Bial - Portela & Cª, S.A

CLINICAL TRIAL PROTOCOL

Synopsis

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

Protocol Number	BIA-2093-213
EudraCT Number	2018-002747-29
Phase	IIa
Version	Final Version 2.0
Date	24-OCT-2018
Product Name	Eslicarbazepine acetate (BIA 2-093)
Indication	Prophylaxis of post-stroke epilepsy
Sponsor	Bial - Portela & Cª, S.A. À Av. da Siderurgia Nacional 4745-457 Coronado (S. Romão e S. Mamede) Portugal Phone: +351 229866100 Fax: +351 229866192 http://www.bial.com
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PROTOCOL SYNOPSIS

Name of Sponsor/company: Bial - Portela & C[a], S.A., À Av. da Siderurgia Nacional, 4745-457 Coronado (S. Romão e S. Mamede), Portugal

Name of active ingredient: Eslicarbazepine acetate (BIA 2-093)

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

Steering Committee:

Prof. Matthias Koepp, MD PhD FRCP, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom

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Trial centres: Up to 22 sites in 7 European countries (Austria, France, Germany, Italy, Spain, Sweden and United Kingdom) and Israel. Other sites and other countries may be added as needed.

Planned duration of the trial: First patient first visit: Q1 2019 Last patient last visit: Q2 2021	Phase of development: IIa

Objectives:

Primary:

To assess if eslicarbazepine acetate (ESL) treatment (started within 96 hours after stroke occurrence and continued for 30 days) changes the incidence of unprovoked seizures (USs) within the first 6 months after randomisation as compared to placebo.

Secondary:

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 as 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 course of the trial - until 18 months after randomisation as compared to placebo
3. To assess the number of acute symptomatic seizures (ASs)

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

4. Time to first US after randomisation
5. Time to first US after stroke occurrence
6. Number and 4-week rate of USs
7. Functional outcome, assessed by Barthel Index original 10-item version (BI)
8. Functional outcome, assessed by National Institutes of Health Stroke Scale (NIHSS)
9. Post-stroke depression, assessed by Patient Health Questionnaire (PHQ-9)
10. Overall survival

Safety:
To assess the effect of ESL treatment on:
11. Treatment emergent adverse events (TEAEs) incl. findings from physical and neurological examinations
12. Laboratory parameters
13. Vital signs
14. Electrocardiogram (ECG)
15. Suicidal ideation and behaviour, assessed by PHQ-9 (question 9)

Exploratory:
16. Electroencephalogram (EEG), optional

Methods/trial design:

The following definitions will be applied for this trial:

Acute symptomatic seizure (AS): Epileptic seizure or status epilepticus (of any type) occurring within 7 days (≤ 7 days) after primary stroke.

Unprovoked seizure (US): Epileptic seizure or status epilepticus (of any type) occurring later than 7 days (> 7 days) after primary stroke.

Re-stroke: If an additional stroke occurs within the first 7 days after the primary stroke, this will be considered as one stroke event and will not lead to withdrawal of the patient.

Post-stroke epilepsy: One unprovoked (or reflex) seizure with a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 USs, occurring over the next 10 years.

This is 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.

At the first visit (screening/baseline, V1a), patients will undergo several examinations to check eligibility. The next visit (V1b) has to be performed within 96 hours after primary stroke occurrence. After eligibility has been confirmed, patients will be randomised (randomisation ratio 1:1) to treatment with ESL 800 mg (Group A) or placebo (Group B). Patients can receive therapies for stroke treatment according to local clinical practice at any time during the trial.

Patients will start treatment with the investigational medicinal product (IMP), i.e. ESL or placebo, within 96 hours after primary stroke occurrence at V1b. They will continue treatment until Day 30 after randomisation and then be tapered off. Thereafter, patients will be followed up until 18 months after randomisation. Patients can concomitantly receive antiepileptic therapies, except commercially available ESL or oxcarbazepine, until Day 30. Concomitant antiepileptic therapies have to be discontinued and down-titration has to be started according to the respective Summary of Product Characteristics (SmPC). If the antiepileptic drugs (AEDs)/benzodiazepine are not already discontinued before, down-titration must be started on Day 31 at the latest.

If one or more AS(s) occur(s) within 7 days after primary stroke, this will not result in change of IMP dose. Patients having a first US will discontinue IMP treatment and will be treated at the discretion of the investigator until 18 months after randomisation, except with commercially available ESL.

Further visits will be 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. Patients

who discontinue trial participation prematurely will be asked to come to the site for an early discontinuation visit (EDV). Unscheduled visits (UNS) will be performed at the discretion of the investigator, as necessary.

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

Number of patients (planned):

Screened:	220
Randomised:	200

Indication and main criteria for inclusion and exclusion:

Indication: Prophylaxis of post-stroke epilepsy

Inclusion criteria:

Patients must meet ALL of the following criteria:

1. Male or female patient aged 18 years or above.
2. Acute intracerebral haemorrhage with a CAVE score ≥ 3 or acute ischaemic stroke with a SeLECT score ≥ 6, in each case confirmed by magnetic resonance imaging (MRI)/computed tomography (CT).
3. Time of stroke occurrence is known and V1b is planned within 96 hours.
4. Brain scan analysis has reliably excluded structural brain lesions that can mimic stroke, e.g. cerebral tumour or brain abscess, etc.
5. a. Patient is able to give informed consent and to write and has signed written informed consent OR
   b. Patient is able to give informed consent, but unable to write and has provided verbal witnessed consent OR
   c. Patient is unable to give informed consent, but likely to regain this ability until V2, and the informed consent is deferred OR
   d. Patient is unable to give informed consent, but likely to regain this ability until V2, and patient's legal representative (according to the respective national/local requirements) has provided written informed consent.
6. Female patients without childbearing potential (2 years postmenopausal, bilateral oophorectomy or tubal ligation, or complete hysterectomy) are eligible. Female patients with childbearing potential must not be pregnant as confirmed by a negative pregnancy test and sexually active females must use a medically acceptable effective non-hormonal method of contraception up to the end of the current menstrual cycle after stopping treatment. Acceptable methods for women are surgical intervention (e.g. bilateral tubal occlusion), intrauterine device, double-barrier methods, true sexual abstinence (i.e. when this is in line with the preferred and usual lifestyle of the patient) and vasectomised male partner, provided that he is the sole partner of that patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The requirements of the relevant ethics committees must be adhered to at all times. Written or verbal witnessed informed consent from the patient must be obtained until V2.

Inclusion criteria at V1b

7. V1b is within 96 hours after stroke occurrence.

Inclusion criteria at V2 (only applicable for patients who were unable to give informed consent at V1a.)

8. a. Patient is able to give informed consent and to write and has signed a written informed consent OR
   b. Patient is able to give informed consent, but unable to write and has provided verbal witnessed consent.

Exclusion criteria:

(as per patient interview, medical records or reported by family members)

Patients are to be excluded from the trial for ANY ONE of the following reasons:

1. Contraindication to ESL, i.e. known hypersensitivity to ingredients of ESL formulation or other carboxamide derivatives (e.g., oxcarbazepine, carbamazepine), or second or third degree atrioventricular (AV) block not corrected with a permanent pacemaker.
2. Known Han Chinese or Thai ancestry.
3. History of previous stroke (other than the one described in inclusion criteria no. 2 - 3).
4. Sinus venous thrombosis.
5. Spontaneous sub-arachnoid haemorrhage due to e.g. aneurysmatic or arteriovenous malformation.
6. History of USs prior to primary stroke.
7. Impaired pre-stroke level of function, i.e. modified Rankin Scale (mRS) score > 3 prior to first stroke occurrence.
8. History of AED use before primary stroke within the last 5 years as defined in the list of not allowed AEDs.
9. Use of ESL, unless provided as IMP of this trial, and oxcarbazepine.
10. Severe hepatic impairment.
11. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (measured at V1a).
12. Known or suspected acute or chronic alcoholism, delirium tremens, or toxic psychosis.
13. History of suicidal ideation or suicide attempt within the past 3 years.
14. Presence of any other significant or progressive/unstable medical condition that, in the opinion of the investigator, would compromise evaluation of the trial treatment or may jeopardise the patient's safety, compliance or adherence to protocol requirements, such as significant psychiatric, cardiovascular, respiratory, metabolic, endocrine, haematologic, infectious or neurological disease.
15. For women: Pregnancy or breast-feeding.
16. Previous enrolment in this trial or participation in any other investigational drug trial within the past 30 days (or 5 half-lives of IMP whichever is longer) prior to V1a.
17. Persons committed to an institution by virtue of an order issued either by the judicial or other authorities.
18. Employees of the investigator or trial centre, with direct involvement in the proposed trial or other studies under the direction of that investigator or trial centre, as well as family members of the employees or the investigator.

Duration of treatment for the individual patient: Patients will receive IMP for 30 days. Afterwards, they will be tapered-off for 7 days before stopping the intake.

Test product, dose and mode of administration (Group A): 800 mg ESL tablets for oral administration. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

Placebo, dose and mode of administration (Group B): Placebo tablets for oral administration, matching the test product. In case a patient is unable to swallow the whole tablet, the tablet can be crushed or divided into equal doses at the score line.

IMP dosing schedule: IMP treatment will start at V1b (i.e. within 96 hours after primary stroke) and will be continued for 30 days. Thereafter, the IMP will be tapered off. The dosing will be as follows: Patients with an eGFR > 60 mL/min/1.73 m² will receive one tablet once daily, i.e. 800 mg ESL or placebo. Patients with moderate renal impairment at V1a, defined as eGFR 30 - 60 mL/min/1.73 m², will receive half a tablet once daily, i.e. 400 mg ESL or placebo. As soon as eGFR has improved to > 60 mL/min/1.73 m², the dose will be increased to one tablet once daily (800 mg ESL or placebo). Patients developing moderate renal impairment during IMP intake should be adjusted to 400 mg, if applicable.

If one or more AS(s) occur(s) within 7 days after primary stroke, this will not result in change of IMP dose.In case a patient has an US, IMP has to be discontinued and the patient will be treated at the discretion of the investigator, except with commercially available ESL.

Criteria for evaluation:

Primary efficacy endpoint:

Proportion of patients who experience 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 will be counted as treatment failures.

Secondary efficacy endpoints:

1. Proportion of patients who experience the first US during the first 12 months after randomisation (12 months failure rate)
2. Proportion of patients who experience the first US during the course of the trial – until 18 months after randomisation (18 months failure rate)
3. Number of ASs
4. Time to first US after randomisation
5. Time to first US after stroke occurrence
6. Number and 4-week rate of US
7. BI
8. NIHSS
9. PHQ-9
10. Overall survival

Safety endpoints:

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

Exploratory endpoint:

16. EEG, optional

Statistical methods:

Analysis sets:

- Enrolled set (ES): All patients enrolled into this trial.
- Safety set (SS): All patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients will be assigned to treatment groups as treated.
- Full analysis set (FAS): All patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients will be assigned to treatment groups as randomised.
- Per protocol set (PPS): All patients of the FAS without major protocol deviations. Patients will be assigned to treatment groups as treated.
- EEG analysis subset: All patients in the FAS with a baseline and a post-baseline EEG recording available.

The primary hypotheses will be assessed in the FAS by means of a chi-square test with continuity correction on the significance level of 5% (two-sided).

Secondary efficacy analysis includes an analysis of the proportion of patients who experience the first US within the first 12 and within 18 months after randomisation (12 months and 18 months failure rate, respectively), time to first US after randomisation as well as time to first US after stroke by means of Kaplan-Meier estimate, and cause-specific cumulative incidence curves to evaluate the competing risk in case of deaths before the first US, as well as descriptive statistics for number of ASs, number and 4-week rate of USs, the BI, the NIHSS score, the PHQ-9.

EEG parameters will be evaluated exploratively using descriptive statistics.

Safety analysis will focus on the presentation of TEAEs by system organ class (SOC) and preferred term (PT), and the analysis of vital signs, safety laboratory data, ECG, physical and neurological examination, and suicidal behaviours assessed using PHQ-9.

Sample size estimation: Based on historical data, 26% of patients are expected to experience the first US within the first 6 months after stroke (i.e. failure rate) with standard of care. As this is a pilot trial, no empirical estimate of the treatment effect in patients randomised to ESL is available. For the purpose of sample size estimation, the trial is planned to have at least 80% power to demonstrate a significantly lower failure rate under ESL (Group A) compared to placebo (Group B) under the following assumptions:

- An expected failure rate (including death before the first US) of 26% under placebo within the first 6 months after stroke.
- An expected failure rate (including death before the first US) of 8% under ESL within the first 6 months after stroke.
- In order to account for a missing data rate of 5% for reasons other than death before the first US, in each treatment arm, the sample size calculated on adjusted failure rates (including missing data) of 29.7% under placebo and 12.6% under ESL, respectively.

Under these assumptions 100 randomised patients per treatment arm will ensure a power of the trial of at least 80% to demonstrate a significantly lower failure rate under ESL compared

to placebo by means of a two-sided chi-square test with continuity correction on a 5%-level of significance.

Assuming that the failure rate in missing observations equals the failure rate with placebo for both treatment groups, the power of the trial is 87%. Based on the expected failure rates without adjustment for missing data, the power of the trial is 89%.

Schedule of trial procedures

Visits	**V1a[2]**	**V1b[2]**	**V2[15]**	**V3[15]**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[12]**	**EDV[3]**	**UNS[1]**
Days / Weeks after V1b			**+7 days**	**+37 days**	**+12 weeks**	**+26 weeks**	**+38 weeks**	**+52 weeks**	**+ 64 weeks**	**+ 78 weeks**		
On-site visit ⊗/telephone contact ☎	⊗	⊗	⊗	⊗	☎	⊗	☎	⊗	☎	⊗	⊗	⊗/☎
Day	**-3 to -1**	**1 (within 96 h after stroke)**	**8±2**	**38+4**	**85±10**	**183±10**	**267±10**	**365±10**	**449±10**	**547±10**		
Initiation procedures												
Informed consent	●[9]		●[10]									(●)[14]
Demographics	●											
Medical history	●		●[10]									(●)[14]
Prior medication	●		●[10]									(●)[14]
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●
SeLECT score/CAVE score[11]	●[4]											
Modified Rankin Scale (mRS)	●[4]											
Inclusion/exclusion criteria	●	●	●[10]									
Randomisation (1:1)		●										
Medication												
First investigational medicinal product (IMP) administration		●										
Dispense IMP		●										(●)
IMP accountability				●							●[13]	(●)
Efficacy												
Issue diary (seizures)	●		●	●		●		●				(●)
Review and collect diary		●[8]	●	●		●		●		●	●	(●)
Seizure screening questionnaire	●	●	●	●	●	●	●	●	●	●	●	●
Record seizures (diary/questionnaire)[16]	●	●	●	●	●	●	●	●	●	●	●	●
Barthel Index (BI)	●			●		●		●		●	●	(●)
National Institutes of Health Stroke Scale (NIHSS)	●[4]		●	●		●		●		●	●	(●)
Patient Health Questionnaire (PHQ-9)	●			●		●		●		●	●	(●)
Electroencephalogram (EEG, optional)[5]	(●[4])									(●)		(●)

Visits	**V1a[2]**	**V1b[2]**	**V2[15]**	**V3[15]**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[12]**	**EDV[3]**	**UNS[1]**
Days / Weeks after V1b			**+7 days**	**+37 days**	**+12 weeks**	**+26 weeks**	**+38 weeks**	**+52 weeks**	**+ 64 weeks**	**+ 78 weeks**		
On-site visit ⊗/telephone contact ☎	⊗	⊗	⊗	⊗	☎	⊗	☎	⊗	☎	⊗	⊗	⊗/☎
Day	**-3 to -1**	**1 (within 96 h after stroke)**	**8±2**	**38+4**	**85±10**	**183±10**	**267±10**	**365±10**	**449±10**	**547±10**		
Safety												
Adverse events (AEs)	●	●	●	●	●	●	●	●	●	●	●	●
Vital signs (blood pressure, heart rate, tympanic body temperature)	●		●	●		●		●		●	●	(●)
Blood withdrawal (haematology and biochemistry)[6]	●		●	●							●[13]	(●)
Urinalysis	●		●	●							●[13]	(●)
12-lead electrocardiogram (ECG)	●[4]		●	●							●[13]	(●)
Physical and neurological examination	●		●	●		●		●		●	●	(●)
Serum pregnancy test[7]	●											
Urine pregnancy test[7]	●		●	●							●[13]	(●)

1. Unscheduled visits (UNSs) will be performed at the discretion of the investigator. Assessments in brackets are optional and can be performed at the discretion of the investigator.
2. If all conditions for V1a and V1b are fulfilled, V1a and V1b can be performed on the same day.
3. An early discontinuation visit (EDV) should be performed within 10 days, if possible, on withdrawal.
4. If examination was done after primary stroke, the results should be used and the examination does not need to be repeated at V1a.
5. EEGs are optional assessments and will be performed at the discretion of the investigator.
6. Including eGFR and coagulation. At V1a also thyroid function.
7. Only in women of childbearing potential. Frequency may be adapted to meet specific country-specific/local requirements.
8. The diary will only be reviewed but not be collected at V1b.
9. If a patient is unable to give written or verbal consent at V1a, patient consent can be deferred or the patient's legal representative must provide written informed consent (according to country specific requirements). Written or verbal witnessed informed consent from the patient must be obtained until V2.
10. Only applicable for patients who were unable to give informed consent at V1a.
11. The scores for "**Se**verity of stroke, **L**arge-artery atherosclerotic aetiology, **E**arly seizures, **C**ortical involvement, **T**erritory of middle cerebral artery" (SeLECT score) in patients with an acute ischaemic stroke and for "**C**ortical involvement, **A**ge < 65 years, **V**olume of intracerebral haemorrhage > 10 mL and **E**arly seizure within 7 days after intracerebral haemorrhage" (CAVE score) in patients with acute intracerebral haemorrhage.

12. EoT: End of Trial visit
13. Only applicable, if EDV is performed before V3.
14. Only applicable if performed prior to V2 and only for patients who were unable to give informed consent at V1a.
15. The patients will be reminded via phone call on the working day before Day 30 to either take the last tablet on Day 30 (those with ESL 400 mg) or to take half a tablet from Day 31 to Day 37 (those with ESL 800 mg) and (if applicable) to start the down-titration of AED/benzodiazepines according to the respective SmPC on Day 31, if not already discontinued before.
16. Seizure records based on diary entries may be applicable in case of on-site visits, only.