that is approved in Europe for the treatment of focal-onset seizures as monotherapy in adults with newly diagnosed epilepsy, and as adjunctive therapy in adults, adolescents and children aged above 6 years.<sup>11</sup> In the United States, ESL is indicated for the treatment of focal-onset seizures in patients 4 years of age and older.<sup>12</sup> ESL is thought to act on the slow inactivated state of sodium channels.<sup>13</sup> The Euro-Esli study investigated the real-world effectiveness, safety and tolerability of ESL when used in everyday clinical practice in Europe.<sup>14</sup> Euro-Esli included over 2000 patients, representing the largest ESL clinical practice study conducted to date.<sup>14</sup> The size of this cohort allows for meaningful subgroup analyses to be conducted.<sup>14</sup>

The primary objective of this study was to assess the effectiveness and safety/tolerability of ESL in patients with focal seizures associated with PSE who were included in Euro-Esli, in comparison with those who did not have PSE. However, since a previous assessment of Euro-Esli data in special populations demonstrated significant differences in the effectiveness and safety/tolerability of ESL between patients who did and did not have psychiatric comorbidities at study entry,<sup>15</sup> additional subanalyses were conducted to evaluate the impact of this factor on the effectiveness and safety/tolerability of ESL in patients with and without PSE.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Euro-Esli was an exploratory, pooled analysis of data from 14 European clinical practice studies (both prospective and retrospective), full details of which have been published previously.<sup>14</sup> Effectiveness was assessed after 3, 6 and 12 months of ESL treatment and at final follow-up (“last visit”). For the final assessment, monthly seizure frequency was based on the last visit, which could

have been at 3, 6 or 12 months; therefore, seizure frequency at the last visit was based on the number of seizures experienced during at least the previous 3 months. Safety and tolerability were assessed for the duration of ESL treatment. For all assessments, “baseline” was defined as the time point at which ESL was initiated (ie the time point immediately prior to ESL initiation).

### 2.2 | Study population

Studies included in Euro-Esli employed broad inclusion/exclusion criteria, to be representative of patients encountered in clinical practice.<sup>14</sup> All patients who initiated ESL for the treatment of epilepsy were included. Seizure types were originally classified according to the International League Against Epilepsy 1989 definitions,<sup>16</sup> but were subsequently reclassified using the updated 2017 definitions.<sup>17</sup> Most patients were treated for focal seizures, although patients with generalized seizures were not specifically excluded; however, analyses of effectiveness focused on focal seizures, with or without focal to bilateral tonic-clonic seizures. Patients were excluded if records contained insufficient data for analysis. Duplicate data from patients included in more than one study were excluded.

The current analysis included all patients for whom epilepsy aetiology (stroke or other aetiology) was known. Effectiveness and safety/tolerability assessments were analysed and compared for patients with stroke as aetiology (“PSE patients”) versus patients without stroke as aetiology (“non-PSE patients”). An additional subanalysis was conducted for PSE and non-PSE patients to compare the effectiveness and safety/tolerability of ESL in those who did and did not have psychiatric comorbidities (including depression) at baseline.

### 2.3 | Study assessments

Effectiveness was assessed by evaluating rates of response, seizure freedom and retention. Response was defined as  $\geq 50\%$  seizure frequency reduction from baseline. Seizure freedom was defined as the occurrence of no seizures since at least the prior visit (either 3 or 6 months). For analysis of retention rate, the censored event was defined as discontinuation of ESL treatment for any reason.

Safety was assessed by evaluating adverse events (AEs). Tolerability was assessed by evaluating discontinuation due to AEs.

### 2.4 | Statistical methodology

Details of the statistical methodology employed in Euro-Esli have been published previously.<sup>14</sup> The safety population was defined as all patients who initiated ESL treatment; the effectiveness population, as all patients who initiated ESL treatment with  $\geq 1$  effectiveness assessment.

Effectiveness, safety and tolerability data were not available for all patients at all time points. Missing data were not imputed, except

in cross-sectional studies, in which the last visit data were captured and included in the established cut-off points (3, 6 or 12 months). The denominator used for all frequency assessments was the total number of patients for whom the data in question were available. Patients who withdrew from ESL treatment were included in the analysis up until the time of withdrawal, and the last visit time point was created in order to capture the patients' last recorded observation for each assessment.

Comparison between subgroups of patients was performed using the chi-squared test for qualitative variables and Student's *t* test (or Mann-Whitney *U* test, if parametric criteria were not met) for quantitative variables. Changes between the initial and final number of concomitant AEDs used were assessed using the Wilcoxon signed-rank test. Time to ESL discontinuation was assessed using Kaplan-Meier methodology. Mean time on ESL treatment was calculated with 95% confidence intervals (CIs) and compared between patient subgroups using the log-rank test. The Statistical Package for the Social Sciences version 19.0 was used for all analyses, and the significance level was 5%.

### 3 | RESULTS

#### 3.1 | Patient population

Euro-Esli included a total of 2058 patients.<sup>14</sup> In the current subgroup analysis, information on aetiology was known for 1656 patients (Table 1). Of these 1656 patients, 76 (4.6%) had PSE, of whom 60.5% were male, and 1580 (95.4%) had non-PSE, of whom 51.7% were male. In comparison with patients with non-PSE, patients with PSE were significantly older at baseline ( $P < .001$ ) and at onset of epilepsy ( $P < .001$ ), had significantly shorter duration of epilepsy ( $P < .001$ ), and had significantly lower baseline seizure frequency (total seizures [ $P < .001$ ], focal aware seizures [ $P = .036$ ], focal impaired awareness seizures [ $P < .001$ ] and focal to bilateral tonic-clonic seizures [ $P < .001$ ]). Patients with PSE had also been treated with significantly fewer previous AEDs ( $P < .001$ ) than patients with non-PSE.

#### 3.2 | ESL treatment and concomitant AEDs

In PSE and non-PSE patients, the main reason for initiating ESL was lack of effectiveness of prior treatment (Table 1). However, there were statistically significant differences between the groups in reasons for initiating ESL, with a lower proportion of PSE versus non-PSE patients initiating ESL due to lack of effectiveness with prior treatment (63.5% vs 79.9%) and a higher proportion of PSE vs non-PSE patients initiating ESL due to adverse reaction(s) with prior treatment (34.9% vs 24.5%) ( $P = .008$ ). At the time of ESL initiation, there was no significant difference in ESL dosing in patients with PSE versus non-PSE (mean [standard deviation; SD] dose, 565.2 [247.0] vs 571.3 [267.5] mg/day;  $P = .954$ ). However, at the last visit, ESL

dosing was significantly lower in patients with PSE versus non-PSE (mean [SD] dose, 887.7 [260.3] vs 983.3 [325.8];  $P = .024$ ). The number of concomitant AEDs was significantly lower in patients with PSE versus non-PSE at baseline (mean [SD], 1.3 [0.7] vs 1.8 [1.1];  $P < .001$ ) and at last visit (mean [SD], 0.6 [0.8] vs 1.5 [1.1];  $P < .001$ ), and the number of concomitant AEDs decreased significantly from baseline to last visit in patients with PSE and non-PSE ( $P < .001$  for both subgroups).

#### 3.3 | Effectiveness

At the last visit, the responder rate was significantly higher in PSE versus non-PSE patients (72.9% vs 60.6%;  $P = .040$ ; Figure 1A). There were no significant differences between groups in responder rates at other time points. Seizure freedom rates were significantly higher in PSE versus non-PSE patients at all time points, except 12 months ( $P = .070$ ) (Figure 1B). At the last visit, seizure freedom rates were 48.6% in PSE patients versus 31.7% in non-PSE patients ( $P = .003$ ).

Retention on ESL treatment over 12 months of follow-up was higher in PSE patients than in non-PSE patients (Figure 2), and after 12 months of follow-up, retention was significantly higher in PSE patients versus non-PSE patients (87.8% vs 77.4%;  $P = .035$ ). The primary reasons for discontinuation in PSE and non-PSE patients were adverse drug reactions (5.4% and 9.2%, respectively), lack of efficacy (5.4% and 6.4%, respectively) and adverse drug reactions plus lack of efficacy (1.4% and 2.9%, respectively). During the first 12 months, 8.1% of PSE patients and 12.3% of non-PSE patients were lost to follow-up. After 12 months of follow-up, the mean (95% CI) times on ESL treatment for PSE versus non-PSE patients were 11.2 (10.7-11.8) versus 10.2 (10.0-10.3) months ( $P = .023$ ).

#### 3.4 | Safety and tolerability

The relative percentage of AEs was similar for patients with PSE versus non-PSE (36.0% vs 35.8%;  $P = .966$ ) (Table 2). The most frequently reported AEs ( $\geq 5\%$  in either group) were somnolence (PSE 10.7% vs non-PSE 5.6%), dizziness (6.7% vs 6.9%) and fatigue (2.7% vs 5.7%). The relative percentage of AEs of the System Organ Class "Psychiatric Disorders" was also similar for the PSE and non-PSE groups (2.7% vs 3.0%).

The incidence of AEs leading to discontinuation was lower in patients with PSE versus non-PSE, although the difference was not significant (6.8% vs 14.5%;  $P = .063$ ). The most frequently reported AEs leading to discontinuation ( $\geq 2\%$  patients in either group) were instability/ataxia (PSE 2.7% vs non-PSE 1.3%), fatigue (1.4% vs 2.1%) and dizziness (0% vs 2.7%). AEs of the System Organ Class "Psychiatric Disorders" led to discontinuation of 1.3% of patients with non-PSE, compared with 0% of patients with PSE.

Hyponatraemia (defined according to the criteria of the treating physician) was reported as an AE in a similar proportion of patients

**TABLE 1** Demographic and baseline characteristics in patients with PSE and non-PSE

	PSE (N = 76)	Non-PSE (N = 1580)	P
<b>Demographics</b>			
<b>Sex</b>			
N <sup>a</sup>	76	1579	.134 <sup>b</sup>
Male, n (%)	46 (60.5)	817 (51.7)	
Female, n (%)	30 (39.5)	762 (48.3)	
<b>Age, years</b>			
N <sup>a</sup>	76	1579	<.001 <sup>c,B</sup>
Mean (SD)	60.4 (17.3)	42.9 (15.1)	
Median (range)	63.0 (18-87)	41.4 (14-88)	
<b>Psychiatric comorbidities</b>			
N <sup>a</sup>	45	841	-
Any psychiatric comorbidity, n (%)	10 (22.2)	242 (28.8)	
<b>Most frequently reported types of psychiatric comorbidity (≥2% of patients), n (%)</b>			
Depression	6 (13.3)	112 (13.3)	
Anxiety	3 (6.7)	55 (6.5)	
Mood disorder	0	36 (4.3)	
Personality disorder	1 (2.2)	12 (1.4)	
Irritability	1 (2.2)	3 (0.4)	
<b>Epilepsy-related characteristics</b>			
<b>Age at onset of epilepsy, years</b>			
N <sup>a</sup>	75	1497	<.001 <sup>d</sup>
Mean (SD)	50.9 (23.6)	23.7 (18.5)	
Median (range)	54.0 (0-85)	20.0 (0-87)	
<b>Duration of epilepsy, years</b>			
N <sup>a</sup>	75	1497	<.001 <sup>d</sup>
Mean (SD)	9.6 (13.1)	19.4 (14.9)	
Median (range)	4.0 (0-56)	17.0 (0-73)	
<b>Monthly seizure frequency</b>			
<b>Any seizure</b>			
N <sup>a</sup>	65	1401	<.001 <sup>d</sup>
Mean (SD)	4.3 (9.3)	13.8 (53.2)	
Median (range)	1.3 (0.1-60)	3.0 (0.1-1230.0)	
<b>Focal aware seizures</b>			
N <sup>a</sup>	16	270	.036 <sup>d</sup>
Mean (SD)	3.0 (3.4)	17.6 (70.5)	
Median (range)	1.7 (0.7-12.5)	3.3 (0.3-900.0)	
<b>Focal impaired awareness seizures</b>			
N <sup>a</sup>	34	776	<.001 <sup>d</sup>
Mean (SD)	3.4 (7.1)	8.3 (19.2)	
Median (range)	1.2 (0.3-30.0)	3.0 (0.2-240.0)	
<b>Focal to bilateral tonic-clonic seizures</b>			
N <sup>a</sup>	24	494	<.001 <sup>d</sup>
Mean (SD)	1.1 (3.0)	2.9 (6.9)	
Median (range)	0.3 (0.2-15.0)	1.0 (0.1-70.0)	

(Continues)

TABLE 1 (Continued)

	PSE (N = 76)	Non-PSE (N = 1580)	P
AED treatment			
Total number of previous AEDs <sup>e</sup>			
N <sup>a</sup>	70	1438	<.001 <sup>d</sup>
Mean (SD)	1.9 (1.9)	4.4 (3.6)	
Median (range)	1.0 (1-12)	3.0 (0-20)	
Total number of concomitant AEDs			
N <sup>a</sup>	76	1579	<.001 <sup>d</sup>
Mean (SD)	1.3 (0.7)	1.8 (1.1)	
Median (range)	1.0 (0-5)	2.0 (0-6)	
Number of concomitant AEDs			
N <sup>a</sup>	76	1579	-
0	3 (3.9)	78 (4.9)	
1	57 (75.0)	649 (41.1)	
2	11 (14.5)	499 (31.6)	
3	4 (5.3)	234 (14.8)	
4-6	1 (1.3)	119 (7.5)	
Reason for initiating ESL treatment			
N <sup>a</sup>	63	880	.008 <sup>b</sup>
Lack of effectiveness	38 (60.3)	627 (71.3)	
Adverse reaction	20 (31.7)	140 (15.9)	
Both	2 (3.2)	76 (8.6)	
Other	3 (4.8)	37 (4.2)	

Abbreviations: AED, antiepileptic drug; ESL, eslicarbazepine acetate; PSE, post-stroke epilepsy; SD, standard deviation.

<sup>a</sup>N refers to the total number of patients for whom data in question were available.

<sup>b</sup> chi-squared test.

<sup>c</sup>Student's *t* test.

<sup>d</sup>Mann-Whitney *U* test.

<sup>e</sup>Excluding concomitant AEDs.

with PSE versus non-PSE (4.0% vs 3.7%). None of the patients with PSE discontinued due to hyponatraemia, compared with 1.1% of patients with non-PSE.

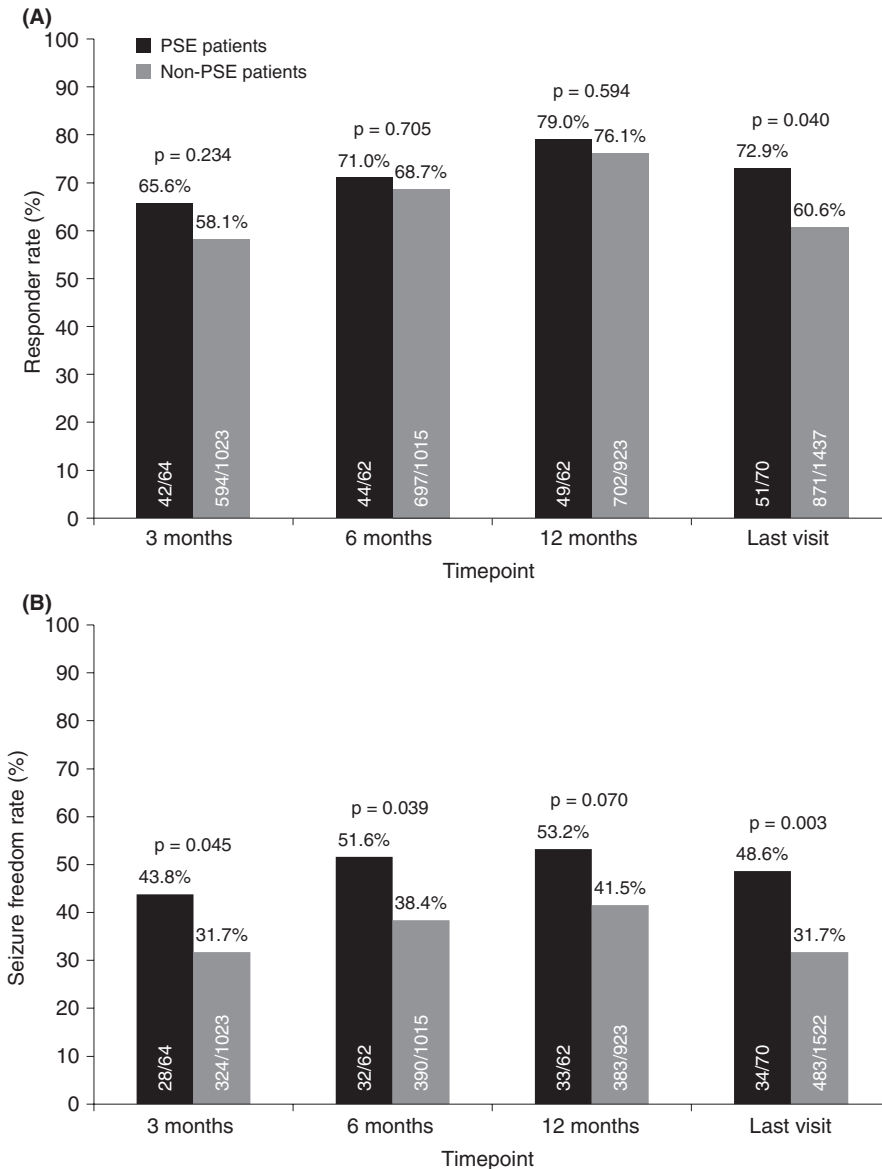
### 3.5 | Subgroup analysis of patients with/without psychiatric comorbidities (including depression) at baseline

The presence/absence of psychiatric comorbidities (including depression) was known for 45 patients with PSE and 841 patients with non-PSE. Overall, 10/45 (22.2%) PSE patients and 242/841 (28.8%) non-PSE patients for whom data were available had psychiatric comorbidities at baseline (Table 1). The most frequent psychiatric comorbidities were depression (13.3% in both groups) and anxiety (PSE, 6.7%; non-PSE, 6.5%).

In patients with psychiatric comorbidities, responder rates were similar in PSE and non-PSE patients, except at the last visit, where the responder rate in PSE patients was significantly higher than in

non-PSE patients (100% vs 61.4%;  $P = .015$ ; Figure 3A). Seizure freedom rates were higher in PSE patients with psychiatric comorbidities than in non-PSE patients with psychiatric comorbidities at all time points, but the difference was only statistically significant at the last visit (80.0% vs 33.2%;  $P = .004$ ; Figure 3B). In patients without psychiatric comorbidities, responder and seizure freedom rates were not significantly different in PSE versus non-PSE patients at any time point.

In patients with psychiatric comorbidities, the retention rate over 12 months of follow-up was higher in PSE versus non-PSE patients, although the difference was not statistically significant (100.0% vs 76.3%;  $P = .123$ ). The mean time on ESL treatment was not statistically compared because all PSE patients were retained on ESL treatment. Similarly, in patients without psychiatric comorbidities, the retention rate over 12 months of follow-up was higher in PSE versus non-PSE patients, but the difference was not statistically significant (91.2% vs 79.6%;  $P = .121$ ). The mean (95% CI) times on ESL treatment for PSE versus non-PSE patients were 11.5 (10.9-12.1) versus 10.4 (10.1-10.7) months ( $P = .089$ ).



**FIGURE 1** Effectiveness of ESL in patients with PSE and non-PSE: (A) Responder rate and (B) Seizure freedom rate. Response was defined as  $\geq 50\%$  seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit; therefore, seizure freedom rates at 3 months, 6 months and the last visit represent the percentages of patients who had no seizures for  $\geq 3$  months, and the seizure freedom rate at 12 months represents the percentage of patients who had no seizures for  $\geq 6$  months. Statistical comparisons were conducted using the chi-squared test. ESL, eslicarbazepine acetate; PSE, post-stroke epilepsy

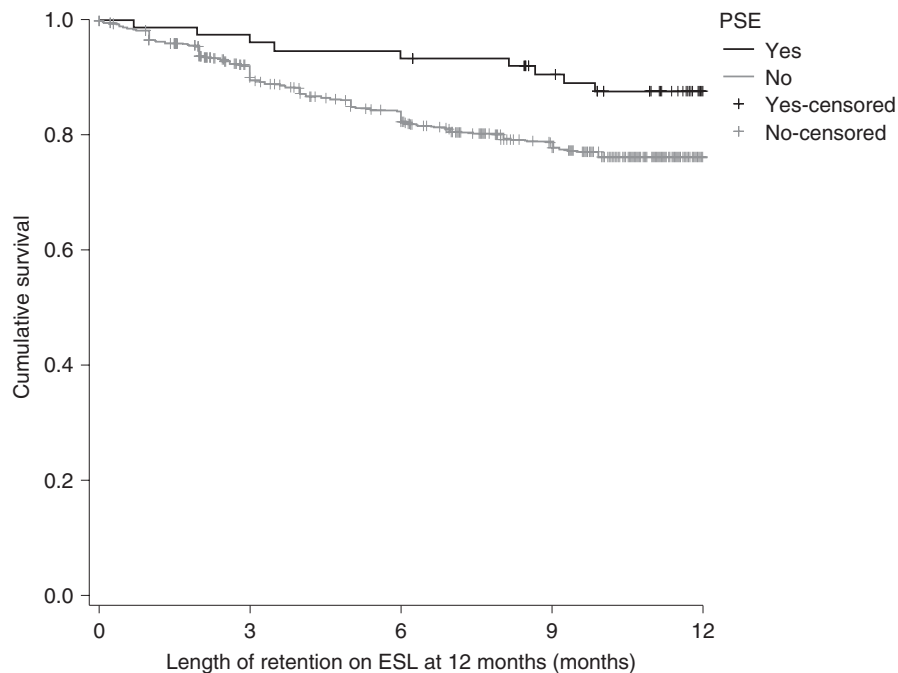
In patients with psychiatric comorbidities, the incidence of AEs was similar for patients with PSE versus non-PSE (50.0% vs 43.4%;  $P = .680$ ). The incidence of AEs leading to discontinuation was lower in patients with PSE versus non-PSE, but the difference was not statistically significant (0% vs 16.3%;  $P = .369$ ). Similarly, in patients without psychiatric comorbidities, the incidence of AEs was comparable for patients with PSE versus non-PSE (28.6% vs 34.6%;  $P = .468$ ). The incidence of AEs leading to discontinuation was again lower in patients with PSE versus non-PSE, but the difference was not statistically significant (2.9% vs 13.8%;  $P = .070$ ).

## 4 | DISCUSSION

In this *post hoc* analysis of Euro-Esli, which was conducted under clinical practice conditions in Europe, ESL was shown to be effective

and well tolerated in PSE and non-PSE patients. Although ESL was effective and well tolerated in both groups, there were some differences, and, overall, the effectiveness of ESL (based on retention, responder and seizure-free rates) was greater in patients with PSE, compared with those without PSE. In addition, the safety/tolerability profile of ESL was similar in patients with and without PSE. Taken together, these findings might suggest that patients with PSE are less refractory to treatment than those with non-PSE. This notion is supported by the comparison of demographic and baseline characteristics, which demonstrated that PSE patients were earlier in their disease course and/or less refractory to treatment than those with non-PSE, since they had a significantly shorter duration of epilepsy, significantly lower baseline seizure frequency, had been treated with significantly fewer previous AEDs, and were being treated with significantly fewer concomitant AEDs at study entry (and at the last visit). Nevertheless, given that the PSE patients were earlier in their disease course, this study's findings therefore demonstrate that PSE

**FIGURE 2** Kaplan-Meier plot of retention on ESL treatment over 12 months of follow-up in PSE patients and non-PSE patients. ESL, eslicarbazepine acetate; PSE, post-stroke epilepsy



is challenging to treat, since less than 50% of patients achieved seizure freedom at the last visit. However, they also indicate that ESL may have relevant role to play in this setting. It is also important to note that the PSE patients were significantly older than the non-PSE patients (median age at baseline, 63.0 vs 41.4 years). Studies conducted in patients with newly diagnosed epilepsy have indicated that outcomes are more favourable in older versus younger patients.<sup>18,19</sup> Although it is probable that the majority of patients included in the current study did not have newly diagnosed epilepsy (since > 95% were being treated with concomitant AEDs at baseline), the older age of the PSE versus non-PSE patients, together with their shorter duration of epilepsy, may have contributed to the more favourable effectiveness observed in those with PSE versus non-PSE.

This study additionally demonstrated that ESL was more effective in PSE versus non-PSE patients regardless of the presence or absence of psychiatric comorbidities (including depression) at baseline. However, the greater effectiveness of ESL in PSE versus non-PSE patients was more marked in patients with psychiatric comorbidities than in those without psychiatric comorbidities: at the last visit, responder and seizure freedom rates were significantly greater for PSE versus non-PSE patients in those with psychiatric comorbidities, but the differences were not statistically significant in those without psychiatric comorbidities. Although evidence for the prevalence of psychiatric comorbidities in PSE is currently lacking, post-stroke depression is known to be highly prevalent, affecting up to one third of stroke survivors,<sup>20,21</sup> and the treatment of depression represents an unmet need in the long-term care of stroke patients.<sup>22</sup> The risk of psychiatric comorbidity is also substantially increased in epilepsy patients, the prevalence of psychiatric disorders being twice as high in epilepsy patients as in the general population.<sup>23</sup> Psychiatric comorbidities—in particular, depression—have a deleterious impact on the quality of life and functional capacity of patients with epilepsy.<sup>9,10,24</sup>

Moreover, treatment with certain AEDs can cause or exacerbate psychiatric comorbidities.<sup>25,26</sup> Results of prospective audits have indicated that patients treated with AEDs that work primarily as sodium channel blockers are significantly less likely to develop intolerable psychiatric problems than patients treated with AEDs possessing other mechanisms of action.<sup>26</sup> Consistent with this, a previous subanalysis of Euro-Esli has demonstrated that ESL (which is thought to act primarily by enhancing the slow inactivation of voltage-gated sodium channels<sup>13</sup>) may be effective in patients with focal epilepsy and with concomitant psychiatric comorbidities.<sup>15</sup> The findings from the current study thus add to existing evidence indicating that ESL is a potentially useful AED treatment option for patients with focal seizures who also have psychiatric comorbidities.

Although of differing study designs, the results of the current analyses are also consistent with those of an observational study of patients included in the Mainz Epilepsy Register (MAINZ-EPIREG) and Marburger Stroke Register (MARSTREG) in Germany, which compared different AED monotherapies (ESL, levetiracetam, lacosamide, lamotrigine and sodium valproate) in the treatment of patients with PSE, and concluded that ESL and lacosamide had the most favourable efficacy and safety profiles in this setting.<sup>8</sup> The authors speculated that AEDs that facilitate the slow inactivation of sodium channels (such as ESL) may have the most favourable properties for the treatment of PSE.<sup>8</sup>

Other evidence for the use of AEDs in patients with PSE is limited. Only two randomized controlled trials, both open-label, have specifically investigated the use of AEDs in this setting.<sup>27,28</sup> A prospective study in which 64 patients with symptomatic post-stroke seizures were randomized to receive monotherapy with either lamotrigine or controlled-release carbamazepine and followed up for 12 months demonstrated a higher seizure freedom rate with lamotrigine versus controlled-release carbamazepine, although the difference

**TABLE 2** Summary of AEs and AEs leading to discontinuation in patients with PSE and non-PSE

	PSE	Non-PSE
Patients with AEs		
N <sup>a</sup>	75	1555
n (%)	27 (36.0)	556 (35.8)
Most frequently reported AEs (≥2% of patients)		
N <sup>a</sup>	75	1555
Somnolence, n (%)	8 (10.7)	87 (5.6)
Dizziness, n (%)	5 (6.7)	107 (6.9)
Fatigue, n (%)	2 (2.7)	88 (5.7)
Hyponatraemia, n (%)	3 (4.0)	58 (3.7)
Instability/ataxia, n (%)	2 (2.7)	56 (3.6)
Other laboratory abnormality, n (%)	2 (2.7)	8 (0.5)
Anxiety, n (%)	2 (2.7)	5 (0.3)
Diplopia/blurred vision, n (%)	0	53 (3.4)
Disturbance in attention/concentration, n (%)	0	35 (2.3)
Rash, n (%)	0	31 (2.0)
Patients with AEs leading to discontinuation		
N <sup>a</sup>	74	1493
n (%)	5 (6.8)	216 (14.5)
Most frequently reported AEs leading to discontinuation (≥1% of patients)		
N <sup>a</sup>	74	1493
Instability/ataxia, n (%)	2 (2.7)	20 (1.3)
Fatigue, n (%)	1 (1.4)	32 (2.1)
Hypoesthesia/paraesthesia, n (%)	1 (1.4)	1 (0.1)
Pruritus/burning, n (%)	1 (1.4)	1 (0.1)
Joint pain, n (%)	1 (1.4)	1 (0.1)
Muscle tone disturbance, n (%)	1 (1.4)	0
Dizziness, n (%)	0	40 (2.7)
Rash, n (%)	0	22 (1.5)
Disturbance in attention/concentration, n (%)	0	19 (1.3)
Nausea, n (%)	0	17 (1.1)
Hyponatraemia n (%)	0	16 (1.1)

Abbreviations: AE, adverse event; PSE, post-stroke epilepsy

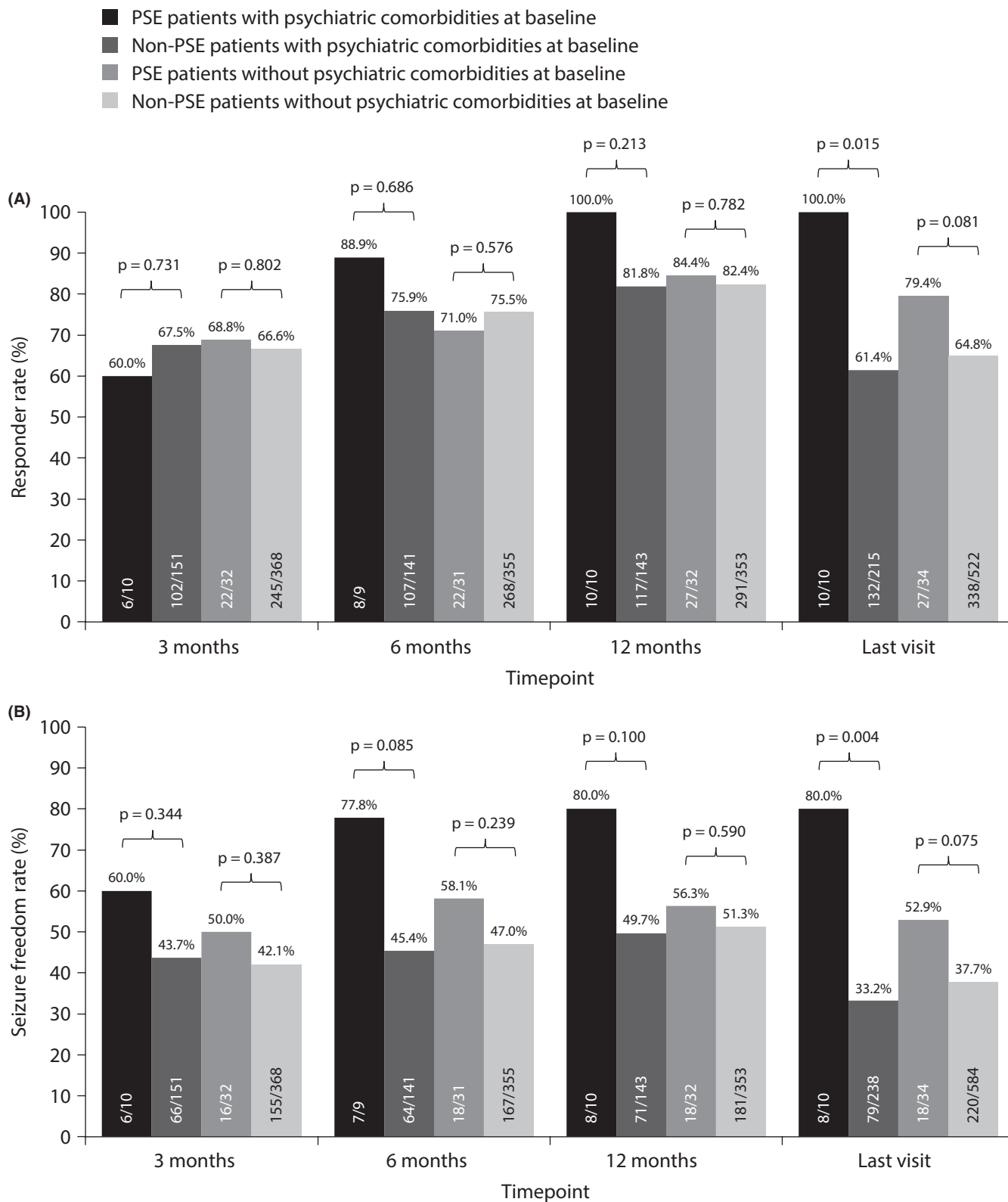
did not attain statistical significance due to the small sample size (71.9% versus 43.8%;  $P = .06$ ).<sup>27</sup> However, the number of patients who discontinued due to AEs was significantly lower for lamotrigine versus carbamazepine (3.1% vs 31.3%;  $P = .02$ ).<sup>27</sup> The incidence of AEs relating to the central nervous system that led to discontinuation was low with lamotrigine (3.1%),<sup>27</sup> as it was for ESL in the current study (4.1%). A multicentre, randomized, open-label study in which 128 patients with post-stroke seizures were randomized

to receive monotherapy with either levetiracetam or sustained-release carbamazepine and followed up for 12 months demonstrated no significant difference in seizure freedom rate at the end of the study for levetiracetam versus carbamazepine (94% vs 85%;  $P = .08$ ), although time to first seizure recurrence tended to be longer with levetiracetam than with carbamazepine.<sup>28</sup> The incidence of AEs was significantly lower for levetiracetam versus carbamazepine (32.7% vs 38.9%;  $P = .02$ ), and attention deficit, frontal executive functions and functional scales (Activities of Daily Living and Instrumental Activities of Daily Living indices) were significantly worse with carbamazepine than with levetiracetam.<sup>28</sup> An important limitation of the study was that 22 of the 128 randomized patients discontinued prematurely and were therefore not included in the analyses.<sup>28</sup>

In an uncontrolled prospective observational study in which 35 patients with newly diagnosed late-onset post-stroke seizures were treated with levetiracetam monotherapy, seizure freedom (defined as 1 year without seizures) was achieved by 77.1% of patients and the rate of discontinuation due to AEs was 11.4%.<sup>29</sup> Another uncontrolled trial, conducted in 71 patients with first post-stroke late seizures, evaluated the long-term efficacy and tolerability of gabapentin monotherapy over a mean follow-up duration of 30 months.<sup>30</sup> Overall, 81.7% of patients remained seizure free; the incidence of AEs was 38.0%, and the rate of discontinuation due to AEs was 2.8%.<sup>30</sup> A large population-based cohort study conducted in Taiwan, using data on the new occurrence of PSE from a national health insurance database, examined the effectiveness of a range of AEDs in controlling seizures in 3622 late-onset PSE patients, by evaluating the number of recurrent seizures requiring either emergency room (ER) visits or hospitalization.<sup>31</sup> The incidences of ER visits for patients treated with phenytoin, valproic acid, carbamazepine and "new AEDs" (defined as oxcarbazepine, vigabatrin, tiagabine, lamotrigine, topiramate, gabapentin, levetiracetam and pregabalin) were 1.26, 0.70, 0.43 and 0.38 per 100 person-months, respectively.<sup>31</sup> Compared with phenytoin, the adjusted hazard ratios for ER visits were 0.56 (95% CI, 0.42-0.74;  $P < .001$ ) for valproic acid, 0.37 (95% CI, 0.18-0.75;  $P = .006$ ) for carbamazepine and 0.28 (95% CI, 0.15-0.52;  $P < .001$ ) for new AEDs.<sup>31</sup> Similar results were observed for the adjusted hazard ratios for hospitalizations for seizure recurrence.<sup>31</sup>

The 12-month seizure freedom rate in PSE patients treated with ESL in the current study (53.2%) refers to the rate of seizure freedom for at least 6 months, which is not comparable with the 12-month seizure freedom rates observed with other AEDs in the aforementioned studies.<sup>28</sup> It is also noteworthy that all of these other studies examined the effectiveness of AEDs as monotherapy in patients with post-stroke seizures, whereas only 3.9% of PSE patients in the current analysis were treated with ESL as monotherapy. A recent *post hoc* analysis of PSE patients included in the ESL Phase III monotherapy trial demonstrated that seizure freedom (defined as no seizures during the entire 26-week evaluation period) was achieved by 69.6% of patients treated with ESL monotherapy versus 69.0% of patients treated with controlled-release carbamazepine monotherapy.<sup>32</sup>

The incidence of AEs in PSE patients in the current analysis (36.0%) was similar to incidences observed with levetiracetam



**FIGURE 3** Effectiveness of ESL in patients with PSE and non-PSE who did and did not have psychiatric comorbidities (including depression) at baseline: (A) Responder rate and (B) Seizure freedom rate. Response was defined as  $\geq 50\%$  seizure frequency reduction from baseline. Seizure freedom was defined as no seizures since at least the prior visit; therefore, seizure freedom rates at 3 months, 6 months and the last visit represent the percentages of patients who had no seizures for  $\geq 3$  months, and the seizure freedom rate at 12 months represents the percentage of patients who had no seizures for  $\geq 6$  months. Statistical comparisons were conducted using the chi-squared test. ESL, eslicarbazepine acetate; PSE, post-stroke epilepsy

(32.7%) and carbamazepine (38.9%) in the previously mentioned head-to-head comparison.<sup>28</sup> Similarly, the rate of ESL discontinuation due to AEs observed in PSE patients in the current analysis (6.8%) was generally favourable in comparison with the aforementioned trials, in which rates of discontinuation due to AEs ranged from 2.8% for gabapentin<sup>30</sup> to 31% with controlled-release carbamazepine<sup>27</sup>; however, as previously stated, these trials were in the monotherapy setting and therefore not directly comparable with the current study. The safety/tolerability results in the current study are also broadly consistent with those of ESL according to data from several clinical studies to 6 years of post-marketing surveillance.<sup>33</sup> In the pooled analysis of four Phase III studies, the most frequently reported treatment-emergent AEs ( $\geq 10\%$  of patients) were dizziness, somnolence, headache and nausea.<sup>33</sup> As previously noted, the PSE patients in the current study were significantly older than the non-PSE patients, with a median age of 63 years. Clinical trials conducted in patients with late-onset epilepsy have reported high rates of tolerability problems, illustrating the challenges associated with treating epilepsy in the elderly; for example, the incidence of AEs reported with lamotrigine, carbamazepine and levetiracetam was in region of 86–94%.<sup>34,35</sup> Although tolerability in clinical practice studies is typically better than that reported in clinical trials (since treatment in clinical practice is individualized rather than protocol-defined), it is notable that the tolerability of ESL observed in the PSE patients included in the current study was relatively favourable, the overall incidence of AEs being 36%.

The current analysis was limited in being a *post hoc* analysis of a pooled analysis of prospective and retrospective studies that were heterogeneous in terms of objectives and designs.<sup>14</sup> In Euro-Esli, individual patient data were previously reviewed by the authors of the individual studies, but were not reviewed systematically *post hoc*.<sup>14</sup> In addition, across all endpoints and assessments, data were not available for all patients at all time points, due to the heterogeneous nature of the studies included in Euro-Esli.<sup>14</sup> The study was also limited by the relatively small subgroup sizes involved, which may have had an impact on the observed findings. Furthermore, assessment of effectiveness was not adjusted for baseline seizure frequency, which differed between the PSE and non-PSE groups. As this was a non-randomized, retrospective, *post hoc* analysis of pooled real-world data, all statistical comparisons (p-values) should be interpreted with caution, since the subgroups were imbalanced in terms of patient characteristics, ESL dosing/exposure and concomitant medications, and there were missing data for most assessments; therefore, the study was essentially descriptive in nature. Similarly, descriptive comparisons of safety/tolerability between subgroups should be viewed with caution, since the subgroups may have differed in terms of duration of treatment/ESL exposure. As previously mentioned, it should also be borne in mind that seizure freedom was not defined as “no seizures since the initiation of ESL treatment,” but, rather, as “no seizures since at least the prior visit,” which could have been 3 or 6 months, depending on the time point concerned.

In conclusion, despite these limitations, the findings of this study suggest that ESL may be an effective and well-tolerated treatment

option for patients with PSE. ESL might also be useful for certain types of PSE patients, such as those with psychiatric comorbidities. These data warrant further investigation.

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## CONFLICT OF INTEREST

FS has received speaker's honoraria and/or consultancy fees from Bial and Eisai. JC has received speaker's honoraria and/or consultancy fees from Bial and Eisai, and a research bursary from Tecnifar. RM is a current employee of Eisai Europe Ltd. RL and HF are current employees of Bial – Portela & C<sup>a</sup>, SA. VV has participated in advisory boards and pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, Bial, Pfizer, GSK, Esteve, Novartis and GW Pharma.

## COMPLIANCE WITH ETHICAL STANDARDS

The Euro-Esli study protocol was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe, Valencia, Spain, as an extension of the local audit and the study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients included in Euro-Esli provided informed consent before entering the study.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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