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

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Summary

Objective: We assessed the efficacy and safety of once-daily eslicarbazepine acetate in comparison with twice-daily (BID) controlled-release carbamazepine (carbamazepine-CR) monotherapy in newly diagnosed focal epilepsy patients.

Methods: This randomized, double-blind, noninferiority trial (NCT01162460) utilized a stepwise design with 3 dose levels. Patients who remained seizure-free for the 26-week evaluation period (level A: eslicarbazepine acetate 800 mg/carbamazepine-CR 200 mg BID) entered a 6-month maintenance period. If a seizure occurred during the evaluation period, patients were titrated to the next target level (level B: eslicarbazepine acetate 1200 mg/carbamazepine-CR 400 mg BID, level C: eslicarbazepine acetate 1600 mg/carbamazepine-CR 600 mg BID) and the evaluation period began again. The primary endpoint was the proportion of seizure-free patients for 6 months after stabilization in the per protocol set. The predefined noninferiority criteria were −12% absolute and −20% relative difference between treatment groups.

Results: Eight hundred fifteen patients were randomly assigned; 785 (388 in the eslicarbazepine acetate group and 397 in the carbamazepine-CR group) were included in the per protocol set, and 813 (401 in the eslicarbazepine acetate group and 412 in the carbamazepine-CR group) were included in the full analysis set for the primary analysis. Overall, 71.1% of eslicarbazepine acetate–treated patients and 75.6% of carbamazepine-CR–treated patients were seizure-free for ≥6 months at the last evaluated dose (average risk difference = −4.28%, 95% confidence interval [CI] = −10.30 to 1.74; relative risk difference = −5.87%, 95% CI = −13.50 to 2.44) in the per protocol set. Rates of treatment-emergent adverse events were similar between groups for patients in the safety set. Noninferiority was also demonstrated in the full analysis set, as 70.8% of patients with eslicarbazepine acetate and 74.0% with carbamazepine-CR were seizure-free at the last evaluated dose (average risk difference = −3.07, 95% CI = −9.04 to 2.89).
1 | INTRODUCTION

A major goal of medical management for the >50 million adults and children worldwide with epilepsy is achieving seizure freedom with minimal or no adverse effects.\(^1\) For newly diagnosed patients, a monotherapy approach is preferred due to a lower risk of side effects, better compliance, and avoidance of pharmacokinetic and pharmacodynamic drug interactions.\(^2\) Because no single antiepileptic drug has yet been shown to be clearly superior in terms of efficacy or tolerability,\(^3\) clinicians must tailor the choice of drug to each patient—taking into account several patient factors such as age, comorbidities, and childbearing potential as well as drug characteristics such as tolerability and potential for drug interactions.\(^4,5\) Thus, we need more and better-tolerated antiepileptic drugs for use as monotherapy for improved individualization of treatment,\(^4\) namely to overcome the suboptimal characteristics of currently available treatments.

Once-daily (QD) eslicarbazepine acetate is a voltage-gated sodium channel blocker currently approved by the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), and Health Canada as an adjunctive therapy in adults for the treatment of focal onset seizures, and was granted FDA approval for monotherapy in the treatment of focal onset seizures in adults with or without secondary generalization in August 2015.\(^6\) FDA approval was based on evidence resulting from successful outcomes in 2 conversion-to-monotherapy trials in patients medically uncontrolled by 1 or 2 antiepileptic drugs.\(^7\) However, the EMA requires monotherapy studies to be randomized, double-blind active-controlled trials that aim to demonstrate at least a similar benefit/risk balance of the test product as compared to an acknowledged standard product at its optimal dose. Such guidance is endorsed by the International League Against Epilepsy (ILAE), which further recommends that active-controlled trials are conducted with a duration of at least 48 weeks, without forced exit criteria, and with efficacy assessment based on a minimum 24-week seizure freedom for all seizure types.\(^8\)\(^-\)\(^11\)

The objective of this phase III study was to demonstrate that monotherapy with QD eslicarbazepine acetate (800-1600 mg) was not inferior to monotherapy with twice-daily (BID) controlled-release carbamazepine (carbamazepine-CR; 200-600 mg) in adults with newly diagnosed focal onset seizures. Carbamazepine-CR is often used as first-line monotherapy for newly diagnosed epilepsy, and its efficacy and safety as monotherapy for focal onset seizures has been established by several class I studies.\(^3\)\(^-\)\(^14\)

2 | MATERIALS AND METHODS

2.1 | Study design

This phase III randomized, double-blind, noninferiority trial recruited patients from 170 clinical centers across 31 countries. The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines and approved by the independent ethics committee at each center before patient enrollment was commenced. The trial was designed in accordance with the recommendations of the EMA and the ILAE guidelines, which include a clinically meaningful outcome, a minimum duration of 1 year, and a flexible dosing design, to reflect clinical practice as close as possible. The study is registered with ClinicalTrials.gov and EudraCT (NCT01162460 and 2009-011135-13, respectively).
2.2 | Participants

Adult patients (≥18 years old) with newly diagnosed epilepsy were eligible for inclusion provided they had at least 2 well-documented, unprovoked, clinically evaluated and classified focal onset seizures (with or without secondary generalization) within 12 months of screening visit and at least 1 seizure during the previous 3 months. Patients had to have had an electroencephalogram and brain computerized axial tomography or magnetic resonance imaging (to exclude a progressive neurological lesion) in the previous 12 months. All patients needed to provide written informed consent before undergoing any study-related activities, and demonstrate cooperation and willingness to complete the study. Further details are given in online Methods supporting information (Table S1).

2.3 | Randomization and masking

Patients were randomly assigned in a 1:1 ratio to either eslicarbazepine acetate or carbamazepine-CR using a randomization schedule software (Rando; Accovion, Eschborn, Germany). Complete blocks were assigned dynamically to each study site to achieve balanced assignment of treatment groups within a site. A site-stratified block randomization was used with a block size of 4. Within each block, the same number of patients were allocated to each of the 2 treatment groups. The block size was not revealed to the site. To ensure blinding, both active treatments were identically overencapsulated and matching placebo capsules were provided so that the same numbers of oral capsules were taken in the double-blind setting. Patients, investigators, and clinical research and sponsor personnel, who administered medication, assessed outcomes, and analyzed data, were masked to the allocation until all data for the primary analysis were collected.

2.4 | Procedures

The study utilized a stepwise design with 3 predefined target doses for each treatment (Figure 1A). Randomized patients
received either eslicarbazepine acetate 400 mg QD (BIAL-Portela & Cª S.A., manufactured by Patheon, Toronto, Ontario, Canada) or carbamazepine-CR 200 mg QD (Novartis, Surrey, UK), before increasing to the first target dose level (dose level A: eslicarbazepine acetate 800 mg QD, carbamazepine-CR 200 mg BID). Patients who remained seizure-free for the 26-week evaluation period entered the maintenance period and a subsequent extension phase (both conducted under double-blind conditions). However, if a seizure occurred during the 26-week evaluation phase, the patient’s dose was escalated to dose level B (eslicarbazepine acetate 1200 mg QD or carbamazepine-CR 400 mg BID) within 7 days of the seizure and they started a second evaluation period. If a further seizure occurred in the level B evaluation period, patients’ doses were again escalated to level C (eslicarbazepine acetate 1600 mg QD or carbamazepine-CR 600 mg BID) and they began a third evaluation period. Patients who experienced a seizure during the evaluation period at dose level C, or at any dose during the maintenance period or the extension phases, were withdrawn from the study. Considering the 3 possible dose levels, the maximum trial duration was 121 weeks per patient. Patients recorded the number of seizures occurring on each day by date, time of occurrence, and duration in an electronic seizure diary.
2.5 | Outcomes

The primary endpoint was the proportion of patients who were seizure-free for the entire evaluation phase at the last evaluated dose level. Patients who dropped out during or before the evaluation phase were considered non–seizure-free. Secondary efficacy variables were: proportion of seizure-free patients during 1-year of treatment; time to first seizure at the last evaluated dose (treatment failure time); seizure characteristics of the first seizure during the evaluation period; treatment retention time (defined as the time to withdrawal due to adverse events [AEs] or lack of efficacy); dose level at which patients reached 26-week seizure freedom and changes in quality-of-life, assessed using the validated Quality of Life in Epilepsy Inventory-31 (QOLIE-31) survey.

Safety and tolerability were assessed by incidence of treatment-emergent AEs (TEAEs), and vital signs were recorded throughout the study. AEs were coded with the Medical Dictionary for Regulatory Activities (version 16.1). A 12-lead electrocardiographic (ECG) recordings, physical and neurological examinations, standard laboratory safety tests, Columbia Suicide Severity Rating Scale (C-SSRS), and Bond-Lader visual analogue scales (BL-VAS) were measured at prespecified time points.

2.6 | Populations analyzed

Population sets were defined as: (1) the full analysis set (FAS), which included all patients randomized who took at least 1 dose of study drug; (2) the per protocol set, which included all patients from the FAS without major protocol deviations (eg, did not meet inclusion criteria, or medication compliance with <80% or >120% of scheduled drug intake during the evaluation period); and (3) the per protocol subset (SPP), which included all patients in the per protocol set who completed the 26-week evaluation phase and 1-year maintenance phase. Safety was analyzed in the FAS. Dropouts were not excluded from any analysis set. Selected analyses were repeated for the SPP.

2.7 | Noninferiority margin and determination of sample size

The noninferiority margin was specified as a 12% absolute difference in proportions between treatment groups for the primary endpoint. The null hypothesis was rejected (proving noninferiority) if the 1-sided 97.5% confidence interval (CI) for difference in proportions (average risk difference [ARD]) did not exceed the prespecified noninferiority margin of –12% in the per protocol set. Based on the assumption that the proportion of patients who were seizure-free for 26 weeks would be 60%, a sample size of 360 patients per treatment group was estimated to have a power of at least 90% to establish noninferiority of eslicarbazepine acetate compared to carbamazepine-CR.

2.8 | Statistical analyses

All data were analyzed with SAS 9.4. Continuous variables are summarized using descriptive statistics and categorical variables are summarized by using frequency counts and percentages. Logistic regression with factors last evaluated dose and region was used for primary analyses. An estimate of the difference in seizure freedom, the average risk difference (ARD)\(^{15,16}\) of the primary endpoint, was calculated from the estimated logistic regression coefficients so that ARD is adjusted for stratification by the following 7 regions: Western Europe, Central Europe, Eastern Europe, Russia, Great Britain/Ireland/Australia, South America, and India. The multivariate delta method was used to calculate standard errors and CIs for ARD\(^{17,18}\). Noninferiority was demonstrated if the lower limit of the 1-sided 97.5% CI for ARD did not exceed the prespecified noninferiority margin of 12%. A prespecified sequential testing procedure ensures that the family wise error rate (2.5% 1-sided) is controlled; if noninferiority was shown in the per protocol set, subsequent tests for noninferiority and afterward for superiority were performed in the FAS. To ensure consistency between primary and secondary analyses, 2-sided 95% CIs are presented throughout, of which the lower limit corresponds to the 1-sided 97.5% CI of the primary test. As a secondary endpoint, the relative risk difference was defined as the ratio of the risk difference between both treatment groups and the proportion in the carbamazepine group and was compared in an exploratory manner against the noninferiority margin of –20%.

The statistical analyses focus on the events after start of last evaluated dose except for the treatment retention time and safety analyses, which include all observations after start of the first dose of dose level A. All patients with an unknown seizure status for the respective period (eg, due to early withdrawal) are considered as treatment failures for the estimation of risk differences. In the analysis of treatment failure and retention rates, withdrawals are classified. Patients who withdrew during the titration period were further excluded from the analysis of the treatment failure time. Further details are given in online Methods supporting information.

3 | RESULTS

Between the January 27, 2011 and September 24, 2015, a total of 929 patients were enrolled in the study, of whom
815 were randomized. Two patients randomized to carbamazepine-CR were discontinued from the study before receiving treatment (1 patient was unable to swallow the capsule, and 1 patient withdrew because study medication was delivered late to the study site). Baseline characteristics are presented in Table 1.

The majority of patients (eslicarbazepine acetate: 67.6%, carbamazepine-CR: 76.9%) remained on treatment at dose level A; 17.5% of eslicarbazepine acetate–treated patients and 14.8% of carbamazepine-CR–treated patients were treated at dose level B, and 15% of eslicarbazepine acetate–treated patients and 8.3% of carbamazepine-CR–treated patients were treated at dose level C. A similar proportion of patients (70.8% in the eslicarbazepine acetate group and 74.5% in the carbamazepine-CR group) completed the 26-week evaluation phase at their relevant dose (Table S2).

The most common reasons for discontinuation during the evaluation phase were AEs (Figure 1B). The overall proportions of seizure-free, discontinued, and uptitrated patients at each dose level are presented in Figure 2.

The primary objective of the study was met; treatment with eslicarbazepine acetate was noninferior to carbamazepine-CR (ARD = −4.28, 95% CI = −10.30% to 1.74), with 71.1% of patients classified as seizure-free at their last evaluated dose in the eslicarbazepine acetate group and 75.6% in the carbamazepine-CR group (per protocol set; Figure 3A,B). Noninferiority was also demonstrated in the FAS, as 70.8% of patients with eslicarbazepine acetate and 74.0% with carbamazepine-CR were seizure-free at the last evaluated dose (ARD = −3.07, 95% CI = −9.04 to 2.89). Sensitivity analyses performed in the SPP after excluding patients discontinuing the study for any reason not linked to efficacy supported the results for the per protocol and FAS (lower limit of 95% CI for ARD = −9.13%). The overall proportion of seizure-free patients at each dose level was similar in the eslicarbazepine acetate (54% for 800 mg, 11% for 1200 mg, and 6% for 1600 mg) and in the carbamazepine-CR groups (60% for 200 mg, 12% for 400 mg, and 4% for 600 mg; Figure 2).

In the per protocol population, QD eslicarbazepine acetate remained noninferior to BID carbamazepine-CR for seizure freedom during 1 year of treatment (ARD = −5.46, 95% CI = −11.88 to 0.97%), with 64.7% patients classified as seizure-free in the eslicarbazepine acetate group and 70.3% in the carbamazepine-CR group. Results were once again similar in the FAS (ARD = −4.72, 95% CI = −11.07 to 1.64%; Figure 3C,D).

At the end of the evaluation phase (day 182), the probability of treatment failure (ie, first seizure) was higher in the eslicarbazepine acetate group (12%) than in the carbamazepine-CR group (6%; Table 2). A post hoc analysis of time to treatment failure was conducted considering the

| Characteristic | ESL, N = 401 | CBZ-CR, N = 412 |
|---------------|-------------|----------------|
| Gender, n (%) | Male        | Female        |
|               | 228 (56.9)  | 220 (53.4)    |
| Age, y, mean (SD) | 37.6 (15.8) | 38.7 (16.3)    |
| Ethnicity, n (%) | Caucasian/white | 322 (80.3)          | 336 (81.6)          |
|               | African/black | 2 (0.5)        | 4 (1.0)             |
|               | Asian        | 37 (9.2)       | 36 (8.7)            |
|               | Other        | 40 (10.0)      | 36 (8.7)            |
| Body mass index, kg/m², mean (SD) | 25.2 (4.8) | 25.4 (5.1)    |
| Age at onset of epilepsy, y, mean (SD) | 37.3 (15.6) | 38.4 (16.4) |
| Time since last seizure, d, mean (SD) | 17.0 (18.5) | 18.5 (19.4) |
| Family history of epilepsy present, n (%) | 26 (6.5) | 24 (5.8)    |
| Etiology, n (%) | Idiopathic | Infectious diseases |
|               | 5 (1.2) | 6 (1.5)    |
|               | 8 (2.0) | 14 (3.4)  |
|               | 10 (2.5) | 9 (2.2)    |
|               | 8 (2.0) | 3 (0.7)   |
|               | 35 (8.7) | 45 (10.9) |
|               | 34 (8.5) | 34 (8.3)  |
|               | 1 (0.2) | 0           |
| Other | 33 (8.2) | 47 (11.2) |
| Unknown | 269 (67.1) | 256 (62.0) |
| Number of seizures during the 12 mo, mean (SD) | 20.0 (64.6) | 19.0 (65.0) |
| Simple partial | 8.5 (45.7) | 9.1 (53.1) |
| Complex partial | 9.8 (45.5) | 8.3 (34.6) |
| Partial evolving to secondarily generalized | 1.8 (2.8) | 1.6 (1.9) |
| Unclassified | 0 | 0          |
| Number of seizures during the previous 3 mos, mean (SD) | 7.5 (17.8) | 8.1 (33.3) |
| Total seizures | 2.9 (12.5) | 3.9 (30.1) |
| Complex partial | 3.4 (12.8) | 3.2 (14.7) |
| Partial evolving to secondarily generalized | 1.1 (1.3) | 1.0 (1.2) |
| Unclassified | 0 | 0          |

CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; n, number of patients in analysis set; SD, standard deviation.
end date to be the exact withdrawal date (instead of last intake of study medication, as this may be different due to visit scheduling) for all patients who discontinued due to other reasons. Under this criterion, the probability of treatment failure at the end of the evaluation phase remained slightly higher in the eslicarbazepine acetate versus the carbamazepine-CR group (7% vs 3%; Table 2). However, for both analyses, the lower limit of the 95% CI for the difference between groups was well above the 12% noninferiority margin set (Table 2).

Overall, the treatment retention time was similar between the treatment groups (Table 2) for patients in the FAS. The probability of patients withdrawing due to either AEs or lack of efficacy (eslicarbazepine acetate vs carbamazepine-CR) was 26% vs 21% at 1 year. For the lowest dose level, on which most patients remained throughout the study, treatment retention time was numerically superior for eslicarbazepine acetate compared to carbamazepine-CR. The probability of withdrawing treatment due to either AEs or lack of efficacy on dose level A (eslicarbazepine acetate 800 mg QD vs carbamazepine-CR 200 mg BID) was 14% vs 16% after 1 year (Table 2).

A similar proportion between treatment groups was found for seizure-free patients during the evaluation period by most frequent baseline seizure type (Table 2). Comparable improvements from baseline in the QOLIE-31 scores were observed at the maintenance period visit and the final endpoint visit (Table 2) for patients in the per protocol set.

Overall, the percentage of patients who experienced at least 1 TEAE was similar (eslicarbazepine acetate: 76.3%, carbamazepine-CR: 79.6%; Table 3) for patients in the safety set. Most TEAEs were of mild intensity, and the most frequently reported possibly related TEAEs (≥5% of total patients) were dizziness, headache, somnolence, fatigue, nausea, and increased \( \gamma \)-glutamyl transferase (GGT).

Overall, serious TEAEs and possibly related serious TEAEs were reported in a similar proportion of patients in both treatment groups for patients in the safety set. Most TEAEs were of mild intensity, and the most frequently reported possibly related TEAEs (≥5% of total patients) were dizziness, headache, somnolence, fatigue, nausea, and increased \( \gamma \)-glutamyl transferase (GGT).

Overall, serious TEAEs and possibly related serious TEAEs were reported in a similar proportion of patients in both treatment groups for patients in the safety set. The most frequently reported serious TEAEs included status epilepticus and epilepsy in the eslicarbazepine acetate group and syncope, convulsion, appendicitis, atrial fibrillation, head injury, inguinal hernia, partial seizures, and pulmonary embolism in the carbamazepine-CR group. At dose level C, 10 patients in the eslicarbazepine acetate group
and 1 in the carbamazepine-CR group reported serious TEAEs. Of these, only 2 cases were considered at least possibly related in the eslicarbazepine acetate group, and none in the carbamazepine-CR group. Both events (Adams-Stokes syndrome and atrioventricular block) occurred in the same patient. Four deaths were reported in the study (glioblastoma multiforme and cardiac arrest in the eslicarbazepine acetate group; suicide and lung adenocarcinoma in the carbamazepine-CR group); of these, only suicide in the carbamazepine-CR group was considered possibly related to treatment.

A lower percentage of patients discontinued treatment due to AEs in the eslicarbazepine acetate group (14.0% vs 18.4%; Table 3) for patients in the safety set. Of the most common events leading to treatment discontinuation (≥0.7 patients in any group), fatigue and disturbance in attention led to more patients discontinuing eslicarbazepine acetate, whereas more patients discontinued carbamazepine-CR due to allergic dermatitis, headache, convulsion, increased GGT, and hypersensitivity. Most patients in both treatment groups had sodium values > 130 mEq/L. Sodium levels ≤ 125 mEq/L were found in 1.5% patients in the eslicarbazepine acetate group and in 0.7% in the carbamazepine-CR group. Only 1 patient (in the carbamazepine-CR group) discontinued due to hyponatremia. No relevant changes over time or differences between the treatment groups were observed for the parameters of hematology, coagulation, and thyroid function or for bone turnover markers. More patients in the carbamazepine-CR group (25.7% vs 10.2%) had increased GGT values compared to baseline. Clinically significant increases (≥2 times the upper normal limit) of GGT values were more common in carbamazepine-CR patients (18.7% vs 10.2%) at any postbaseline visit. Although total bilirubin decreased over time at most postbaseline visits in both treatment groups, values remained within the normal range at endpoint for >93% of patients compared to baseline. Twelve events of leukopenia (4 with eslicarbazepine acetate group; 8 with carbamazepine-CR group) were identified; 2 patients have discontinued due to leukopenia in the carbamazepine-CR group, and there were no TEAEs leading to discontinuation (leukopenia) in the eslicarbazepine acetate group. There were no clinically
relevant changes over time or differences between treatment groups in vital signs, neurological examinations, or ECGs. Few patients in either treatment group reported suicidal ideation or behavior recorded via the C-SSRS, and improvement in suicidal ideation was similar between the groups at endpoint. Mean scores for alertness based on the BL-VAS improved similarly from baseline in both treatment groups.

### DISCUSSION

This phase III study demonstrated class I evidence for non-inferiority of QD eslicarbazepine acetate to BID carbamazepine-CR for seizure freedom rates. Effects were maintained over 1 year of treatment, and the consistency of the other secondary efficacy measures and sensitivity analyses support the robustness of our findings.

According to the guidelines of the EMA and the ILAE, this study used an established comparator, a clinically meaningful primary outcome, had a minimum total duration of 1 year, and used flexible dosing to mimic real-life practice as much as possible. Carbamazepine-CR was chosen as the active comparator because it is considered one of the primary standards of monotherapy treatment for patients with newly diagnosed epilepsy, and the doses chosen (200 mg BID, 400 mg BID, and 600 mg BID) were based on those used in previous head-to-head trials. The lowest dose of eslicarbazepine acetate (800 mg) was chosen on the basis of previous clinical studies where lower doses were not effective as add-on therapy. Previous experience with oxcarbazepine, another voltage-gated sodium channel blocker, has shown that higher doses may be required when used as monotherapy compared to add-on therapy. We therefore set the highest target dose of eslicarbazepine acetate at 1600 mg. Although this dose is higher than currently used for add-on therapy, it has been shown to be well-tolerated in healthy volunteers and studies of eslicarbazepine acetate for other indications.

In the present study, patients started at a low dose, which was slowly titrated over time, allowing patients to remain on the lowest effective dose. Most patients (eslicarbazepine acetate: 67.6%, carbamazepine-CR: 76.9%) remained on treatment at dose level A (eslicarbazepine acetate 800 mg QD or carbamazepine-CR 200 mg BID),

### TABLE 2 Secondary endpoints (per protocol set and full analysis set)

|                          | Per protocol set | Full analysis set |
|--------------------------|------------------|-------------------|
|                          | ESL, N = 388     | CBZ-CR, N = 397   |
| Probability of treatment failure at 26 wk, % | 12%              | 6%                |
| Probability of post hoc treatment failure at 26 wk, % | 7%              | 3%                |
| Probability of treatment retention on last evaluated dose level at 52 wk, % | 26%              | 21%               |
| Probability of treatment retention on lowest dose level at 52 wk, % | 14%              | 16%               |

Seizure freedom during the evaluation period by seizure type, n/M (%)^a^ | Simple partial | Complex partial | Partial evolving to secondarily generalized |
|---|---|---|
| 64/90 (71.1) | 84/110 (76.4) | 0.16 |

QOLIE-31 scores, mean (SD) | Score at baseline | Change from baseline to end of evaluation phase | Change from baseline to end of maintenance phase |
|---|---|---|
| 65.7 (14.9) | 5.7 (11.9) | 6.3 (12.3) |

Probability of treatment failure and retention was estimated as cumulative incidences taking withdrawals as censored into account. CBZ-CR, controlled-release carbamazepine; CI, confidence interval; ESL, eslicarbazepine acetate; n, number of patients seizure-free; N, number of patients in the analysis set; M, number of patients in the respective subgroup; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SD, standard deviation.

^aAverage risk difference by the most frequent baseline seizure type.
and only a small proportion of patients required uptitration to higher doses. However, more patients in the eslicarbazepine acetate group needed to be uptitrated to dose level C than in the carbamazepine-CR group. The treatment retention time by the last evaluated dose has been recommended as a valuable analysis to estimate the proportion of directly treatment-related discontinuations, as it combines aspects of efficacy, tolerability, and patient’s preference.27

For the lowest dose level, on which most patients remained throughout the study, treatment retention time was numerically superior for eslicarbazepine acetate compared to carbamazepine-CR, and this was mainly because patients

| Summary of TEAEs at last evaluated individual dose | ESL, N = 401, n (%) | CBZ-CR, N = 412, n (%) |
|---------------------------------------------------|---------------------|-----------------------|
| Any TEAE                                          | 306 (76.3)          | 328 (79.6)            |
| At least possibly related TEAEs                   | 169 (42.1)          | 212 (51.5)            |
| Any serious TEAE                                  | 43 (10.7)           | 49 (11.9)             |
| At least possibly related serious TEAEs           | 8 (2.0)             | 11 (2.7)              |
| TEAEs leading to discontinuation                   | 56 (14.0)           | 76 (18.4)             |

TEAEs considered at least possibly related to study drug [≥2% of patients in either treatment group]

| Dizziness                                         | 30 (7.5)            | 29 (7.0)              |
| Headache                                          | 27 (6.7)            | 28 (6.8)              |
| Somnolence                                        | 21 (5.2)            | 32 (7.8)              |
| Fatigue                                           | 20 (5.0)            | 18 (4.4)              |
| Nausea                                            | 18 (4.5)            | 30 (7.3)              |
| Gamma-glutamyl transferase increaseda              | 14 (3.5)            | 54 (13.1)             |
| Hypometrexa                                        | 10 (2.5)            | 4 (1.0)               |
| Hypothyroidismb                                   | 9 (2.2)             | 4 (1.0)               |
| Vertigo                                           | 8 (2.0)             | 13 (3.2)              |
| Vomiting                                          | 8 (2.0)             | 11 (2.7)              |
| Weight increased                                  | 8 (2.0)             | 15 (3.6)              |
| Alanine aminotransferase increased                | 2 (0.5)             | 9 (2.2)               |

TEAEs leading to discontinuation of study drug [≥0.7% of patients in either treatment group]

| Any event                                         | 56 (14.0)           | 76 (18.4)             |
| Fatigue                                          | 7 (1.7)             | 3 (0.7)               |
| Nausea                                           | 5 (1.2)             | 5 (1.2)               |
| Dizziness                                        | 4 (1.0)             | 4 (1.0)               |
| Rash                                             | 4 (1.0)             | 4 (1.0)               |
| Disturbance in attention                          | 3 (0.7)             | —                     |
| Somnolence                                       | 4 (1.0)             | 3 (0.7)               |
| Dermatitis allergic                               | 2 (0.5)             | 7 (1.7)               |
| Headache                                         | 3 (0.7)             | 5 (1.2)               |
| Convulsion                                        | 1 (0.2)             | 4 (1.0)               |
| Gamma glutamyl transferase increaseda             | 1 (0.2)             | 3 (0.7)               |
| Hypersensitivity                                  | —                   | 4 (1.0)               |

CBZ-CR, controlled-release carbamazepine; ESL, eslicarbazepine acetate; n, number of patients with events; N, number of patients in the analysis set; TEAE, treatment-emergent adverse event.

aReference value intervals (in U/L) were 8-36 and 8-61 in females and males, respectively.

bReference value intervals for total thyroxine, free thyroxine, triiodothyronine, free triiodothyronine, and thyroid-stimulating hormone were 66-181 (nmol/L), 12-22 (pmol/L), 1.23-3.07 (nmol/L), 2.93-7.83 (pmol/L), and 0.27-4.2 (μmol/L), respectively.
treated with carbamazepine-CR 200 mg had a higher probability of discontinuation due to an AE or lack of efficacy compared to patients treated with eslicarbazepine acetate 800 mg QD.

Due to its low potential for drug interactions, eslicarbazepine acetate has been recommended as adjunctive therapy for patients receiving polypharmacy.28 In the pivotal phase III (add-on) trials of eslicarbazepine acetate, most AEs were mild to moderate in severity and included dizziness, headache, somnolence, nausea, diplopia, and fatigue.19–21,29 This trial was conducted in the absence of pharmacodynamic and pharmacokinetic influences of concomitant antiepileptic drugs (thus reflecting a "cleaner" AE profile of the drug) and found a similar safety and tolerability profile. Hyponatremia and rash have been reported as common TEAEs in patients treated with eslicarbazepine acetate in clinical trials (3.0% and 3.2%, respectively).23 Of note, although more patients in the eslicarbazepine acetate group reported hyponatremia as possibly related to the study drug (2.5% vs 1.0%), only 1 patient (in the carbamazepine-CR group) discontinued due to this AE. Likewise, rash was reported as a TEAE in 3.2% of eslicarbazepine acetate–treated and 3.2% of carbamazepine-CR–treated patients (considered serious in 1 patient with carbamazepine-CR) and led to discontinuation in 4 patients per group.

Although rates of AEs were similar between the 2 treatment groups, it is notable that fewer patients discontinued eslicarbazepine acetate treatment (14.0%) compared with carbamazepine-CR (18.4%) and that this difference was primarily driven by lower rates of discontinuation due to AEs. Poor treatment adherence to medication is well known to be a major barrier to sustained remission and functional restoration.30 Because most studies to date have shown equivalent efficacy of available antiepileptic drugs,8,9,11,31–33 practical features such as good tolerability, a low potential for drug interactions, and ease of dosing are important drivers of medication choice.5 In this respect, the QD dosing regimen of eslicarbazepine acetate is of practical relevance, because recent "real-world" studies show that nonadherence to antiepileptic drugs is significantly more common with BID dosing versus QD dosing.34

Although noninferiority monotherapy trials are designed to closely resemble routine clinical practice, they have been criticized as having uncertain assay sensitivity (ie, the trial does not answer questions regarding the superiority of the active comparator agent over an inferior treatment or placebo in the current setting). However, they are currently the design preferred by the EMA, as they compare drugs as they are used in real life and in a manner that is more meaningful for physicians. In line with other recent monotherapy trials,8,11 we set an absolute noninferiority margin of 12% for the primary endpoint, which assumed a 20% relative margin to carbamazepine-CR, and a conservative risk of seizure recurrence in an unselected epilepsy population of 60%.35 However, the proportion of patients classified as seizure-free for the entire 26-week evaluation period was 75.6% for the carbamazepine-CR group (per protocol set). Using this higher rate of seizure freedom, the 20% relative difference would be 15%, which is the margin proposed by the EMA and ILAE.3,36 Thus, the lower limit of 10.3% achieved in this trial is above the conservative 12% noninferiority margin and is well above the 15% ILAE guidance.3,36 Furthermore, in the per protocol set, the lower limit of the 95% CI for ARD of the proportion of seizure-free patients for the 1-year maintenance phase in the eslicarbazepine acetate and carbamazepine-CR groups was −11.88%. Other study considerations are those inherent to all studies in early epilepsy such as rate of misdiagnosis and difficulties in assigning the cause and the type (eg, focal vs generalized epilepsy).

In conclusion, this large-scale, adequately powered study provides class I evidence that monotherapy with QD eslicarbazepine acetate (800-1600 mg) is noninferior to BID carbamazepine-CR (200-600 mg) in adults with newly diagnosed epilepsy experiencing focal onset seizures. Treatment with eslicarbazepine acetate at the study doses had a favorable safety and tolerability profile. Our findings suggest that eslicarbazepine acetate is a suitable treatment option for patients with newly diagnosed epilepsy with the advantage of having a QD formulation.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors participated in the design of the study. P.S.S. and J.F.R. participated in study implementation and data analysis. B.K. and K.L. were responsible for statistical analysis. All authors were involved in data interpretation and together discussed the initial ideas presented in the introduction and discussion of this article. ET was the principal coordinating investigator and wrote the first draft of the manuscript. E.B.-M., P.A.K., C.E., B.K., and K.L. made substantial contributions to revising the manuscript. J.F.R. and P.S.S. provided critical review. All authors approved the final submitted manuscript.

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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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