SYNOPSIS

Title of trial:

Prevention of epilepsy in stroke patients at high risk of developing unprovoked seizures: anti-epileptogenic effects of eslicarbazepine acetate

Trial number: BIA-2093-213

EudraCT number: 2018-002747-29

Sponsor details:

Bial - Portela & C[a], S.A.
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4745-457 Coronado (S. Romão e S. Mamede), Portugal
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Name of finished product: Eslicarbazepine acetate (BIA 2093)

Name of active ingredient: Eslicarbazepine acetate (ESL)

Investigators:

The trial was conducted in 19 active sites in 7 European countries and Israel: Austria (4 sites), Germany (6 sites), Italy (2 sites), Israel (2 sites), Portugal (1 site), Spain (1 site), Sweden (1 site) and in the United Kingdom (2 sites).

Publication (reference):

Koepp MJ, Trinka E, Mah YH, Bentes C, Knake S, Gigli GL, Serratosa JM, Zelano J, Magalhães LM, Pereira A, Moreira J, Soares-da-Silva P. Antiepileptogenesis after stroke-trials and tribulations: Methodological challenges and recruitment results of a Phase II study with eslicarbazepine acetate. Epilepsia Open. 2023 Sep;8(3):1190-1201. doi: 10.1002/epi4.12735. Epub 2023 Jun 12. PMID: 36944588; PMCID: PMC10472381.

Studied period (years):

Date of first enrolment: 29-MAY-2019
Date of last patient completed: 11-SEP-2023

Reporting period:

This report includes the data of the final analysis stage. For the reporting period, please refer to the dates of the studied period.

Phase of development: IIa

Background and rationale:

About 5-15% of all stroke patients experience a seizure within 2 years of stroke and stroke is the most common cause of epilepsy in the elderly population. Post-stroke seizures are classified according to their temporal occurrence after acute stroke in acute symptomatic seizures (ASSs, occurring up to 7 days after stroke) and unprovoked seizures (USs, occurring more than 7 days after acute stroke). Unprovoked seizures have a frequency peak within 6 to 12 months after stroke and common predictors for USs are stroke severity, cortical involvement, and ASSs. The occurrence of one US after stroke is considered epilepsy according to the current classification of the International League Against Epilepsy (ILAE) as the probability of further seizures within the subsequent 10 years is approximately 71.5%.

Eslicarbazepine acetate (BIA 2-093) is approved as monotherapy for adult patients newly diagnosed with focal-onset epilepsy and adjunctive therapy for the treatment of focal-onset seizures in patients above 6 years of age (both with or without secondary generalisation, approved in patients above 4 years by the FDA) in several countries worldwide. From preclinical data, it was concluded that transitory ESL treatment attenuates the functional and morphological sequelae of status epilepticus and thus has a possible anti-epileptogenic effect. The anti-epileptogenic properties of ESL might be explained by the inhibition of the neuronal T-type Ca^{2+} channel $Ca_V3.2$ which plays a major role in epileptogenesis.

Based on these experimental results and the need for further research in this area, the trial was planned to investigate the anti-epileptogenic effect of prophylactic ESL treatment in stroke patients at high risk for USs.

Objectives:

Primary:

The primary objective of this trial was to assess if ESL treatment (started within 96 hours after stroke occurrence* and continued for 30 days) changed the incidence of USs within the first 6 months after randomisation compared to placebo.

Secondary:

Efficacy

1. To assess if ESL treatment (started within 96 hours after stroke occurrence* and continued for 30 days) changes the incidence of USs within the first 12 months after randomisation compared to placebo
2. To assess if ESL treatment (started within 96 hours after stroke occurrence* and continued for 30 days) changes the incidence of USs during the trial until 18 months after randomisation compared to placebo
3. To assess the number of ASSs

To assess the effect of ESL treatment over an 18-month follow-up period on:

4. Time to first US after randomisation

   Time to first US after stroke occurrence (omitted with statistical analysis plan [SAP], Final version 1.0, 22-NOV-2023)
5. Number and 4-week rate of USs (4-week rate of USs was omitted with SAP, Final version 1.0, 22 NOV 2023)
6. Functional outcome, assessed by Barthel Index original 10-item version (BI)
7. Functional outcome, assessed by the National Institutes of Health Stroke Scale (NIHSS)
8. Post-stroke depression, assessed by Patient Health Questionnaire (PHQ-9)
9. Overall survival

* Based on the clinical trial protocol (CPT) Final Version 3.0, 20-JAN-2020, ESL treatment had to be started within 120 hours after stroke occurrence.

Safety

10. Treatment emergent adverse events (TEAEs) incl. findings from physical and neurological examinations
11. Laboratory parameters
12. Vital signs
13. Electrocardiogram (ECG)
14. Suicidal ideation and behaviour, assessed by PHQ-9 (question 9)

Exploratory

15. Electroencephalogram (EEG), optional assessment

Methods:

This was a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial in patients with acute intracerebral haemorrhage with a CAVE score ≥ 3 or an acute ischaemic stroke with a SeLECT score ≥ 6. With CPT Final Version 3.0, 20-JAN-2020, patients at high risk of developing USs after acute intracerebral haemorrhage or an acute ischaemic stroke could be included; the CAVE and SeLECT scores were no longer used as eligibility criteria.

At the first visit (screening/baseline, V1a, Day 3 to 1), patients underwent several examinations to check eligibility. The next visit (V1b) had to be performed within 96 hours after the primary stroke occurrence (based on CTP Final Version 3.0, 20-JAN-2020, V1a and V1b were to be performed within 120 hours after the primary stroke occurrence, or since the last time seen well). After eligibility had been confirmed, patients were randomised (randomisation ratio 1:1) to treatment with ESL 800 mg or placebo. Patients could receive therapies for stroke treatment according to local clinical practice at any time during the trial.

Patients were to start treatment with the investigational medicinal product (IMP) at V1b and treatment was to be continued until Day 30 after randomisation and then be tapered off. Thereafter, patients were followed up until 18 months after randomisation. Patients could concomitantly receive anti-seizure medication, except commercially available ESL or oxcarbazepine until Day 30.

Patients who had the first US were to discontinue IMP treatment and were to be treated at the discretion of the investigator until 18 months after randomisation, except with commercially available ESL.

Further visits were performed 7 days (V2, on-site), 37 days (V3, on-site), 12 weeks (V4, telephone), 26 weeks (V5, on-site), 38 weeks (V6, telephone), 52 weeks (V7, on-site), 64 weeks (V8, telephone) and 78 weeks (End of Trial [EoT] visit, on-site) after V1b. Due to the Coronavirus disease 2019 (COVID-19) pandemic, visits V3/early discontinuation visit (EDV), V5, V7, and EoT could be performed as telephone visits. Patients who discontinued trial participation prematurely were to be asked to come to the site for an EDV.

Patients or their caregivers (as applicable) were instructed to contact the site immediately after a seizure and to document seizure information in the patient diary.

Number of patients (planned and analysed)

Number of Patients	**Number of Patients**
Planned to be screened	220
Planned to be randomised	200
Enrolled	129
Randomised	125
Withdrawn from the study	41
Completed the study	84
Analysed (full analysis set; efficacy)	123
Analysed (safety set)	123

Following sponsor's decision, recruitment was closed by the end of February 2022, since due to the unforeseen COVID-19 pandemic circumstances, recruitment had not progressed as initially estimated, this already taking in consideration revised and extended timelines. This decision was not based on safety concerns or circumstances related to the IMP.

Diagnosis and main criteria for inclusion and exclusion:

Male or female patients aged 18 years or above with an acute intracerebral haemorrhage or acute ischaemic stroke at high risk for USs could be included in the trial if the time of stroke occurrence was known and V1b was planned within 96 hours after stroke occurrence (within 120 hours after primary stroke occurrence, or since last time seen well based on CTP Final Version 3.0, 20-JAN-2020).

Patients with a history of previous stroke (with a clinical cerebral cortical stroke within the last 2 years since CTP Final Version 3.0, 20-JAN-2020), a history of USs prior to the primary (index) stroke, a modified Rankin Scale (mRS) score > 3 prior to first stroke occurrence, a history of anti-seizure medication (ASM) use before primary stroke within the last 5 years ASM use within the last 2 years with CTP Final Version 3.0, 20JAN2020) were not eligible for this trial.

Paediatric regulatory details:

Not applicable.

Measures of protection of patients taken:

Eslicarbazepine acetate (BIA 2-093) is an approved once-daily ASM for the treatment of focal-onset (focal-onset) seizures in adults and children above 6 years of age. This trial was conducted in compliance with the trial protocol, by trial personnel, qualified by education, training, and experienced in their roles. The patients were closely monitored during the trial. Patients who discontinued trial participation prematurely were asked to come to the site for an EDV to exclude the possibility of an adverse event (AE) being the cause and otherwise to assess if the AE had any potential relationship to the trial medication. Serious AEs (SAEs) which were still ongoing after the patient's final visit were to be followed up and follow-up information was to be recorded by the investigators. In case of SAEs detected after the end of the observation period, the investigator was instructed to contact the sponsor to determine how to document and report these SAEs.

In case of unusual symptoms or questions, the patients could always contact the investigator and arrange an unscheduled visit. The planned trial procedures, standard examinations, and questionnaires did not pose a risk to the patients other than those associated with assessments in general common clinical practice.

Test products, dose and mode of administration, batch number:

Tablets for oral administration containing 800 mg ESL each were used in this trial. The dosing was as follows: Patients with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2 were to take 1 tablet once daily (800 mg ESL). Patients with moderate renal impairment at V1a, defined as eGFR 30 - 60 mL/min/1.73 m^2 were to take half a tablet once daily (400 mg ESL). As soon as eGFR had improved to > 60 mL/min/1.73 m^2, the dose was to be increased to 1 tablet once daily (800 mg ESL). Patients developing moderate renal impairment during IMP intake were to be adjusted to 400 mg, if applicable. Worsening of renal function with an eGFR < 30 mL/min/1.73 m^2 had to lead to discontinuation of IMP intake (dose independent) without down-titration (see CTP Final Version 3.0, 20-JAN-2020).

If one or more ASS(s) occurred within 7 days after the primary stroke, this was not to result in a change of IMP dose. In case a patient had a US during IMP intake, IMP had to be discontinued (including a 7-day down-titration, if applicable) and the patient was to be treated at the discretion of the investigator until 18 months after randomisation, except with commercially available ESL.

Batch number: 190005

Duration of treatment:

Treatment with IMP started at V1b and was to be continued for 30 days. Afterwards, patients taking 1 tablet once daily (800 mg ESL or placebo) had to be down-titrated for 7 days before stopping intake of IMP i.e. those patients were to take half a tablet (400 mg ESL or placebo) from Day 31 to Day 37. Patients taking half a tablet once daily (400 mg ESL or placebo) on Day 30 did not require down-titration i.e. they took the last IMP on Day 30.

Reference therapy, dose and mode of administration, batch number:

Placebo tablets for oral administration, matching the test product. For dosing instruction please refer to Paragraph “Test products, dose and mode of administration, batch number”.

Batch number: 190006

Endpoints:

<u>Primary efficacy endpoint</u>

The proportion of patients who experienced the first US within the first 6 months after randomisation (failure rate). Deaths before the first US or patients without evaluable assessment of the primary endpoint were also counted as treatment failures.

Secondary efficacy endpoints

1. Proportion of patients who experienced the first US during the first 12 months after randomisation (12 months failure rate; same criteria for treatment failure rate as for the primary endpoint)
2. Proportion of patients who experienced the first US during the trial - until 18 months after randomisation (18 months treatment failure rate; same criteria for failure rate as for the primary endpoint)
3. Number of ASSs
4. Time to first US after randomisation

   Time to first US after stroke occurrence (omitted with SAP, Final version 1.0, 22-NOV-2023)
5. Number and 4-week rate of US (4-week rate of USs was omitted with SAP, Final version 1.0, 22-NOV-2023)
6. BI
7. NIHSS
8. PHQ-9
9. Overall survival

Secondary safety endpoints

10. TEAEs including findings from physical and neurological examinations
11. Laboratory parameters (haematology and biochemistry, including eGFR and coagulation, urinalysis)
12. Vital signs
13. ECG
14. Suicidal ideation and behaviour, assessed by PHQ-9 (question 9)

Exploratory endpoints

15. EEG, optional

Statistical methods:

The **safety set** was defined as all patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients were assigned to treatment groups as treated.

The **full analysis set (FAS)** was defined as all patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients were assigned to treatment groups as randomised.

The **per-protocol set (PPS)** was defined as all patients of the FAS without any major PDs and with verbal witnessed or signed written consent. Patients were assigned to treatment groups as randomised.

All analyses of the primary efficacy endpoint were performed in the FAS and PPS. As this is a proof-of-concept study, corresponding p-value from primary efficacy analysis shall be considered exploratory.

The primary efficacy endpoint was the proportion of patients who experienced the first US within 6 months (until Day 182) after randomisation (failure rate). First US within the first 6 months, deaths before the first US and patients without evaluable assessment of the primary endpoint were counted as treatment failures. The first occurring event was used for this analysis e.g. if a patient experienced a US and died later, this patient was included as a patient with a US. If a patient experienced a re-stroke, the patient was counted as a withdrawal with the date of re-stroke as 'Date of withdrawal'.

The primary efficacy endpoint was assessed in the FAS by using a Chi-square test with continuity correction on the significance level of 5% (two-sided), which corresponds to one-sided 2.5% to compare the proportion of treatment failures between both arms. The odds ratio for ESL vs. placebo and corresponding 95% Confidence Interval (CI) were provided. The risk difference between ESL and placebo with corresponding 95% continuity-corrected Newcombe CI was also calculated. Additionally, the p-value of Fisher's exact test was provided.

Sensitivity analyses were conducted to assess the impact of missing data and to analyse the group differences in terms of observed USs only.

Secondary efficacy analyses were based on the FAS and PPS and were considered in an explanatory manner.

The same statistical analysis employed for the primary efficacy endpoint was used for the analysis of the 12-month failure rate (until Day 365) and the 18-month failure rate (until Day 547 or scheduled EoT). Sensitivity analyses were conducted to assess the impact of missing data and to analyse the group differences in terms of observed USs only. The number of ASSs and USs were summarised by means of descriptive statistics by treatment group and in total.

The time to first US after randomisation was analysed and presented by a Kaplan Meier plot (including censored data e.g. withdrawals) for all trial data collected during 18 months after randomisation and a log-rank test was conducted.

Bathel index, NIHSS, and PHQ-9 total scores and their changes from baseline at each time of examination were summarised using summary statistics. Differences between the treatment groups were planned to be evaluated exploratively using the exact Wilcoxon-Mann-Whitney Test and exact Hodge-Lehmann CIs at each time of examination. In addition, subgroup analyses of cumulative incidence curves of USs for the BI, NIHSS and PHQ-9 total scores by category were presented by Kaplan-Meier curves.

Overall survival was analysed and presented by Kaplan-Meier curves (including censored data e.g. withdrawals) for all trial data collected during 18 months after randomisation to assess the survival rates.

Categorical data such as defined TEAE categories and terms, physical, neurological and ECG examination findings were summarised by default frequency tabulations (number and percentage of patients), while continuous data such as vital signs parameter were displayed by default summary statistics on absolute values and changes from baseline. All laboratory values were summarised by default frequency tabulations (number and percentage of patients) and by default summary statistics.

Suicidal ideation and suicidal behaviour as assessed by the PHQ-9 question 9 were summarised by the number and frequency of patients in each response category.

The analyses of all safety endpoints were based on the safety set.

Following the current recommendation of the International League Against Epilepsy, the terms anti-epileptic drug (AED) and anti-epileptic therapy were changed to anti-seizure medication (ASM) in this study report but not in the statistical output. Additionally, the acronym "AS" for acute symptomatic seizures was changed to "ASS" and the term anti-convulsant was changed to anti-seizure.

SUMMARY OF RESULTS

PATIENT DISPOSITION:

A total of 129 patients were enrolled at 19 active trial centres in Europe and Israel. Of these, 125 patients were randomised. According to the protocol, approximately 200 patients (1:1) should have been randomised in this study. Following a sponsor's Executive Board decision, recruitment was closed earlier. The recruitment termination was not related to safety issues or other circumstances related to the IMP. Two randomised patients did not take the IMP due to withdrawal of consent (patient or patient's family decision). Thus, a total of 123 (98.4%) randomised patients received at least one dose of IMP (safety set) including 61 (98.4%) ESL group patients and 62 (98.4%) placebo group patients. The FAS and the safety set were identical.

Overall, of 125 (100%) patients in the randomised set, 92 (73.6%) patients completed the 6-month period, 86 (68.8%) patients completed the 12-month period and 84 (67.2%) patients completed the 18-month period. In general, the percentage of completers was similar between ESL and placebo at any timepoint. A total of 41 (32.8%) patients prematurely terminated the trial with similar frequencies in both treatment groups, most of them before Visit 3 (total: 19.2%; ESL: 16.1%; placebo: 22.2%). The most frequently reported reasons overall for premature trial termination were "at their own or legal representative's request (withdrawal of consent)" (10.4%, ESL: 6.5%, placebo: 14.3%), "intolerable AE" (7.2%, ESL: 11.3%, placebo: 3.2%) and "stroke more than 7 days after primary stroke" (6.4%, ESL: 3.2%, placebo: 9.5%).

The mean (SD) patients' age in the total population (safety set) was 65.7 (14.16) years ranging from 26 to 90 years. Similar mean ages and age ranges were observed in both treatment groups.

Most patients were white (117 patients, 95.1%) and male patients prevailed in this trial (78 male patients, 63.4%). Similar percentages were observed in both treatment groups.

Overall, most patients had an acute ischaemic stroke (93 patients, 75.6%) compared to 30 (24.4%) haemorrhagic stroke patients with similar percentages in both treatment groups. The mean (SD) SeLECT score of patients with an acute ischaemic stroke was 5.6 (0.80) points and the mean (SD) CAVE score of patients with an acute intracerebral haemorrhage was 2.9 (0.56) points. The mean SeLECT score was identical and the mean CAVE score similar in both treatment groups. The mean (SD) mRS before stroke was 0.2 (0.61) points and similar in both treatment groups.

The most frequent previous medical conditions beside stroke by PT in the total population were thrombectomy (9 patients, 7.3%) and pyrexia (5 patients, 4.1%). For these PTs, the percentages of patients were higher in the ESL group (thrombectomy: 9.8%; pyrexia: 8.2%) compared to the placebo group (thrombectomy: 4.8%; pyrexia: 0 patients). The most frequent ongoing medical conditions by PT were hypertension (75 patients, 61.0%), atrial fibrillation (19 patients, 15.4%), hyperlipidaemia (16 patients, 13.0%), as well as carotid artery stenosis (15 patients, 12.2%). Differences ≥ 10% between the treatment groups were not observed.

The most frequently used concomitant substance was acetylsalicylic acid (68.3%), followed by atorvastatin (61.0%), amlodipine (37.4%) and enoxaparin (35.8%). Differences ≥ 10% between the ESL and placebo group were observed for ramipril (27.9% vs. 17.7%, respectively) and levothyroxine (3.3% vs. 16.1%, respectively).

Concomitant ASMs including antiepileptics and benzodiazepines with anti-seizure properties were used by 25 (20.3%) patients. The percentage of placebo group patients (15 patients, 24.2%) taking any ASM was about 1.5 times higher than in ESL group patients (10 patients, 16.4%). Most frequently used concomitant ASMs were levetiracetam (8.9%), diazepam and midazolam (4.1%, each). Differences ≥ 5% between the ESL and placebo group were observed for diazepam (6.6% vs. 1.6%). The treatment group difference with regard to the number of patients using any concomitant ASMs was even higher in the PPS (ESL: 12.7%, placebo: 25.0%).

The mean (SD) treatment compliance was 94.6% (28.15) in the ESL group and 91.6% (25.93) in the placebo group. A total of 17.1% of patients had missing overall compliance due to IMP bottles which were not returned. Patients with at least 4 consecutive treatment days (first IMP intake until last IMP intake) were considered reaching a steady-state serum level of ESL.

EFFICACY RESULTS:

The primary endpoint was defined as the **proportion of patients who experienced the first US within the first 6 months after randomisation (failure rate)**. Deaths before the first US or patients without evaluable assessment of the primary endpoint were counted as treatment failures.

The 6 months failure rate was lower in the ESL group than in the placebo group, although the treatment group difference was not statistically significant. The odds ratio as well as risk difference of failing seemed to show a favourable effect of ESL compared to placebo. The lower treatment failure rate in the ESL group compared with the placebo group was driven by fewer patients with a US and by fewer withdrawals. The reported deaths occurred in patients in the ESL group only (please refer to the table below), all were assessed by the investigator and the sponsor as not related or unlikely related to ESL.

Overview of the Analyses of Treatment failure Rates after 6 months (Primary Endpoint), 12 and 18 Months (Secondary Endpoints)

Characteristic	Statistic	ESL (N=61)	Placebo (N=62)
Failures 6 months (primary endpoint)	n (%)	17 (27.9)	23 (37.1)
Unprovoked seizure	n (%)	2 (3.3)	7 (11.3)
Death	n (%)	3 (4.9)	0
Withdrawn	n (%)	12 (19.7)	16 (25.8)
	p-value (*)	0.3682	
	p-value (**)	0.3369	
	RD (95% CI)	-0.0923 (-0.2605; 0.0835)	
	OR (95% CI)	0.6551 (0.3073; 1.3976)	
Failures 12 months	n (%)	19 (31.1)	26 (41.9)
Unprovoked seizure	n (%)	3 (4.9)	8 (12.9)
Death	n (%)	3 (4.9)	0
Withdrawn	n (%)	13 (21.3)	18 (29.0)
	p-value (*)	0.2915	
	p-value (**)	0.2624	
	RD (95% CI)	-0.1079 (-0.2790; 0.0724)	
	OR (95% CI)	0.6264 (0.2995; 1.3105)	
Failures 18 months	n (%)	23 (37.7)	27 (43.5)
Unprovoked seizure	n (%)	5 (8.2)	9 (14.5)
Death	n (%)	4 (6.6)	0
Withdrawn	n (%)	14 (23.0)	18 (29.0)
	p-value (*)	0.6340	
	p-value (**)	0.5831	
	RD (95% CI)	-0.0584 (-0.2351; 0.1235)	
	OR (95% CI)	0.7846 (0.3820; 1.6117)	

N: Number of patients in the full analysis set, n: Number of patients with data available, %: Percentage is based on N, CI: Confidence interval
p-value (*) from Chi-square test with continuity correction with 1 degree of freedom
p-value (**) from Fisher's exact test
RD: Risk difference ESL - Placebo
OR: Odds ratio ESL vs. Placebo
Corrected Newcombe CI is provided for RD. Score CI is provided for OR.

Secondary efficacy endpoints (presented for the FAS)

The **12 months and 18 months failure rates** including deaths before the first US and withdrawals were lower in the ESL group than in the placebo group, both without statistically significant treatment group differences (Chi-square test with continuity correction; Fisher's exact test). The odds ratios as well as risk difference of failing seemed to show a favourable effect of ESL compared to placebo (please refer to the table above). The treatment effect was maintained along the full trial period.

The **number of patients with at least one US** was lower in the ESL group (5 patients, 8.2%, 9 USs) than in the placebo group (9 patients, 14.5%, 20 USs).

Sensitivity analyses based on observed USs as failure rate only for the 12- and 18- month failure rates supported the results with favourable ESL effect versus placebo.

The proportion of patients who experienced at least one ASS was lower in the ESL group than in placebo treatment group (10 patients, 16.4%, 13 ASSs vs. 15 patients, 24.2%, 17 ASs). Comparing the ESL and the placebo group, a similar mean **number of ASSs** (1.3 vs. 1.1, respectively) was observed. In both treatment groups, the number of ASSs reached from 1 to 3 ASSs. All these ASSs were reported before the intake of first IMP except for 3 ASSs in 3 placebo group patients (4.8% of patients, calculated by the author) which were reported after 1 day or 2 days of IMP intake.

Regarding the **time to first US after randomisation**, the performed tests revealed no statistically significant difference between the ESL and placebo group (log-rank test: $p = 0.2081$; Gray's test: p-value: 0.1812). However, comparing the ESL group with the placebo group, the incidence of USs was reduced within the first 6 months and the time to develop USs within 12 and 18 months was delayed in the ESL group compared to the placebo group: the estimated probability to experience a seizure was lower in the ESL group than in the placebo group within 6 months, 12 months and 18 months after randomisation. The incidence of USs started to increase in the placebo group after the first month, i.e. after concomitant ASMs were withdrawn. The use of concomitant ASMs was allowed per protocol during the first month until Day 30, down-titration had to be started on Day 31.

Careful interpretation for the subgroups shall be taken due to smaller sample size in subgroups and/or different sample sizes between subgroups for all secondary endpoints.

With regard to functional outcomes, assessed by **BI total score and NIHSS total score,** no statistically significant differences were observed between ESL and placebo at endpoint (Wilcoxon-Mann-Whitney test). The BI increased from baseline to endpoint in both treatment groups and a median BI total score of 100.0 points in both treatment groups indicated that patients should be able to live independently. The NIHSS total scores decreased from baseline to endpoint in both treatment groups corresponding to a mild stroke severity at endpoint.

For the BI total score category $\leq$ 79 points (dependence), the estimated probability to experience a US was lower in the ESL group after 6, 12 and 18 months than in the placebo group, whereas similar estimated probabilities were observed for the BI total score category 80 to 100 points (patient should be able to live independently).

For the NIHSS total score categories $\geq$ 11 points (severe stroke) and < 11 points (mild and moderately stroke severity), the estimated probabilities to experience a US after 6 months, 12 months and 18 months were lower in the ESL group compared to the placebo group, however with higher treatment group differences for the category severe stroke.

No statistically significant difference in **Patient Health Questionnaire-9** total scores was observed between ESL and placebo at endpoint (Wilcoxon-Mann-Whitney test) with similar mean and median PHQ-9 total scores at baseline and endpoint in both treatment groups corresponding to minimal depression severity.

For the PHQ-9 total score category > 4 (mild to severe depression), the estimated probabilities to experience a US was lower after 6 months, 12 months and 18 months in the ESL group compared to the placebo group, whereas similar estimated probabilities were calculated for the PHQ-9 total score category $\leq$ 4 (minimal depression).

The **survival probability** estimate at 6 months, 12 months and 18 months was lower in the ESL group compared to the placebo group but revealed no statistically significant treatment group difference ($p = 0.0542$, log-rank test). Noteworthy, deaths occurred in ESL group were assessed by the investigators as not related or unlikely related to ESL.

SAFETY RESULTS:

Overall, 101 (82.1%) patients experienced TEAEs with similar frequencies in both treatment groups.

Out of the 123 enrolled patients, 35 (28.5%) patients in total experienced at least one possibly related TEAE. These TEAEs were reported with a higher frequency in patients in the ESL group (23 patients, 37.7%) than in the placebo group (12 patients, 19.4%). Hyponatraemia (5 patients, 8.2% in the ESL group vs. 1 patient, 1.6% in the placebo group) was the most frequently reported TEAE by PT assessed as at least possibly related.

During the trial, 6 deaths were reported. One patient died before randomisation due to a myocardial infarction and 5 patients who died were treated with ESL. Of these fatal events in the ESL group, pneumonia aspiration (Day 2) and pulmonary sepsis (Day 45) were treatment emergent, whereas haemorrhage intracranial (re-stroke), multiple organ dysfunction syndrome and pneumonia occurred more than 14 days after the last IMP intake. All deaths were categorised as not related or unlikely related to IMP by the investigators.

The frequency of other serious TEAEs was similar between the ESL and placebo group (12 patients, 19.7% vs. 13 patients, 21.0%). Of these, 3 events (nodal arrhythmia, hepatic failure, and hyponatraemia) were assessed as at least possibly related to IMP. All occurred in patients in the ESL group (3 patients, 4.9%). Nodal arrhythmia and hepatic failure were reported as SUSARs.

Most patients in total reported TEAEs classified as mild (73.2% of patients) or moderate (39.0% of patients). The frequency of patients with at least one severe TEAE was similar between both treatment groups (9 patients, 14.8% in the ESL group, vs. 8 patients, 12.9 % in the placebo group).

The frequency of patients with TEAEs leading to discontinuation of IMP was higher in the ESL group (16 patients, 26.2%) than in the placebo group (6 patients, 9.7%). Thereby, dizziness and hyponatraemia (2 patients, 3.3% each) were the TEAEs leading to discontinuation of IMP reported in more than one patient.

At the endpoint, decreased sodium levels i.e. < 135 mmol/L were reported by 4 (7.8%) patients in the ESL group, whereas all patients in the placebo group had sodium levels ≥ 135 mmol/L. No clinically relevant changes over time or differences between the treatment groups were found for any other laboratory parameter.

No clinically relevant changes over time or differences between the treatment groups were found based on vital sign or physical findings. The number of patients with CS ECG findings decrease from baseline to endpoint to a similar extend in both treatment groups. The number of patients with CS neurological findings also decreased from baseline to endpoint for all parameter in both treatment group. At endpoint, relevant frequency differences between the treatment groups (≥ 5%) were observed for cranial nerve (2 ESL patients, 3.8% vs. 4 placebo patients, 9.3%) and co-ordination (no ESL patient vs. 3 placebo patients, 7.0%). Both were in favour of ESL.

Suicidal ideation and behaviours were evaluated during the trial using PHQ-9 question 9. Throughout the trial, the mean (SD) PHQ-9 question 9 score remained low in both treatment groups (0.1 [0.45] points at endpoint each), indicating that most patients had no suicidal ideation and behaviour.

OTHER RESULTS:

Not applicable.

CONCLUSION:

- The primary endpoint, defined as treatment failure rate during the first 6 months after randomisation (composed by the occurrence of a first US, any death happening before first US, or any withdrawal happening before first US) was not statistically met in this trial, although the rate was lower in ESL compared to placebo.
- ESL 800 mg once daily for 30 days as a prophylactic treatment in stroke patients at high risk of development of post-stroke epilepsy, showed a favourable clinical trend with lower incidence of USs compared to placebo in the first 6, 12 and 18 months after randomization although no statistically significant treatment group difference was seen. A decrease of treatment group differences in US failure rates was observed within 18 months compared to the 6-month data.
- The time to first US occurring after randomisation showed a lower incidence of USs and a slight delayed time to develop first USs within 18 months of follow-up from randomisation in the ESL group compared to the placebo group without a statistically significant difference.
- For the functional outcomes assessed in this trial, the NIHSS total score showed a similar clinically meaningful improvement in both treatment groups, the PHQ-9 total score remained stable in both treatment groups, whilst the BI total score slightly improved in both treatment groups.
- Lower estimated probabilities to experience a first US after 6 months, 12 months and 18 months were observed in the ESL group in particular for categories of severe stroke (NIHSS total score $\geq$ 11 points), dependence (BI total score $\leq$ 79 points) and depression (PHQ-9 total score > 4) compared to the placebo group.
- Despite the higher frequency of at least possibly related serious TEAEs and related TEAEs as well as TEAEs leading to discontinuation of IMP in the ESL group compared to the placebo group, ESL has shown a safety profile in this vulnerable patient population aligned with previous safety data. Considering the critical clinical status of these patients after stroke, ESL 800 mg did not show any new safety concern.

Date of the report:

19-AUG-2024