Safety and efficacy of eslicarbazepine acetate for seizure prevention in patients with stroke at high risk of developing post-stroke epilepsy: a proof-of-concept, phase 2a, randomised, double-blind, placebo-controlled antiepileptogenesis trial

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Summary

Background Eslicarbazepine acetate is an antiseizure medication that has shown potential antiepileptogenic effects in preclinical models of epilepsy. We aimed to investigate whether eslicarbazepine acetate could prevent or reduce the incidence of unprovoked seizures after acute ischaemic stroke or acute intracerebral haemorrhage.

Methods Study BIA-2093-213 was an exploratory, proof-of-concept, phase 2a, double-blind, randomised, placebo-controlled trial conducted in adults (aged ≥18 years) after an acute ischaemic stroke or acute intracerebral haemorrhage, who were considered at high risk of developing unprovoked seizures based on a severity of stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery (SeLECT) score of 5 or greater or a cortical involvement of intracerebral haemorrhage, age, volume, and early seizure after intracerebral haemorrhage (CAVE) score of 2 or greater. Patients were recruited from 19 university hospitals across Austria, Germany, Italy, Israel, Portugal, Spain, Sweden, and the UK, and eligible for inclusion if randomisation was planned within 96 h since the known time of stroke, or last time seen well (prolonged to 120 h to allow detection of acute seizures within 5 days post-stroke following a protocol modification implemented early in recruitment). Participants were randomly assigned (1:1) to receive eslicarbazepine acetate 800 mg/day or placebo, administered orally, for 30 days and followed up for 17 additional months. All patients who received one dose of study drug were included in safety and efficacy analyses. The primary endpoint was the proportion of patients who had a first unprovoked seizure, died, or discontinued (for any reason) within the first 6 months after randomisation. This trial is registered on the EudraCT database (EudraCT 2018-002747-29).

Findings Between May 29, 2019, and Feb 28, 2022, 129 patients were screened and 125 were randomly assigned (62 to eslicarbazepine acetate and 63 to placebo). The between-group difference for the primary endpoint (17 [28%] of 61 with eslicarbazepine acetate *vs* 23 [37%] of 62 with placebo) was not significant (odds ratio 0·66 [95% CI 0·31–1·40]; p=0·37). Treatment-emergent adverse events were reported with similar frequency in both eslicarbazepine acetate and placebo groups (50 [82%] of 61 *vs* 51 [82%] of 62). The most common treatment-emergent adverse events were hyponatraemia (five [8%] of 61 in the eslicarbazepine acetate group *vs* one [2%] of 62 in the placebo group), dizziness (three [5%] *vs* none). Serious treatment-emergent adverse events were reported in 12 (20%) patients in the eslicarbazepine acetate group and 13 (21%) in the placebo group. Three serious related treatment-emergent adverse events occurred in the eslicarbazepine acetate group (none in the placebo group): nodal arrhythmia, hepatic failure, and hyponatraemia (one patient each). Five patients died after randomisation (all in the eslicarbazepine acetate group), but deaths were deemed unrelated or unlikely to be related to the study drug.

Interpretation The proportion of patients who had a first unprovoked seizure, died, or discontinued at 6 months did not differ significantly between the eslicarbazepine acetate and placebo groups. However, the trial was underpowered owing to slow recruitment and the COVID-19 pandemic, producing wide confidence intervals. The findings indicate that antiepileptogenesis studies are feasible, and guide the design of adequately powered trials with clinically meaningful endpoints.

Funding BIAL.

Research in context

Evidence before this study

We searched PubMed using the terms "acute stroke", "intracerebral haemorrhage/hemorrhage", "post-stroke epilepsy", "post-stroke seizures", "antiseizure medication", "antiepileptic drug", "antiepileptogenic", and "antiepileptogenesis" in various combinations, for all articles published from database inception to June 20, 2025, filtering for clinical trials. These searches were supplemented with the authors' knowledge of previous clinical trials to allow assessment of the available evidence for the use of antiseizure medications to prevent seizures in the acute stroke setting. No treatments currently exist to prevent post-stroke epilepsy, partly because antiepileptogenesis studies in this setting are particularly challenging to conduct and partly because there are not enough data on the efficacy of antiseizure medications to prevent post-stroke epilepsy. Before the current study, only five randomised controlled trials on post-stroke epilepsy prevention were completed, none of which showed a clear antiepileptogenic effect for the study interventions. Preclinical models have shown a potential antiepileptogenic effect for the antiseizure medication eslicarbazepine acetate, but this has not previously been investigated in clinical research.

Added value of this study

Our Article presents the results of a randomised, double-blind, placebo-controlled trial exploring the potential antiepileptogenic effects of eslicarbazepine acetate in adults at high risk of developing unprovoked seizures after an acute intracerebral haemorrhage or acute ischaemic stroke. To address the challenges encountered in post-stroke epilepsy prevention trials (eg, the absence of validated biomarkers, the need for a large sample size and long follow-up, and uncertain optimal timing of intervention), a novel study design was used, including an enriched trial population with a high risk of post-stroke epilepsy at 18 months, and only a 4-week-long intervention period followed by long-term (17 months) observation.

Implications of all the available evidence

Our study further illustrates the challenges associated with designing and conducting an antiepileptogenesis trial but, importantly, shows that such trials are feasible in the acute post-stroke setting. This trial was underpowered, which was exacerbated by recruitment difficulties during the COVID-19 pandemic, with the primary composite outcome (ie, the proportion of patients who had a first unprovoked seizure, died, or discontinued within 6 months) not statistically significant. However, the event rate in controls was consistent with predictions based on the severity of stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery (SeLECT) and cortical involvement of intracerebral haemorrhage, age, volume, and early seizure after intracerebral haemorrhage (CAVE) scores, suggesting the validity of specifically enriching the study population with these scores among the eligibility criteria. Another important learning from our study is that future antiepileptogenesis trials should prioritise clinically meaningful endpoints, such as the number needed to treat and the relative risk reduction for unprovoked seizure occurrence, since these endpoints are most relevant to both patients and clinicians. Since most post-stroke seizures occur within the first year and later-onset seizures are generally more responsive to treatment, short-term intervention in the acute post-stroke phase (≤4 weeks with up to 12 months of follow-up) warrants further investigation.

Introduction

About 6% of stroke survivors develop post-stroke epilepsy—the most common cause of acquired epilepsy in high-income countries—accounting for 11% of all epilepsy cases and nearly half of new epilepsy diagnoses in individuals older than 60 years.[1–3] A latent interval of weeks to months typically precedes post-stroke epilepsy onset, offering a therapeutic window, yet no interventions have been shown to prevent post-stroke epilepsy.[4] The development of such interventions is therefore a major unmet need.[5,6]

Evidence to guide post-stroke epilepsy prevention is scarce, and current guidelines offer only weak recommendations.[7] Five clinical studies have evaluated antiseizure medications for primary prevention: valproic acid,[8] levetiracetam,[9,10] diazepam,[11] and perampanel.[12] Interventions ranged from 3 days (diazepam)[11] to 84 days (levetiracetam and perampanel),[9,12] with follow-up between 3 months (diazepam)[11] and 1 year.[8–10,12] None of these interventions showed a clear reduction in post-stroke seizures. However, a subgroup analysis in patients with anterior-circulation cortical infarcts showed a statistical difference in favour of diazepam,[13] and one small study (n=50) reported a significant reduction in the occurrence of early electrographic seizures with levetiracetam but this study was underpowered for clinical endpoints.[10] The second levetiracetam study enrolled only 16 participants, with only one patient (in the placebo group) developing post-stroke epilepsy.[9] An interim analysis of 82 patients included in the perampanel study showed very low event rates, with three post-stroke epilepsy cases, all in the placebo group (Patrick Kwan, Monash University, personal communication; trial registration number: ACTRN12618001984280). These studies highlight the challenges of antiepileptogenesis research, including low incidence rates, difficulties with recruitment, and limited power.

Eslicarbazepine acetate is a once-daily, voltage-gated sodium channel modulator approved for focal-onset seizures.[14,15] Preclinical studies have shown potential antiepileptogenic properties,[16,17] attributed partly to inhibition of $Ca_v3{\cdot}2$ T-type Ca^{2+} channels, which are

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See Online for appendix

critical mediators of epileptogenesis.[17–19] In a murine chronic epilepsy model, transient eslicarbazepine acetate exposure reduced epileptiform activity, axonal sprouting, neuronal damage, and behavioural impairment, suggesting disease-modifying effects.[16]

We aimed to investigate whether eslicarbazepine acetate could prevent or reduce the incidence of unprovoked seizures in people at high risk of developing post-stroke epilepsy after acute ischaemic stroke or acute intracerebral haemorrhage.

Methods

Study design and participants

Study BIA-2093-213 was an exploratory, proof-of-concept, phase 2a, double-blind, randomised, placebo-controlled, parallel-group trial done in patients at high risk of developing unprovoked seizures after an acute intracerebral haemorrhage or acute ischaemic stroke.[20] The trial was conducted at 19 university hospitals across Austria (n=4), Germany (n=6), Italy (n=2), Israel (n=2), Portugal (n=1), Spain (n=1), Sweden (n=1), and the UK (n=2). It was registered on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; 2018-002747-29), and conducted in accordance with the Declaration of Helsinki, valid national and local laws of the participating countries, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guideline for Good Clinical Practice (E6), and European Commission Directives 2001/20/EC and 2005/28/EC.[20] Ethics approval was obtained at all sites.[20]

Adults aged 18 years or older with acute ischaemic stroke or intracerebral haemorrhage were eligible if considered at high risk of post-stroke epilepsy based on a SeLECT (severity of stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery) score[21] of 5 or greater or a CAVE (cortical involvement of intracerebral haemorrhage, age, volume, and early seizure after intracerebral haemorrhage) score[22] of 2 or greater.[20] Randomisation was planned within 120 h of stroke onset or last known well time (appendix p 6).[20] Patients could receive all necessary standard stroke therapies (at any time during the study), according to local practice, and concomitant antiseizure medications except for eslicarbazepine acetate or oxcarbazepine through to day 30 only.[20] If concomitant antiseizure medications were not already discontinued before day 30, down-titration had to commence on day 31 at the latest.[20] All participants (or legal representatives) provided written informed consent.[20] Patient sex was self-reported (male or female, the latter with a sub-option for childbearing potential).

Randomisation and masking

Randomisation was done centrally with validated SAS software (version 9.4 or highest available).[20] A dedicated unmasked statistician (not involved in any other trial-related activities and not involved in the statistical analysis) was allocated to the trial, who was responsible for the creation of the randomisation list and documentation of the details of the process, which provides relevant information to allow for complete reproduction of the randomisation list. Eslicarbazepine acetate and placebo tablets were identical in size, colour, taste, and appearance, including packaging and labelling.[20] Each patient's investigational medicinal product (IMP) was assigned according to a random number. Each investigational site received IMP stock covering at least one full randomisation block, the size of which was not disclosed to investigators. Patients were randomly assigned by assigning the lowest available random number (IMP bottle) at the site. No stratification was applied. No one involved in the trial had access to the randomisation code before the blinding was officially broken. The success of masking was not formally assessed. Unblinding only occurred in the event of an emergency when knowledge of the patient's randomisation code could affect medical treatment (appendix p 3).[20]

Procedures

Following initial screening (visit 1a), participants were randomly assigned (1:1; visit 1b) to receive eslicarbazepine acetate 800 mg/day or placebo, administered orally and initiated within 120 h after primary stroke occurrence (appendix p 14).[20] Patients with moderate renal impairment (estimated glomerular filtration rate 30–60 mL/min per 1·73 m²) received eslicarbazepine acetate 400 mg/day or placebo.[20] Treatment continued until day 30, followed by tapering at the start of the 17 months of follow-up.[20] Following treatment initiation, further visits were done at 7 days (visit 2; on-site), 37 days (visit 3; on-site), 12 weeks (visit 4; telephone), 26 weeks (visit 5; on-site), 38 weeks (visit 6; telephone), 52 weeks (visit 7; on-site), 64 weeks (visit 8; telephone), and approximately 18 months (end of trial visit; on-site) after visit 1b. If all conditions for visit 1a (consent) and 1b (randomisation) were fulfilled, both visits were performed on the same day.[20] Participants or caregivers were instructed to report any seizure immediately and record details in a diary.[20] In addition to seizure reporting and patient diaries, at each scheduled trial visit participants (or caregivers) completed a standardised seizure questionnaire administered by study staff to verify diary entries, identify any unreported events, and collect information on seizure characteristics and associated symptoms.[20]

Key protocol modifications implemented early in recruitment included lowering eligibility thresholds (SeLECT from 6 to 5; CAVE from 3 to 2) and extending the randomisation window from 96 h to 120 h (appendix p 3).

Outcomes

The primary efficacy endpoint (assessed locally by the investigators) was the proportion of participants who had

a first unprovoked seizure, died, or discontinued for any reason within the first 6 months after randomisation (appendix p 7).

Secondary efficacy endpoints were the proportion of participants who had a first unprovoked seizure, died, or discontinued for any reason within 12 months and 18 months after randomisation, number of acute symptomatic seizures, probability of first unprovoked seizure, number of unprovoked seizures, functional outcomes (Barthel Index [BI] original 10-item version score;[23] US National Institutes of Health Stroke Scale [NIHSS] score[24]), depressive symptoms (Patient Health Questionnaire-9 [PHQ-9] score[25]), and overall survival. Only the first occurring event (ie, unprovoked seizure, died, or discontinued for any reason) contributed to composite rate analyses. For example, if a patient had an unprovoked seizure and died later, they were categorised as having an unprovoked seizure; if a patient had a re-stroke, they were categorised as a withdrawal, with the date of the re-stroke as the date of withdrawal. Overall survival was analysed with an intention-to-treat approach, where all deaths occurring after randomisation were considered events regardless of withdrawal status. Definitions of unprovoked seizures and acute symptomatic seizures are provided in the appendix (p 3).

Safety assessments included evaluation of treatment-emergent adverse events; laboratory parameters (haematology, biochemistry, estimated glomerular filtration rate, coagulation, all assessed centrally, urinalysis assessed locally with dipsticks); vital signs; ECG; physical and neurological examination; and PHQ-9 item 9 for suicidality. The study did not have an independent data safety monitoring board because at the time of the study eslicarbazepine acetate had already been on the market for several years with a known safety profile; no new adverse events were expected in the target population. Medical monitoring was conducted by the contract research organisation and two further medical monitors were appointed by the sponsor.

Statistical analysis

The trial was designed with a planned sample size of 200 randomly assigned participants (100 per group) to provide at least 80% power to detect a significant difference in the primary endpoint between placebo (expected to be 26% on the basis of historical data[21,22]) and eslicarbazepine acetate (expected to be 8%), using a two-sided 5% level of significance. The safety set and full analysis set included all randomly assigned patients who received at least one dose of study drug.[20]

6-month, 12-month and 18-month proportions of participants who had a first unprovoked seizure, died, or discontinued for any reason were analysed with a χ^2 test with continuity correction (appendix p 3).[20] Time to event outcomes were evaluated with Kaplan–Meier curves and log-rank testing. Cause-specific cumulative incidence curves were created to account for death as a competing risk before the first unprovoked seizure.[20] No multiplicity adjustments were applied.

Descriptive statistics summarised acute symptomatic seizures, unprovoked seizures, functional scales (BI, NIHSS), PHQ-9, baseline characteristics, and safety.[20] Additional measures of unprovoked seizure occurrence at 6, 12, and 18 months included incidence risk, absolute risk, absolute risk reduction (ARR; placebo minus eslicarbazepine acetate), relative risk (risk ratio [RR]; eslicarbazepine acetate divided by placebo), relative risk reduction (RRR; 1–RR), and number needed to treat (NNT; [1/ARR]×100; to avoid occurrence of one unprovoked seizure).

Prespecified subgroup analyses were conducted to compare the Kaplan–Meier cumulative incidence curves for unprovoked seizures by BI total score 80–100 at baseline (ability to live independently), BI total score of 79 or lower at baseline (dependent living), NIHSS total score less than 11 at baseline (mild and moderate stroke severity), NIHSS total score of 11 or greater at baseline (severe stroke severity), PHQ-9 total score of 4 or lower at baseline (minimal depression), and PHQ-9 total score greater than 4 at baseline (mild to severe depression).

Post-hoc analyses examined the proportions of participants who had a first unprovoked seizure, died, or discontinued for any reason over 18 months starting from 14 days after last study drug administration (not randomisation), corresponding to drug full washout (Kaplan–Meier and log rank tests). Only participants with data available beyond 14 days after last study drug

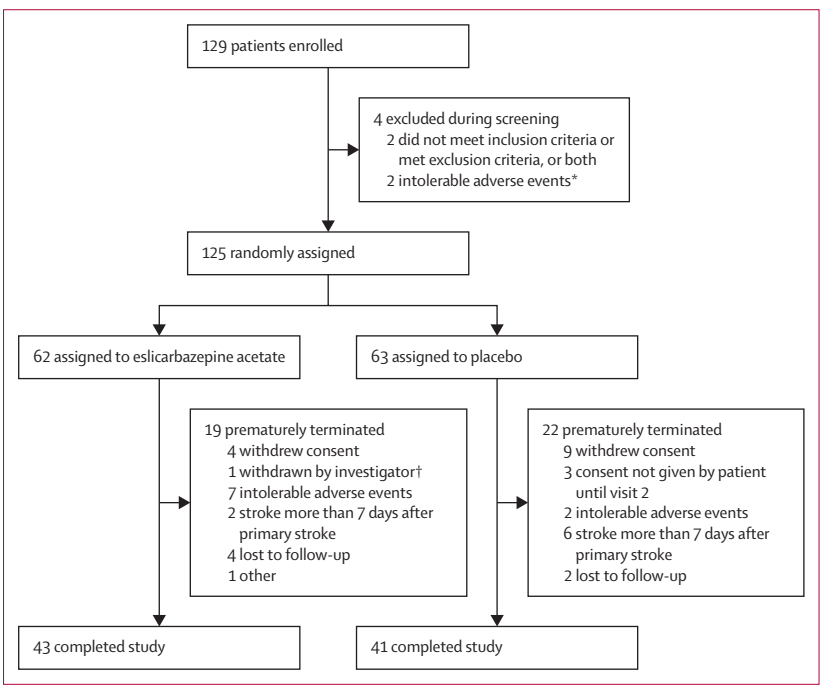

Figure 1: **Trial profile**
*Not specified to what agent; patients had not received any investigational drug yet. †In the investigator's opinion, for reasons of safety or ethics, continuation in trial would have been detrimental to the patient's wellbeing.

administration were included; those who had a first unprovoked seizure, died, or discontinued for any reason were excluded. Baseline characteristics of patients included in this analysis did not differ from those in the safety set (appendix p 8). Competing risk analyses assessed how accounting for death and withdrawal affected unprovoked seizure incidence estimates (sensitivity analyses). Two sets of analyses were conducted. First, Kaplan–Meier estimates of the occurrence of unprovoked seizures after 6, 12, and 18 months were compared against estimates calculated as a cumulative incidence function incorporating two competing risks: death alone and death and withdrawal (any reason). Second, competing risk regression was conducted with three Fine–Gray models with different considerations about deaths and withdrawals as competing risks for the occurrence of unprovoked seizures: both death and withdrawal as competing risks, death only as a competing risk with withdrawal censored; and no competing risks considered (Cox proportional hazards).

For the first competing risk analysis, Kaplan–Meier and cumulative incidence function estimates of the occurrence of unprovoked seizures after 6, 12, and 18 months were descriptively compared for incidence risk (ie, absolute risk), ARR, RR, RRR, and NNT. For the three competing risk regression analyses (Fine–Gray models), between-group differences (eslicarbazepine acetate *vs* placebo) in the occurrence of unprovoked seizures were calculated as competing risk regression coefficients, sub-distribution hazard ratios, standard errors, and respective p values. For the sub-distribution hazard ratios, the proportional hazards assumption was tested and assumed based on the non-significant p value of the Schoenfeld residual test (p=0·59).

All uncertainty estimates for ARR, RR, RRR, and NNT were derived via a non-parametric bootstrap procedure (5000 resamples). Bootstrap percentile 95% CIs were calculated. For NNT, two-sided percentile CIs were computed by inversion of the ARR limits ($NNT_{low}=1/ARR_{high}$; $NNT_{high}=1/ARR_{low}$) when both ARR limits were positive. When the bootstrap ARR 95% CI included zero ($ARR_{low} < 0 < ARR_{high}$), only the finite lower (best-case) limit, defined as $1/ARR_{high}$, was reported, with the upper limit considered unbounded.[26]

All statistical analyses were done with SAS software (version 9.4). Competing risk analyses were conducted with R software (version 4.3.1).

	Eslicarbazepine acetate (n=61)	Placebo (n=62)	Total (N=123)
Mean age, years	66·1 (14·5)	65·3 (13·9)	65·7 (14·2)
Age category, years			
≥18 to <65	30 (49%)	27 (44%)	57 (46%)
≥65 to <85	25 (41%)	33 (53%)	58 (47%)
≥85	6 (10%)	2 (3%)	8 (7%)
Sex			
Male	38 (62%)	40 (65%)	78 (63%)
Female	23 (38%)	22 (36%)	45 (37%)
Race			
White	57 (93%)	60 (97%)	117 (95%)
Black or African American	3 (5%)	1 (2%)	4 (3%)
Asian	1 (2%)	0	1 (1%)
Multiple	0	1 (2%)	1 (1%)
Acute ischaemic stroke	46 (75%)	47 (76%)	93 (76%)
Total SeLECT score			
Number of patients with data available	43	40	83
Median (IQR)	5·0 (5·0–6·0)	5·0 (5·0–6·0)	5·0 (5·0–6·0)
Acute intracerebral haemorrhagic stroke	15 (25%)	15 (24%)	30 (24%)
Total CAVE score			
Number of patients with data available	14	15	29
Median (IQR)	3·0 (3·0–3·0)	3·0 (3·0–3·0)	3·0 (3·0–3·0)
Patients with any concomitant antiseizure medication	10 (16%)	15 (24%)	25 (20%)
Types of concomitant antiseizure medications			
Levetiracetam	5 (8%)	6 (10%)	11 (9%)
Diazepam	4 (7%)	1 (2%)	5 (4%)
Midazolam	2 (3%)	3 (5%)	5 (4%)
Lorazepam	0	3 (5%)	3 (2%)
Clonazepam	2 (3%)	0	2 (2%)
Gabapentin	1 (2%)	1 (2%)	2 (2%)
Valproic acid	0	1 (2%)	1 (1%)
Zonisamide	0	1 (2%)	1 (1%)

Data are n (%), unless otherwise indicated. Percentages might not total 100 due to rounding. CAVE=cortical involvement of intracerebral haemorrhage, age, volume, and early seizure within 7 days of intracerebral haemorrhage. SeLECT=severity of stroke, large artery atherosclerosis, early seizure, cortical involvement, and territory of the middle cerebral artery.

Table 1: **Demographic and baseline characteristics of the safety set**

Role of the funding source

The sponsor and funder of the trial (BIAL) was involved in study design, data collection and analysis, data interpretation, and writing of the report. No patient-level data were available to the sponsor and funder.

Results

Between May 29, 2019, and Feb 28, 2022, 129 individuals were screened and 125 were randomly assigned (62 to eslicarbazepine acetate and 63 to placebo; figure 1). Overall, 123 participants received at least one study dose (61 in the eslicarbazepine acetate group and 62 in the placebo group). Completion rates at 18 months were 69% (43 of 62) for eslicarbazepine acetate and 65% (41 of 63) for placebo. 41 (33%) participants prematurely terminated the trial, with similar proportions in both groups (figure 1). Most early terminations occurred before visit 3 (24 [19%]): ten (16%) in the eslicarbazepine acetate group and 14 (22%) in the placebo group (appendix p 7).

The mean age was 65·7 (SD 14·2) years and 78 (63%) of 123 patients were male (table 1). Ischaemic stroke accounted for 76% (93 of 123) of cases and intracerebral haemorrhage accounted for 24% (30 of 123). Recruitment began on May 29, 2019, and the sponsor decided to close recruitment in Feb 28, 2022, owing to

slow accrual during the COVID-19 pandemic and because recruitment had not progressed as initially estimated despite the protocol modification extending the randomisation window. This decision was not based on safety concern or circumstance related to the study drug. The last follow-up visit was on Sept 11, 2023. The median treatment duration was 36·0 (IQR 18·0–37·0) days (mean 28·2 [SD 12·5]) for eslicarbazepine acetate and 37·0 (27·0–37·0) days (mean 29·6 [12·9]) for placebo. The median eslicarbazepine acetate dose was 724·3 (IQR 571·4–800·0) mg/day (mean 678·7 [SD 139·0]).

Baseline characteristics were generally balanced, except for lower concomitant antiseizure medication use in the eslicarbazepine acetate groups versus placebo group (ten [16%] of 61 *vs* 15 [24%] of 62). Use of short-acting benzodiazepines (diazepam, midazolam, lorazepam, and clonazepam) for acute symptomatic seizures (none given prophylactically) or other indications was similar in both groups (eight [13%] of 61 with eslicarbazepine acetate *vs* seven [11%] of 62 with placebo). Levetiracetam was the most frequently used concomitant antiseizure medication as standard of care, with comparable distribution (five [8%] of 61 in the eslicarbazepine acetate group *vs* six [10%] of 62 in the placebo group). Median SeLECT and CAVE scores were similar (SeLECT: 5·0 [IQR 5·0–6·0] for both; CAVE: 3·0 [3·0–3·0] for both; table 1). No difference was observed in stroke severity, large artery atherosclerosis, cortical involvement and territory of the middle cerebral artery, or early seizures (appendix p 9).

The between-group difference in the primary endpoint (ie, the proportion of participants who had a first unprovoked seizure, died, or discontinued for any reason at 6 months) was not significant: 28% (17 of 61; two unprovoked seizures, three deaths, 12 withdrawn) for eslicarbazepine acetate and 37% (23 of 62; seven unprovoked seizures, no deaths, 16 withdrawn) for placebo (p=0·37). The risk difference (RD) for the primary endpoint was –0·09 (95% CI –0·26 to 0·08) and the OR was 0·66 (95% CI 0·31 to 1·40; figure 2).

The between-group differences of participants who had a first unprovoked seizure, died, or discontinued for any reason (secondary endpoints) were 19 (31%) of 61 in the eslicarbazepine acetate group versus 26 (42%) of 62 in the placebo group (RD –0·11 [95% CI –0·28 to 0·07]; OR 0·63 [95% CI 0·30 to 1·31]) at 12 months and 23 (38%) of 61 versus 27 (44%) of 62 (RD –0·06 [–0·24 to 0·12]; OR 0·78 [0·38 to 1·61]) at 18 months (figure 2). The Fine–Gray model, considered the most conservative and clinically realistic, yielded a hazard ratio favouring eslicarbazepine acetate (eslicarbazepine acetate *vs* placebo) of 0·54 (95% CI 0·18–1·60; appendix p 11).

The probability of first unprovoked seizure (a secondary endpoint) did not differ between groups (table 2; appendix p 15). ARRs for unprovoked seizure occurrence were 8·01% (95% CI –1·67 to 17·72) after 6 months, 7·99% (–1·77 to 17·72) after 12 months, and 6·32% (–5·05 to 17·66) after 18 months. Compared to placebo, RRs for an unprovoked seizure for eslicarbazepine acetate were 0·29 (95% CI 0·00 to 1·19) after 6 months, 0·38 (0·00 to 1·36) after 12 months, and 0·56 (0·12 to 1·63) after 18 months, which relates to RRRs of 71% (95% CI –19 to 100) after 6 months, 62% (–36 to 100) after 12 months, and 44% (–63 to 100) after 18 months (table 2).

The proportion of patients who had at least one unprovoked seizure over 18 months (a secondary endpoint) was numerically lower with eslicarbazepine acetate versus with placebo (five [8%] of 61 *vs* nine [15%] of 62); in these patients, the mean number of unprovoked seizures was numerically lower for eslicarbazepine acetate versus placebo (1·8 [SD 0·8] *vs* 2·2 [2·3]; table 2). The NNT (95% CI) to prevent one case of post-stroke epilepsy was 12 (6 to infinity [Inf]) at 6 months,

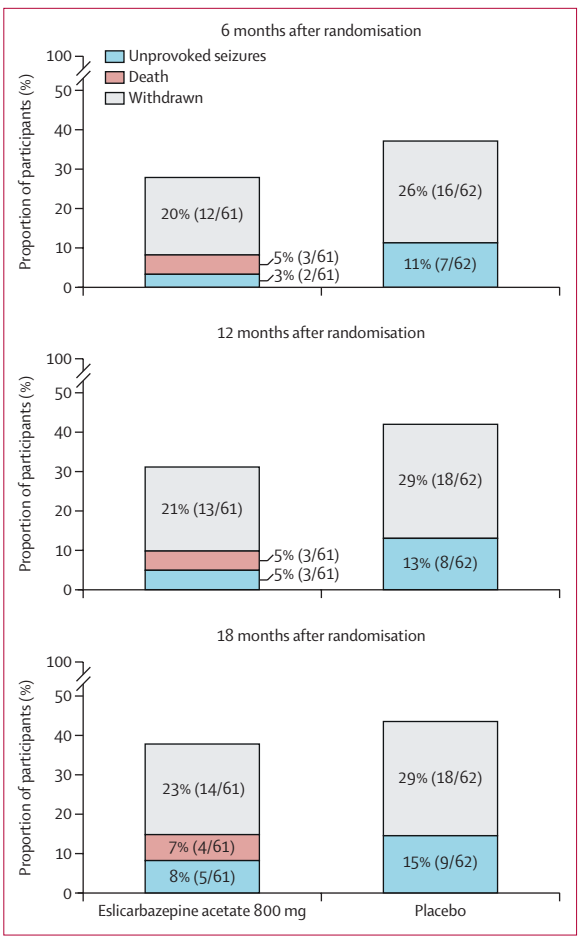

Figure 2: **Proportion of participants who had a first unprovoked seizure, died, or discontinued for any reason 6, 12, and 18 months after randomisation in the full analysis set**

One patient treated with eslicarbazepine acetate who died after an intracranial haemorrhage (re-stroke) was categorised according to the first occurring event under "withdrawn" rather than "death". RD=risk difference (eslicarbazepine acetate minus placebo).

	Eslicarbazepine acetate (n=61)	Placebo (n=62)
Probability of first unprovoked seizure by timepoint (95% CI)		
Estimated probability of first unprovoked seizure within 6 months	3·5% (0·0 to 9·0)	14·6% (5·7 to 25·4)
Estimated probability of first unprovoked seizure within 12 months	5·7% (0·0 to 13·0)	16·9% (6·7 to 28·4)
Estimated probability of first unprovoked seizure within 18 months	10·3% (2·3 to 19·8)	19·2% (8·6 to 31·3)
Number of patients who completed the 6-month period	46 (75%)	46 (74%)
Unprovoked seizures (6 months)		
Number of unprovoked seizures	2 (3%)	7 (11%)
Incidence risk (95% CI)	3·3% (0·0–8·2)	11·3% (4·8 to 19·4)
Absolute risk reduction (95% CI)	8·01% (–1·67 to 17·72)	..
Relative risk (95% CI)	0·29 (0·00 to 1·19)	..
RRR (95% CI)	71% (–19 to 100)	..
NNT (95% CI)	12 (6 to Inf)	..
Number of patients who completed the 12-month period	45 (74%)	41 (66%)
Unprovoked seizures (12 months)		
Number of unprovoked seizures	3 (5%)	8 (13%)
Incidence risk (95% CI)	4·9% (0·0 to 11·5)	12·9% (4·8 to 21·0)
Absolute risk reduction (95% CI)	7·99% (–1·77 to 17·72)	..
Relative risk (95% CI)	0·38 (0·00 to 1·36)	..
RRR (95% CI)	62% (–36 to 100)	..
NNT (95% CI)	13 (6 to Inf)	..
Number of patients who completed the 18-month period	43 (71%)	41 (66%)
Unprovoked seizures (18 months)		
Number of unprovoked seizures	5 (8%)	9 (15%)
Incidence risk (95% CI)	8·2% (1·6 to 16·4)	14·5% (6·5 to 24·2)
Total number of unprovoked seizures (all patients), mean (SD); median (IQR)	0·1 (0·5); 0 (0·0 to 0·0)	0·3 (1·1); 0 (0·0 to 0·0)
Total number of unprovoked seizures (patients who had ≥1 unprovoked seizure), mean (SD); median (IQR)	1·8 (0·8); 2·0 (1·0 to 2·0)	2·2 (2·3); 1·0 (1·0 to 2·0)
Absolute risk reduction (95% CI)	6·32% (–5·05 to 17·66)	..
Relative risk (95% CI)	0·56 (0·12 to 1·63)	..
RRR (95% CI)	44% (–63 to 100)	..
NNT (95% CI)	16 (6 to Inf)	..
Acute symptomatic seizures		
Patients with ≥1 acute symptomatic seizure	10 (16%)	15 (24%)
Total number of acute symptomatic seizures, mean (SD); median (IQR)	1·3 (0·7); 1·0 (1·0 to 1·0)	1·1 (0·5); 1·0 (1·0 to 1·0)
BI total score		
Baseline score, n; mean (SD); median (IQR)	61; 66·1 (36·2); 85·0 (25·0 to 100·0)	62; 61·9 (40·1); 72·5 (20·0 to 100·0)
Endpoint* score, n; mean (SD); median (IQR)	53; 87·5 (27·3); 100·0 (95·0 to 100·0)	50; 93·6 (16·1); 100·0 (100·0 to 100·0)
Change from baseline to endpoint*, n; mean (SD); median (IQR)	53; 18·1 (32·4); 5·0 (0·0 to 45·.0)	50; 25·1 (31·9); 7·5 (0·0 to 50·0)
Total score differences (95% CI)†	0·0 (0·0 to 10·0)	..

(Table 2 continues on next page)

13 (6 to Inf) at 12 months and 16 (6 to Inf) at 18 months (table 2).

The proportion of patients who had at least one acute symptomatic seizure (a secondary endpoint) was ten (16%) of 61 eslicarbazepine acetate versus 15 (24%) of 62 with placebo. The mean total number of acute symptomatic seizures was similar (1·3 [SD 0·7] *vs* 1·1 [0·5]; table 2).

Overall survival (a secondary endpoint) did not differ between groups (table 2). 40 (66%) patients in the eslicarbazepine acetate group and 38 (61%) patients in the placebo group were censored (ie, overall survival data were unavailable as the patients discontinued before day 548). Five patients died after randomisation (all in the eslicarbazepine acetate group); four (7%) were included in the efficacy analysis and one died after reaching the primary composite endpoint in the safety analysis. All deaths were deemed unrelated or unlikely to be related to study drug (52–423 days after the last dose). Causes included pulmonary sepsis, aspiration pneumonia, pneumonia, re-stroke, and multiorgan dysfunction.

BI total score, NIHSS total score, and PHQ-9 score were also assessed as secondary endpoints. The median BI total score was higher for eslicarbazepine acetate versus placebo at baseline and increased during the study in both groups (table 2). The estimated probability, based on the Kaplan–Meier model, of unprovoked seizure occurrence was similar between groups with a BI total score of 80–100 at baseline (eslicarbazepine acetate *vs* placebo: 6·0% *vs* 8·0% at 6 months, 10·0% *vs* 12·0%, at 12 months, and 15·0% *vs* 12·0% at 18 months), but numerically lower with eslicarbazepine acetate among those scoring 79 or lower (eslicarbazepine acetate *vs* placebo: 0·0% *vs* 22·0% at 6 months, 0·0% *vs* 22·0% at 12 months, and 5·0% *vs* 27·0% at 18 months; appendix pp 4, 16). NIHSS total scores were similar between groups at baseline and improved comparably during the study (table 2). Estimated unprovoked seizure probability was numerically lower with eslicarbazepine acetate versus placebo in patients with NIHSS total scores of 11 or greater (eslicarbazepine acetate *vs* placebo: 0·0% *vs* 13·0% at all timepoints) and less than 11 at baseline (eslicarbazepine acetate *vs* placebo: 6·0% *vs* 15·0% at 6 months, 10·0% *vs* 19·0% at 12 months, and 17·0% *vs* 22·0% at 18 months; appendix pp 4, 17). PHQ-9 scores were stable and similar between groups (table 2). Eslicarbazepine acetate was associated with a lower estimated probability of unprovoked seizures versus placebo among participants with PHQ-9 scores greater than 4 at baseline (eslicarbazepine acetate *vs* placebo: 0·0% *vs* 41·0% at 6 months and 12 months, and 6·0% *vs* 41·0% at 18 months), but not in those with PHQ-9 scores of 4 or lower (eslicarbazepine acetate *vs* placebo: 6·0% *vs* 3·0% at 6 months, 10·0% *vs* 6·0% at 12 months, and 14·0% *vs* 9·0% at 18 months; appendix pp 4, 18).

The overall incidence of treatment-emergent adverse events was similar between groups (50 [82%] of 61 with eslicarbazepine acetate *vs* 51 [82%] of 62 with placebo) as was the incidence of serious treatment-emergent adverse events (12 [20%] of 61 with eslicarbazepine acetate *vs* 13 [21%] of 62 with placebo; table 3). Treatment-related treatment-emergent adverse events (ie, treatment-emergent adverse events with causality "definite", "probable", "possible", or "missing") were more common with eslicarbazepine acetate than with placebo (23 [38%] of 61 *vs* 12 [19%] of 62), with the most common being hyponatraemia (five [8%] of 61] *vs* one [2%] of 62) and dizziness (three [5%] of 61 *vs* none). Three serious treatment-related adverse events occurred in the eslicarbazepine acetate group: nodal arrhythmia, hepatic failure, and hyponatraemia. Study drug discontinuation due to treatment-emergent adverse events was higher with eslicarbazepine acetate versus placebo (16 [26%] of 61 *vs* six [10%] of 62), with the most common being dizziness and hyponatraemia (both two [3%] of 61 *vs* none). Sex-specific safety findings are reported in the appendix (pp 4, 13).

Six deaths occurred during the trial. One patient died before randomisation (myocardial infarction) and five died after randomisation (all in the eslicarbazepine acetate group): two were deemed as treatment-emergent adverse events leading to death (pulmonary sepsis and aspiration pneumonia), but neither were considered related to eslicarbazepine acetate treatment; three patients had events with a fatal outcome, but these were deemed as non-treatment-emergent adverse events (pneumonia, intracranial haemorrhage [re-stroke], and multiple organ dysfunction syndrome [52, 101, and 423 days after the last study drug intake, respectively]). The patient who died after an intracranial haemorrhage (re-stroke) was categorised according to the first occurring event as withdrawn in the efficacy analysis.

Among the patients reporting hyponatraemia over the course of the trial, at endpoint, sodium concentrations between 130 mmol/L to less than 135 mmol/L were observed in four (8%) patients treated with eslicarbazepine acetate and none in the placebo group. At endpoint, no patients reported sodium concentrations lower than 125 mmol/L, nor did any have a decrease from baseline greater than 10 mmol/L (see appendix p 4 for other safety findings). No new safety concerns emerged.

A post-hoc sensitivity analysis of unprovoked seizure occurrence over 18 months by stroke type (acute ischaemic stroke and acute intracerebral haemorrhagic stroke) revealed no difference between eslicarbazepine acetate versus placebo in either stroke subgroup (appendix p 10). Given the relatively small number of patients with intracerebral haemorrhagic stroke, the study was underpowered to detect modest between-group differences in the efficacy of eslicarbazepine acetate after acute ischaemic stroke versus intracerebral haemorrhagic stroke.

A post-hoc Kaplan–Meier analysis of the composite event rate over 18 months beginning 14 days after the last drug administration (ie, after complete washout[14]) showed a favourable, although non-significant, trend for eslicarbazepine acetate versus placebo (appendix p 19). In the placebo group, unprovoked seizures occurred from baseline onwards, whereas in the eslicarbazepine acetate group, seizure onset generally occurred more than 250 days after washout. This analysis was intended to assess potential disease-modifying rather than purely symptomatic effects.

Overall, there were no significant differences between groups in the post-hoc analysis, but post-hoc competing-risk analyses yielded lower ARRs, higher RRs, and lower RRRs when both death and withdrawal were treated as competing events, compared with analyses using death only or standard Kaplan–Meier approaches (death and withdrawal as censoring; appendix p 11). NNT values also increased but continued to favour eslicarbazepine acetate. Fine–Gray modelling also showed a trend favouring eslicarbazepine acetate, although with a higher hazard ratio than the models with death alone or no parameters considered as competing (appendix p 11).

	Eslicarbazepine acetate (n=61)	Placebo (n=62)
(Continued from previous page)		
NIHSS		
Baseline score, n; mean (SD); median (IQR)	61; 8·5 (5·6); 7·0 (4·0 to 13·0)	62; 8·8 (6·1); 8·0 (4·0 to 13·0)
Endpoint* score, n; mean (SD); median (IQR)	53; 2·9 (3·9); 2·0 (0·0 to 4·0)	45; 1·5 (3·0); 0·0 (0·0 to 1·0)
Change from baseline to endpoint*, n; mean (SD); median (IQR)	53; –5·9 (5·5); –5·0 (–10·0 to –1·0)	45; –6·5 (5·8); –5·0 (–10·0 to –2·0)
Total score differences (95% CI)†	0·0 (–3·0 to 2·0)	..
PHQ-9		
Baseline score, n; mean (SD); median (IQR)	57; 3·7 (3·3); 4·0 (1·0 to 5·0)	54; 3·4 (4·4); 2·0 (0·0 to 5·0)
Endpoint* score, n; mean (SD); median (IQR)	53; 4·1 (4·0); 3·0 (1·0 to 6·0)	48; 4·3 (5·3); 2·0 (0·0 to 6·5)
Change from baseline to endpoint*, n; mean (SD); median (IQR)	51; 0·5 (4·6); 0·0 (–2·0 to 3·0)	46; 0·7 (6·1); 0·0 (–2·0 to 3·0)
Total score differences (95% CI)†	0·0 (–1·0 to 2·0)	..
Overall survival (18 months)		
Patients who died	4 (7%)‡	0
Patients who were censored§	40 (66%)¶	38 (61%)

ARR=absolute risk reduction (placebo minus eslicarbazepine acetate). BI=Barthel Index. Inf=infinity. NIHSS=US National Institutes of Health Stroke Scale. NNT=number needed to treat. PHQ-9=Patient Health Questionnaire-9. RR=risk ratio (eslicarbazepine acetate *vs* placebo). RRR=relative risk reduction (1 minus RR). *Endpoint was the last non-missing value collected after the first study drug intake. †Analysis of total score differences (placebo minus eslicarbazepine acetate) based on Wilcoxon-Mann-Whitney test. ‡All deaths were deemed to be unrelated or unlikely to be related to eslicarbazepine acetate. §Censored=data on overall survival were not available as the patient discontinued before day 548. ¶One patient who died after an intracranial haemorrhage (re-stroke) was categorised as censored (see appendix p 3).

Table 2: **Summary of secondary endpoint results in the full analysis set**

	Eslicarbazepine acetate (n=61)	Placebo (n=62)	Total (N=123)
Patients with at least one TEAE	50 (82%)	51 (82%)	101 (82%)
Most frequently reported TEAEs*			
Hypertension	10 (16%)	13 (21%)	23 (19%)
Headache	4 (7%)	8 (13%)	12 (10%)
Insomnia	4 (7%)	5 (8%)	9 (7%)
Constipation	3 (5%)	6 (10%)	9 (7%)
Urinary tract infection	4 (7%)	5 (8%)	9 (7%)
Depression	3 (5%)	4 (7%)	7 (6%)
Hypokalaemia	4 (7%)	3 (5%)	7 (6%)
Hyponatraemia	6 (10%)	1 (2%)	7 (6%)
Atrial fibrillation	4 (7%)	3 (5%)	7 (6%)
Dizziness	4 (7%)	0	4 (3%)
Patients with at least one treatment-related TEAE†	23 (38%)	12 (19%)	35 (29%)
Most frequently reported treatment-related TEAEs‡			
Hyponatraemia	5 (8%)	1 (2%)	6 (5%)
Dizziness	3 (5%)	0	3 (2%)
Increased hepatic enzyme	2 (3%)	1 (2%)	3 (2%)
Disturbance in attention	2 (3%)	0	2 (2%)
Decreased high-density lipoprotein	2 (3%)	0	2 (2%)
Nausea	2 (3%)	0	2 (2%)
Depression	0	2 (3%)	2 (2%)
Patients with at least one serious TEAE	12 (20%)	13 (21%)	25 (20%)
Patients with at least one serious related TEAE†	3 (5%)	0	3 (2%)
Types of serious related TEAEs			
Nodal arrhythmia	1 (2%)	0	1 (1%)
Hepatic failure	1 (2%)	0	1 (1%)
Hyponatraemia	1 (2%)	0	1 (1%)
Patients with at least one severe TEAE	9 (15%)	8 (13%)	17 (14%)
Patients with TEAEs leading to death	2 (3%)	0	2 (2%)
Types of TEAEs leading to death			
Pulmonary sepsis	1 (2%)	0	1 (1%)
Aspiration pneumonia	1 (2%)	0	1 (1%)
Patients with TEAEs leading to discontinuation of study drug	16 (26%)	6 (10%)	22 (18%)
TEAEs most frequently leading to discontinuation of study drug‡			
Dizziness	2 (3%)	0	2 (2%)
Hyponatraemia	2 (3%)	0	2 (2%)

Data are n (%). TEAE=treatment-emergent adverse event. *At least 5% of patients in any group. †Treatment-related TEAEs were those with causality "definite", "probable", "possible", or "missing". ‡At least 2% of patients in any group.

Table 3: **Summary of treatment-emergent adverse events in the safety set**

Discussion

In this exploratory phase 2a study, designed to investigate the antiepileptogenic potential of eslicarbazepine acetate for the prevention of post-stroke epilepsy, the primary outcome was not statistically significant. However, there was some evidence to suggest that the risk of unprovoked seizures might have been reduced after 30 days of eslicarbazepine acetate treatment—a secondary outcome in the trial—at 6, 12, and 18 months following stroke (71%, 62%, and 44%, respectively), although the 95% CIs were wide and included zero. These findings warrant further investigation of eslicarbazepine acetate in adequately powered trials.

There remains insufficient evidence for the efficacy of antiseizure medications in the primary prevention of post-stroke epilepsy.[27] Antiepileptogenesis studies are challenging to conduct due to the absence of validated biomarkers, the need for a large sample size, long follow-up, and uncertain optimal timing of intervention.[20,28] Only five randomised controlled trials of potential antiepileptogenic therapies had been completed before this study, none showing clear benefit, largely due to minimal efficacy of the antiseizure medications or underpowered sample sizes.[8–11,13,27] The present study was designed to address challenges associated with other antiepileptogenesis studies.[20]

The COVID-19 pandemic exacerbated recruitment difficulties, when face-to-face research activities in this severely ill study population were restricted, necessitating early recruitment termination. Only 125 participants out of a target population of 200 were randomly assigned, which resulted in the trial being underpowered. Importantly, after protocol adjustments and lifting of the lockdown restrictions, recruitment stabilised, and long-term follow-up losses were minimised.

Despite reduced power, there was a trend favouring eslicarbazepine acetate treatment. The 12-month incidence of unprovoked seizures in placebo-treated patients (13%) closely matched published reports for individuals with a SeLECT score of 5–6 (5 being the median score in our study), supporting the validity of our enrichment strategy and study design.[21] By targeting high-risk patients (SeLECT score ≥5), the study was feasible with a planned sample size of 200. Approximately 20% of the original SeLECT cohort (742 of 3911 patients) fell into this category,[21] representing an estimated 300 000 high-risk individuals in Europe in 2025.[29] The 12-month incidence of unprovoked seizures in patients treated with eslicarbazepine acetate (5%) approximated rates for individuals with SeLECT scores of 3–4,[21] indicating that, theoretically, eslicarbazepine acetate might shift stroke patients into a lower-risk category of developing post-stroke epilepsy.

The recruitment window of 4–5 days after primary stroke ensured early randomisation and treatment initiation, which are important for any antiepileptogenesis intervention, but precluded full application of the original SeLECT score, particularly the criterion of "seizure less than or up to 7 days ago". Patients who might have reached a score of 5 or 6 based on seizures occurring on days 6 or 7 were not captured. However, data from the

SeLECT registry show that 94% of acute symptomatic seizures occur within 5 days (92% within 4 days),[30] indicating that our inclusion criteria closely approximated the intended population. Extending the treatment initiation window from 96 h to 120 h facilitated consent in the acute setting without materially affecting outcomes. Moreover, the risk of unprovoked seizures is highest when acute symptomatic seizures occur on the day of stroke onset (adjusted HR 2·3) compared with later seizures, and remains relatively stable for seizures occurring on days 2–7.[30] Thus, enrolment within 120 h was unlikely to introduce major variability in epilepsy risk.

The optimal dose and duration of eslicarbazepine acetate for a prophylaxis effect are unknown. We used the standard dose for focal-onset epilepsy treatment (800 mg/day)[14] although a single fixed dose might be viewed as a limitation. Treatment was intentionally limited to 4 weeks to avoid interference with post-stroke recovery. This short exposure period, together with a composite efficacy endpoint, might have reduced the ability to detect differences in unprovoked seizures between groups. The treatment duration was informed by preclinical evidence showing antiepileptogenic effects with 6 weeks of eslicarbazepine acetate treatment in a mouse model.[16] In designing this first-in-human antiepileptogenesis trial, it was essential to allow sufficient follow-up beyond the treatment phase to distinguish transient seizure-suppressing effects from true antiepileptogenic mechanisms. For the 6-month primary endpoint, our design provided an approximate 1:5 treatment-to-observation ratio, which is appropriate given that most post-stroke seizures and epilepsy cases occur within this timeframe. Extending the treatment period could have increased the risk of interfering with neurological recovery and reduced the ability to detect a lasting effect.

Interpretation of the primary endpoint must account for the 95% CIs of the RDs and ORs. 95% CIs crossed the null, meaning no effect cannot be ruled out. However, given the limited sample size and low event rates, this might represent a false negative result. Importantly, the 95% CIs for the primary endpoint are asymmetrical in the direction favouring eslicarbazepine acetate, suggesting a potential effect that larger trials might be able to detect. Similar considerations apply to the 12-month and 18-month composite proportions.

One important limitation was the conservative nature of the primary composite endpoint, which included all deaths and withdrawals regardless of cause. As the first clinical evaluation of the antiepileptogenic potential of eslicarbazepine acetate, this approach prioritised safety but reduced sensitivity for detecting treatment effects. Competing risk analyses were only performed post hoc. Because death and post-stroke epilepsy represent competing risks, excluding mortality could bias interpretation. All deaths occurred in the eslicarbazepine acetate group, but adjudication established that none was related to eslicarbazepine acetate or occurred after treatment cessation.

Results of the competing risk analyses demonstrated the impact of withdrawals on unprovoked seizure occurrence, showing that when competing risks are present but not accounted for, Kaplan–Meier methods can misrepresent event probabilities and inflate apparent treatment effects, emphasising the importance of using suitable competing-risk models. The Fine–Gray model, considered the most conservative and clinically realistic, yielded a hazard ratio of 0·54 (95% CI 0·18–1·60), still favouring eslicarbazepine acetate. These findings demonstrate that observed trends persist even under conservative assumptions.

Another major limitation is the uncertainty around expected treatment effect, as this was the first study to test eslicarbazepine acetate clinically for antiepileptogenesis. Based on the observed 6-month seizure incidences (3% with eslicarbazepine acetate *vs* 11% with placebo), a future adequately powered phase 2b/3 trial would require 181 participants per group (Fisher's Exact Test) for 80% power and α=0·05, not accounting for potential dropout rates. A further limitation is that the study did not allow for any conclusions to be made about race, as known Han Chinese or Thai ancestry was an exclusion criterion for the study, due to the possible presence of the human leukocyte antigen *(HLA)-B*1502* allele and its association with the risk of developing a severe cutaneous reaction when treated with carbamazepine.[14]

Despite the acknowledged challenges in designing and conducting an antiepileptogenesis trial, in particular recruiting high-risk stroke patients during a global pandemic, this exploratory proof-of-concept study shows the feasibility of antiepileptogenesis trials in acute stroke. No new safety concerns emerged. Retention was high (>65%). Key design features included early exposure after stroke, placebo control in addition to standard of care, rigorous and relatively long follow-up after short post-stroke intervention, and risk enrichment with SeLECT and CAVE criteria, with expected event rates observed in the placebo group.[21,22] Protocol modifications introduced some heterogeneity but were generally conservative. Despite these limitations, consistent trends suggest a possible antiepileptogenic effect of eslicarbazepine acetate in high-risk stroke survivors. Lessons from this study can inform future research: early engagement with patients, families, and stroke care teams is essential for optimising recruitment acceptability; pragmatic inclusion criteria and flexible follow-up strategies can reduce attrition and increase generalisability; adaptive or stepped-wedge designs might enable refinement of interventions in real time; feasibility and implementation outcomes, including adherence and clinician uptake, should accompany traditional efficacy measures; and enhanced monitoring

systems and digital tools could improve data completeness and participant engagement.

In conclusion, future antiepileptogenesis trials should emphasise clinically meaningful endpoints such as NNT and the RRR for unprovoked seizure occurrence, the outcome of greatest relevance to patients and clinicians.[31] Our findings suggest that future phase 2b or 3 trials could limit follow-up to 12 months without compromising the assessment of key outcomes, provided that treatment does not exceed 4 weeks. Because most post-stroke epilepsy events occurred within the first year, and later-onset (>12 months) post-stroke epilepsy is generally more treatment-responsive,[32] short-term intervention in the acute post-stroke phase warrants further investigation.

Contributors

MJK, ET, GC-F, AK, VDF, and MMF were responsible for data analysis as well as drafting, editing, and critical revisions of manuscript. Y-HM, CB, SK, GLG, JMS, JZ, RS, FB, WL, MG, LMM, HG, NP, and JH were responsible for editing and critical revisions of manuscript. JM was responsible for data analysis, editing and critical revisions of the manuscript. DR was responsible for data analysis and critical revisions of the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit the manuscript for publication; all investigators (MJK and ET also participated in the blind data review meeting), JM, LMM, GC-F, HG, AK, and MMF verified the data in the study.

Declaration of interests

MJK reports personal fees as a speaker or consultant from Arvelle, BIAL, Eisai, GW Pharmaceuticals, Novartis, and UCB Pharma. ET reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Alexion, Medtronic, BIAL, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, STOKE Therapeutics, and Actavis. ET is also co-director of the European Consortium on Epilepsy Trials (ECET). ET's institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. Y-HM is supported by an NIHR Senior Clinical and Practitioner Research Award (NIHR304523) and declares no competing interests related to this work. CB reports personal fees as a speaker or consultant from Angelini Pharma, BIAL, LivaNova, Medtronic, Tecnifar, and Eisai. SK reports personal fees as a speaker or consultant from Angelini, Bial, Desitin, Eisai, Jazz Pharma, Merck Serono, and UCB Pharma. GLG reports personal fees from Angelini, Neuraxpharm, and Idorsia, and institutional support from Roche and Penta. JMS reports personal fees as a consultant or advisor from Arvelle Therapeutics, Angelini, BIAL, Eisai, Jazz Pharmaceuticals, Sanofi, UCB Pharma; and speaker honoraria from Arvelle Therapeutics, Angelini, BIAL, Eisai, Jazz Pharmaceuticals, Sanofi, and UCB Pharma. JZ reports speaker honoraria for unbranded lectures and personal fees from Eisai, UCB, Orion Pharma, and Anglini Pharma, and as an employee of Sahlgrenska University (no personal compensation) being an investigator or sub-investigator in clinical trials sponsored by UCB, GW Pharma, Bial, and SK Life Science, and personal fees for advisory board for Sanofi. RS is part funded by the UCLH Biomedical Research Centre. JM, LMM, and GC-F were employees of Bial at the time of the study. HG, VDF, NP, DR, and JH are employed by Bial. MMF is employed by BIAL. AK is employed by Scope International, which was contracted by BIAL as a contract research organisation for the study.

Data sharing

This manuscript does not include identifiable data. The data that support the findings of this study are available from the corresponding author upon reasonable request. Data are not publicly available due to privacy or ethical restrictions.

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