2 STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], S. A. Product: Eslicarbazepine acetate (BIA 2-093) Active ingredient: Eslicarbazepine acetate (ESL)		*(For National Authority Use only)*
Title of study: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial – Part III-V.		
Coordinating investigator: Not applicable		
Study centres: 43 centres in 14 countries (Bosnia and Herzegovina, Czech Republic, France, Hungary, Italy, the Philippines, Poland, Romania, Russia, Serbia, Slovakia, Spain, Ukraine, and United Kingdom) participated during Part III-V.		
Study period: Date first patient enrolled: 07 Dec 2007. Date last patient completed the double-blind treatment period (Part I): 20 Aug 2012. Date last patient completed the first open-label extension period (Part II): 22 Oct 2013. Date last patient in Europe completed the corresponding subsequent open label extension period (Part III-V): 25 Nov 2013 Date last patient overall completed the last open-label extension period (Part V): 24 Aug 2017		Clinical Phase: III
Objectives: The objective pertaining to the open-label extensions of the study (Part II-V) was to assess the maintenance of the therapeutic effect of eslicarbazepine acetate (ESL) during long-term treatment in Part II, Part III, Part IV, and Part V of the study, while ensuring the provision of ESL to the patients who participated in the original investigational plan comprising Parts I and II. This was one of the secondary objectives of the entire study. The primary objective of the study was to assess the efficacy of ESL as an adjunctive therapy in children and adolescents with refractory partial seizures. This objective and all other secondary objectives were addressed using data collected during the double-blind part (Part I) of the study.		
Methodology: This was a multinational phase III study, which consisted of a randomised, double-blind, placebo-controlled, parallel-group part (Part I), and 4 subsequent long-term, open-label extension periods (Part II-V). Part I consisted of an 8-week observational baseline period followed by a 6-week double-blind titration period, a 12-week double-blind maintenance period, an up to 4-week double-blind tapering-off period, and a 4-week observational follow-up period (unless the patient continued with open-label treatment in Part II). The 1:1 randomisation was stratified by age group (2-6 years [stratum I], 7-11 years [stratum II], or 12-18 years [stratum III]). After completion of Part I, patients had the option to enter a long-term, open-label extension period to receive ESL for 1 year (Part II). After completion of		

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Part II, patients had the option to continue treatment in up to 3 subsequent open-label extension periods: Part III (1 year), Part IV (1 year), and Part V (2 years).

The study designs of the 1-year extension Parts III and IV were identical and consisted of a 48-week open-label extension period. Part V was a 2-year open-label extension period and the last planned period of the study.

In each of Parts III, IV, and V, the starting ESL dose was the same dose that the patient was receiving at the end of the previous extension period (i.e. Parts II, III, and IV, respectively), unless the investigator decided to titrate this dose to achieve further reduction in seizure frequency or due to the occurrence of any intolerable adverse events (AEs). The daily dose could be titrated in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight).

At the end of Parts III and IV, patients had the option to continue receiving ESL by entering the subsequent extension period (Part IV or Part V) until marketing authorisation was granted (or clinical development was discontinued) if both parent(s)/guardian(s)/patient and his/her physician agreed that this was in the patient's best interest. If the patient did not continue receiving ESL after an open-label extension period or in case of early discontinuation of ESL during an open-label extension period, the respective patient entered a tapering-off/follow-up period, in which study treatment was down-titrated and standard antiepileptic treatment introduced.

The aim of the study protocol and the request by the European Medicines Agency was that more than 200 patients completed Part I of the study and 100 patients the first 1-year extension (Part II). In fact, 183 patients completed Part II. In May 2013, it was decided by BIAL that in Europe, the study would not be prolonged by any further study extension after Part V. In addition, the complete study ended for each patient in Europe immediately at any time during Part III-V at the time the last patient in the study left Part II of the study. However, any patients, patient's parents, or investigators interested in continuation of ESL treatment were allowed further access to the study drug by means of a compassionate use/donation program, as acceptable by regulatory authorities in each country.

Number of patients:	Planned to be randomised in Part I: 252 patients (126 per treatment group). Treated in Part I: 304 patients (155 with ESL, 149 with placebo). Treated in Part II: 260 patients (128 with ESL in Part I, 132 with placebo in Part I). Treated in Part III: 152 patients (65 with ESL in Part I, 87 with placebo in Part I). Treated in Part IV: 94 patients (44 with ESL in Part I, 50 with placebo in Part I). Treated in Part V: 67 patients (33 with ESL in Part I, 34 with placebo in Part I). Analysed for efficacy in Part III-V: 148 patients (intention-to-treat [ITT]). Analysed for safety in Part III-V: 152 patients (i.e. all treated patients).

Diagnosis and main criteria for inclusion in the entire study (to enter Part I):

- Diagnosis of epilepsy for at least 6 months prior to enrolment; for patients from the Czech Republic: diagnosis of epilepsy for at least 24 months prior to enrolment (Amendment 1 Czech Republic, 05 Oct 2007).
- Children 2-16 years of age; as per Global Amendment 4 (16 Sep 2010): children 2-18 years of age; for patients from Romania: children 2-17 years of age (Amendment 1 Romania, 09 Nov 2010).

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- At least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 1 or 2 antiepileptic drugs (AEDs); for patients from the Czech Republic: at least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 2 AEDs (Amendment 1 Czech Republic, 05 Oct 2007).
- At least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period.
- Stable dose regimen of AEDs during the 8-week baseline period.
- Current treatment with 1 or 2 AEDs (any AED except oxcarbazepine); if present, vagus nerve stimulation is considered an AED (this last addition was introduced per Global Amendment 1 [20 Dec 2007]).

Patients with primarily generalised seizures, known progressive neurological disorders, known second or third degree atrioventricular block (introduced per Global Amendment 4 [16 Sep 2010]), history of status epilepticus within the 3 months prior to enrolment, seizures of non-epileptic origin, Lennox-Gastaut syndrome, or West syndrome were excluded from the study.

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

During Part III-V, all patients received ESL. ESL was provided as an oral suspension (50 mg/mL) for use in the age group of 2–6 years (stratum I) or as white oblong tablets (200 mg) for use in the older children and adolescents (≥7 years of age; strata II and III). Batch numbers are available in the appendix of this clinical study report.

Duration of treatment:

Up to 26 weeks in Part I; 12 months in Parts II, III, and IV, and 24 months in Part V. Thus, the treatment duration in Part III-V was 48 months.

Reference therapy and mode of administration:

Not applicable to Part III-V.

Criteria for evaluation:

Efficacy during Part III-V:

- Standardised seizure frequency per period of Baseline Part I, Baseline Part III-V, each subperiod (by 12-week intervals), and overall.
- Absolute changes in seizure frequency per 12-week interval, defined as the difference between standardised seizure frequencies during each time interval and Baseline Part I and Baseline Part III-V.
- Relative changes in seizure frequency per 12-week interval calculated as absolute changes divided by the standardised seizure frequency at Baseline Part I and Baseline Part III–V.
- Responders per 12-week interval: responders were defined as those patients with a relative seizure reduction of at least 50% in the respective time interval compared to Baseline Part I and Baseline Part III–V.
- Categorised relative change from Baseline Part I and from Baseline Part III–V in seizure

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frequency per 12-week interval (≥25%; >-50% to <25%; ≥-75% to ≤-50%; <-75%).

- Exacerbations in seizure frequency (increase in relative change in seizure frequency of ≥25%) per time interval compared to Baseline Part I and Baseline Part III–V.
- Proportion of patients who are seizure-free per 12-week interval.
- Standardised seizure frequency per 12-week interval by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other); seizures with missing seizure type information were considered as unclassified for the analysis.
- Number of days with seizures (standardised to 4-week time period).
- Seizure duration (as classified in the diary): <30sec, ≥30 sec to <1 min, ≥1 min to <5 min, ≥5 min, unknown.
- Treatment retention time, defined as the time to first occurrence of 1 of the following during treatment: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period of Part I).
- Seizure severity assessed with the 13-item Hague seizure severity scale.

Safety during Part III-V:

Safety was assessed on the basis of the following observations and measurements:

- Reports of AEs, including serious AEs.
- Safety laboratory (haematology, biochemistry, and urinalysis).
- Vital signs.
- 12-lead electrocardiogram (ECG) parameters.
- Physical and neurological examinations.
- Sexual maturation assessment.

Statistical methods:

The methods presented here refer to the analysis of data collected during Parts III, IV, and V of the study. All 3 parts were analysed jointly, i.e. as 1 period. All evaluations were of descriptive nature. No confirmatory analysis was carried out.

Baseline definitions:

- Baseline (OL): Data from the visit when study medication for the open-label extension (Part II) was dispensed.
- Baseline (safety): Baseline (OL) for patients treated with placebo during Part I; baseline visit as defined for the analysis of the double-blind part for patients treated with ESL during Part

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The following baseline periods were defined as reference periods in efficacy analyses:

- Baseline Part I: from Visit V1 (screening visit) to the day before V2 of Part I.
- Baseline Part III–V: the last 4 weeks (in Part II) prior to first intake (Day 1) in Part III–V.

Efficacy analysis for Part III-V:

The efficacy analyses were performed for the ITT set, which included all patients treated with at least 1 dose of ESL during Part III-V and who had at least 1 seizure frequency assessment during Part III-V. Descriptive statistics, including absolute and relative change, are presented for each efficacy variable for Baseline Part I, Baseline Part III-V, each 12-week interval, each subperiod, and overall. Changes from Baseline (safety) and Baseline (OL) are also presented for the summary score of the Hague seizure severity scale. Selected analyses were also performed for subgroups by seizure type, age stratum, the subset of patients who switched to monotherapy during Part III-V, and for completers. Additionally, the Kaplan-Meier estimate for the median treatment retention time and its corresponding 95% confidence interval are presented. This analysis was performed for the safety set.

Safety analysis for Part III-V:

All safety variables were analysed descriptively. Selected analyses were also performed by age stratum.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number and frequencies of patients with treatment-emergent adverse events (TEAEs) are given by primary system organ class (SOC) and preferred term within each SOC and by treatment group for any TEAE category.

The number and frequency of patients with clinically significant values at each visit are presented for vital signs. All laboratory values were classified as normal or abnormal according to the laboratories normal ranges and as clinically significant or not clinically significant according to the investigator. Descriptive summaries, shift tables, and number and frequency of patients with clinically significant laboratory values are presented for all laboratory parameters.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Efficacy findings in Part III-V per variable in the total ITT set were as follows:

- The total responder rate during Part III–V was 26.6% compared to Baseline Part III–V. Responder rates per 12-week intervals ranged between 21.9% (week 13-24) and 52.9% (week 145-156) with at least slightly higher responder rates in Part V (week 97-108 onwards). However, due to high fluctuations between intervals no clear trend could be confirmed. Efficacy findings beyond week 205 should be interpreted with caution due to the small number of patients remaining on study treatment.
- The total median standardised seizure frequency during Part III–V was 2.4, resulting in a median relative change from Baseline Part III–V of -22.9%. The median relative change from Baseline Part III–V reached a decrease of up to -50.0% in the total population during week 145-156. The overall median relative decrease was greater in patients treated with ESL in Part I (-25.8%) than in patients treated with placebo in Part I (-16.4%).
- 12 patients (8.1%) were seizure-free during Part III–V. The proportion of seizure-free patients ranged from 16.7% to 28.8% of patients during each of the 12-week intervals with fluctuations in both previous treatment groups..

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- In the total population, the proportion of patients with a seizure reduction between 50% and 75% compared to Baseline Part III–V was 14.7% (12.5% in patients treated with ESL in Part I and 16.4% in those treated with placebo in Part I), the proportion of patients with a seizure reduction greater than 75% was 11.9% (16.7% in patients treated with ESL in Part I and 8.2% in those treated with placebo in Part I. The overall proportion of patients with exacerbation (increase of ≥25%) compared to Baseline Part III–V was 25.7% and remained below the responder rate for most of the 12-week intervals. No consistent trend over time was observed for the proportion of patients in any category.
- No clinically relevant changes in the total score of the Hague seizure severity scale were seen during Part III–V.
- The median standardised number of days with seizures was 2.3 days overall, fluctuating close to 2 days for most time intervals during the course of the study until the week 133-144 interval and slightly increased to median values close to 3.5 days in most 12-week intervals after the week 145-156 interval.

SAFETY RESULTS:

Safety results during Part III–V did not reveal any findings of concern with regard to the long-term safety of ESL in the included population. Frequencies for AE categories were generally similar between groups by treatment received in Part I.

The main safety results during Part III–V in all patients treated with ESL were as follows:

- 97 patients (63.8%) experienced at least 1 TEAE. Most frequently reported TEAEs were convulsion (20 patients [13.2%]), nasopharyngitis and pyrexia (16 10.5%] each), as well as bronchitis and upper respiratory tract infection (13 [8.6%]).
- 22 patients (14.5%) had at least 1 TEAE that was considered at least possibly related to ESL by the investigator. The most commonly reported such TEAE was increased gamma-glutamyltransferase (GGT) (4 patients [2.6%]).
- 19 patients (12.5%) had at least 1 serious TEAE; the only serious TEAEs reported by more than 1 patient were pneumonia (4 patients [2.6%]) as well as asthma, bronchopneumonia, convulsion, dengue fever, and status epilepticus (2 patients [1.3%] each).
- No serious TEAEs were considered to be related to the study medication by the investigator, and no TEAEs (excluding death) led to treatment discontinuation.
- 2 patients died during Part III–V. One patient died due to a severe case of bronchopneumonia and one patient died due to infection and disseminated intravascular coagulation. For both patients, SAEs leading to death were assessed by the investigator as unrelated to the study drug.
- Changes from a normal laboratory value at Baseline (OL) to an abnormal value at endpoint occurred in no more than 23.1% of patients per laboratory parameter. Changes to abnormally low value were most frequently reported for bicarbonate, free T4 and total T4 while changes to abnormally high values were most frequently observed for GGT. For any laboratory

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parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of GGT (clinically significant for 15 patients [9.9%], leukocytes (clinically significant for 6 patients [3.9%]) and creatine kinase, activated by N-acetyl cysteine (clinically significant for 5 patients [3.3%]).

- The majority of the 148 patients who had post-baseline measurements of sodium levels, had normal sodium levels: 18 patients (11.8%) had low sodium levels and no patients had high sodium levels. Most of the patients (14/18) with low sodium levels had values >130 to 135 mmol/L, and 2 patients each had values >125 to 130 mmol/L and ≤125 mmol/L, respectively. Only one of these sodium levels was considered clinically significant.
- No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index, head circumference or sexual maturation assessment.For 7 patients, ECG abnormalities were reported as TEAEs during Part III–V.

CONCLUSIONS:

In the final 3 open-label treatment periods of this confirmatory, multinational, phase III study in children and adolescents with refractory partial seizures, the improved efficacy after the first 2 parts of the study was maintained or further improved with continued ESL treatment as adjunctive therapy. Safety results were consistent with the known safety profile of ESL without any findings of concern.

Date of final report:19 February 2018