2. STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*
Title of study: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomised, active-controlled, parallel-group, multicenter clinical study. — Open-label ESL Extension —		
Coordinating investigator: Prof. Dr. Eugen Trinka		
Study centres: 60 study centres in 25 countries (Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Ukraine, United Kingdom, Australia, Argentina, Brazil, Chile, and Peru).		
Study period: Date first subject enrolled: 21-Mar-2016 Date last subject completed the study: 11-Sep-2018		Clinical Phase: 3
Objectives: The primary objective of the study was to confirm maintenance of efficacy of eslicarbazepine acetate (ESL) (800 mg to 1600 mg once daily [QD]) monotherapy during long-term treatment in adults (≥18 years) with recently diagnosed epilepsy experiencing partial-onset seizures. The secondary objectives of the study were to further demonstrate the efficacy of ESL in subjects switching from carbamazepine controlled-release (CBZ-CR) treatment, and to demonstrate the safety of ESL in subjects switching from CBZ-CR treatment and in subjects already treated with ESL monotherapy for ≥1 year (i.e. during long-term treatment).		
Methodology: This was a Phase 3, multinational, open-label (OL), non-controlled study conducted in adults (≥18 years) with recently diagnosed epilepsy experiencing partial-onset seizures who were under treatment in the double-blind (DB) Study BIA-2093-311. For all subjects participating in this OL extension study, the last Extension Phase Visit of the DB study was also OL Visit 1 for this study. Subjects who were already treated with ESL in the DB study continued with their last evaluated dose (ESL 800 mg, 1200 mg, or 1600 mg QD) in the OL extension study. Subjects previously treated with CBZ-CR were to start with ESL 400 mg QD for 1 week, followed by up-titration in steps of 400 mg dose increase per week to the ESL target dose, which was equivalent to the last evaluated CBZ-CR dose level (i.e. CBZ-CR 200 mg twice daily [BID] → ESL 800 mg QD [Dose level A]; CBZ-CR 400 mg BID → ESL 1200 mg QD [Dose level B]; CBZ-CR 600 mg BID → ESL 1600 mg QD [Dose level C]). CBZ-CR down-titration for these subjects was to start 2 weeks after first receipt of ESL treatment as part of the DB study. Treatment continued until the End-of-study (EOS) Visit, which took place approximately 24 months±7 days from OL Visit 1. Subjects who discontinued the study medication prematurely were to attend an Early Discontinuation Visit (EDV), which was to take place as soon as possible and within 3 days after the date of discontinuation of study medication. A Post-study Visit was to be performed approximately 4 weeks after EOS or EDV. The maximum study duration for an individual, including the follow-up phase, was expected to be approximately 105 weeks.		

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*

Number of subjects:	Enrolled:	207 subjects (OL Enrolled Set)
	Treated:	206 subjects
	Analysed for efficacy:	206 subjects (OL Full Analysis Set [OL FAS]); 197 subjects (OL Per-protocol [OL PP] Set); 197 subjects (OL Subset-of-per-protocol [OL SPP]; excluding subjects who discontinued before completing CBZ-CR down-titration)
	Analysed for safety:	206 subjects (OL Safety Analysis Set [OL SAF])

Diagnosis and main criteria for inclusion:

Participated in the preceding DB study and were still ongoing in the study at the time of unblinding.

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

ESL tablets were orally administered at the following daily doses: 800 mg QD, 1200 mg QD, and 1600 mg QD.

Duration of treatment:

The total duration of OL treatment for an individual subject was up to approximately 105 weeks.

Reference therapy and mode of administration:

No reference drug or placebo was administered in this study.

Criteria for evaluation:

Efficacy

- Time to treatment failure (TTF)/treatment retention time (TRT), defined as the time from OL Visit 1 (i.e. OL Baseline) until withdrawal of ESL due to an adverse event (AE) or lack of efficacy (i.e. inadequate seizure control).
- Time to withdrawal (TTW), defined as the time from OL Baseline until withdrawal of ESL for any reason.
- Seizure freedom, defined as the number of subjects without seizures.
- Seizure duration and type.
- Standardised seizure frequency (ssf), calculated as 28 days * (number of seizures in interval T/length of T in days).
- Number and frequency of responders, where a responder is defined as a subject with ≥50% reduction in seizure frequency compared to the seizure frequency at DB Baseline.
- Quality of life as assessed by the Quality of Life in Epilepsy Inventory-31 (QOLIE-31). The survey contains 31 questions that are summarised by 7 multi-item scales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning).
- Treatment satisfaction as assessed by investigators and subjects, based on a 4-point scale of "poor", "fair", "good", or "very good".

Safety

- AEs
- Clinical laboratory evaluations (biochemistry, haematology, coagulation, urinalysis, bone turnover markers, thyroid function, pregnancy tests)
- Physical examinations and vital signs measurements
- Neurological examinations
- Electrocardiogram (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Bond-Lader visual analogue scales (BL-VAS)

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*

Statistical methods:

All analyses of the OL extension study were exploratory in nature and primarily involved descriptive statistical methods. In addition, exploratory statistical testing and confidence intervals (CIs) were presented to evaluate trends during long-term use of ESL and to investigate differences between the DB treatment groups after switching from DB treatment. In general, continuous variables were summarised using descriptive statistics, and categorical variables were summarised using frequency counts and percentages.

All efficacy variables were summarised descriptively by DB treatment as randomised and overall. TTF/TRT and TTW were analysed using Kaplan-Meier curves, estimates of monthly failure rates (or monthly withdrawal rates for TTW) and pointwise 95% CIs using the log-log transform, and the 25% percentile, median, and 75% percentile and corresponding 95% CIs were presented by randomised DB treatment and overall. Subjects were right-censored by the day of their last ESL intake + 1 (or by the day of withdrawal for other reasons of withdrawal [i.e. not withdrawal due to an AE or lack of efficacy] + 1 for TTF/TRT).

The time from OL Baseline to the occurrence of the first seizure during the OL extension study was analysed using Kaplan-Meier curves, estimates of monthly seizure rates and pointwise 95% CIs using the log-log transform, and the 25% percentile, median, and 75% percentile and corresponding 95% CIs were presented by randomised DB treatment and overall. Subjects were right-censored by the day of their last ESL intake + 1.

Subgroup efficacy and safety analyses were performed for the subgroup of subjects who remained on monotherapy until EOS/EDV (i.e. did not take any concomitant anti-epileptic drugs [AEDs] before EOS/EDV), hereafter referred to as the Monotherapy Set.

Summary – Results

Disposition:

A total of 207 subjects were enrolled in the study, of which 110 had been treated with ESL in the DB study (the DB ESL/OL ESL group) and 97 had been treated with CBZ-CR in the DB study (the DB CBZ-CR/OL ESL group). One subject in the DB ESL/OL ESL group was a screening failure and was excluded from all analysis sets.

The majority of subjects in both groups remained on monotherapy until OL EOS/EDV and comprised the Monotherapy Set of the OL SAF/OL FAS (96 subjects [88.1%] in the DB ESL/OL ESL group vs. 88 subjects [90.7%] in the DB CBZ-CR/OL ESL group). In addition, the majority of subjects (≥87.6%) either ended the OL extension study on the same ESL dose that they started with (for subjects in the DB ESL/OL ESL group) or reached and maintained their target equivalent ESL dose (for subjects in the DB CBZ-CR/OL ESL group). For the minority of subjects who used concomitant AEDs before OL EOS/EDV (13 [11.9%] vs. 9 [9.3%]), the mean (standard deviation) number of concomitant AEDs (2.8 [4.38] vs. 1.7 [1.00]), start day (310.6 [235.52] vs. 354.9 [305.03]) (i.e. ≥7.8 months after OL Visit 1 in either group), and duration of use (199.1 [239.82] days vs. 209.1 [288.47] days) were similar between groups.

The majority of subjects in both groups completed the OL EOS visit (90 subjects [82.6%] in the DB ESL/OL ESL group vs. 82 subjects [84.5%] in the DB CBZ-CR/OL ESL group). The proportion of subjects who discontinued the study prematurely was similar between groups (19 subjects [17.4%] vs. 15 subjects [15.5%]). In both groups, the most common primary reasons for study discontinuation, as classified by the investigator, were AEs (6 subjects [5.5%] vs. 5 subjects [5.2%]) and withdrawal of consent (5 subjects [4.6%] vs. 4 subjects [4.1%]). None of the subjects discontinued due to protocol violations as the primary reason.

Demographic and baseline characteristics:

Despite the study not being randomised, demographic characteristics were similar between the groups. The mean age was 43.0 years in the DB ESL/OL ESL group and 42.2 years in the DB CBZ-CR/OL ESL

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*

group. Most subjects in the study were <65 years old (96 subjects [88.1%] in the DB ESL/OL ESL group vs. 89 subjects [91.8%] in the DB CBZ-CR/OL ESL group), with a slightly smaller proportion of subjects ≥50 to <65 years of age in the DB ESL/OL ESL group (27 subjects [24.8%]) than in the DB CBZ-CR/OL ESL group (32 subjects [33.0%]). The groups were similar in terms of epilepsy history and characteristics at DB baseline.

Efficacy results:

The results of this study demonstrated the maintenance of the efficacy of ESL during long-term treatment (DB ESL/OL ESL group), and the efficacy of ESL in subjects switching from CBZ-CR treatment (DB CBZ-CR/OL ESL group). These results were consistently supported by the subgroup analyses on the Monotherapy Set of the OL FAS and OL PP Set, which confirmed the efficacy of long-term ESL monotherapy.

The TTF/TRT was similar between groups, with a low probability of treatment failure (i.e. the risk of withdrawal of ESL due to an AE or lack of efficacy) in both groups throughout the OL extension study (<0.07 at any time). The proportion of subjects who withdrew from ESL for any reason was low and similar between groups throughout the OL extension study (19 subjects [17.4%] in the DB ESL/OL ESL group vs. 15 subjects [15.5%] in the DB CBZ-CR/OL ESL group).

During the OL extension study, the proportion of seizure-free subjects was high in both groups, but higher in the DB ESL/OL ESL group (93 subjects [85.3%]) than in the DB CBZ-CR/OL ESL group (74 subjects [76.3%]) (95% CI for the difference in proportions of seizure-free subjects: -0.0173; 0.1979; p=0.0986). Accordingly, the probability of a seizure was low in both groups throughout the OL extension study, but lower in the DB ESL/OL ESL group than in the DB CBZ-CR/OL ESL group. The lower proportion of subjects with seizures in the DB ESL/OL ESL group (16 subjects [14.7%]) compared to the DB CBZ-CR/OL ESL group (23 subjects [23.7%]) was driven by the increased occurrence of seizures in the first 120 days on ESL treatment in the DB CBZ-CR/OL ESL. This increase may be a reflection of the transition period (up-titration of ESL and down-titration of CBZ-CR) for subjects switching from CBZ-CR to ESL. After the first 120 days, seizure frequency remained stable in the DB CBZ-CR/OL ESL group through Day 720 (i.e. approximately the time of the EOS visit).

Of those subjects with seizures, the majority of subjects in both groups had 1 or 2 seizures (9 of 16 subjects [56.3%] in the DB ESL/OL ESL group vs. 15 of 23 subjects [65.2%] in the DB CBZ-CR/OL ESL group), and most seizures lasted <5 min. The overall pattern of seizures by type was similar between groups, except for a lower proportion of subjects in the DB ESL/OL ESL group vs. the DB CBZ-CR/OL ESL group with complex partial seizures (6 subjects [5.5%] vs. 11 subjects [11.3%]) and partial evolving to secondarily generalised seizures (6 subjects [5.5%] vs. 13 subjects [13.4%]).

The decrease in ssf that was achieved during the DB study was maintained in both groups through the OL EOS.

The number of responders (a subject who experienced a ≥50% reduction in seizure frequency compared to the seizure frequency at DB baseline) remained above 80% throughout treatment in both groups.

The improvements in QOLIE-31 scores already observed in the DB study were maintained throughout OL extension study in both groups.

At all treatment visits, the vast majority of both the subjects' and investigators' assessments were either very good or good (≥80% of subjects per visit); no more than 2 subjects in either group had an assessment of poor.

Safety results:

The results of this study demonstrated the safety of ESL during long-term treatment (DB ESL/OL ESL group) and in subjects switching from CBZ-CR treatment (DB CBZ-CR/OL ESL group). In addition, the results of the Monotherapy Set demonstrated the safety of ESL monotherapy in both groups of subjects. The results were consistent with the known safety profile of ESL, and did not reveal new safety concerns related to the long-term use of ESL.

The proportion of subjects who experienced ≥1 treatment-emergent adverse event (TEAE) in the OL extension study was lower in the DB ESL/OL ESL group (63 subjects [57.8%]) than in the DB CBZ-CR/OL ESL group (65 subjects [67.0%]). The majority of TEAEs in both groups were mild or moderate.

The incidence of TEAEs was generally similar (≤5% difference) between groups when evaluated by both System Organ Class (SOC) and Preferred Term (PT), and no individual PT was reported in >10% of subjects in either group. The most frequently reported TEAEs were influenza, blood creatine phosphokinase increased, nasopharyngitis, hypertension, back pain, headache, dizziness, somnolence, bronchitis, and international normalised ratio increased.

The proportion of subjects who experienced TEAEs considered at least possibly related to the investigational medicinal product (IMP) was similar between groups (22 subjects [20.2%] in the DB ESL/OL ESL group vs. 20 subjects [20.6%] in the DB CBZ-CR/OL ESL group).

Three subjects in the DB ESL/OL ESL group died due to TEAEs (cerebral haemorrhage, pulmonary embolism, and sudden death). None of the TEAEs were assessed as related to the IMP by the investigator and sponsor.

The proportion of subjects who experienced serious TEAEs was low and similar between the DB ESL/OL ESL group (10 subjects [9.2%]) and DB CBZ-CR/OL ESL group (7 subjects [7.2%]). No individual serious TEAE PT was reported by >1 subject in either group. One serious TEAE (seizure) in the DB CBZ-CR/OL ESL group was considered possibly related to IMP by the investigator and sponsor.

The proportion of subjects with TEAEs leading to discontinuation of the IMP was low in both groups (3 subjects [2.8%] in the DB ESL/OL ESL group vs. 6 subjects [6.2%] in the DB CBZ-CR/OL ESL group). Similarly, in the Monotherapy Set of the OL SAF, a small proportion of subjects in both groups discontinued the IMP due to TEAEs (3 subjects [3.1%] in the DB ESL/OL ESL group vs. 4 subjects [4.5%] in the DB CBZ-CR/OL ESL group). None of the TEAEs leading to discontinuation were reported in >1 subject, except for hyponatraemia (1 subject in each group in the overall OL SAF, and 1 subject in the DB ESL/OL ESL group in the Monotherapy Set of the OL SAF).

The proportion of subjects with TEAEs of special interest by AE group was similar between groups, and the most frequently reported TEAEs of special interest (dizziness, headache, and somnolence) were consistent with the known safety profile of ESL. Hepatic disorder TEAEs were reported in a low and similar proportion of subjects in both groups (9 subjects [8.3%] in the DB ESL/OL ESL group vs. 5 subjects [5.2%] in the DB CBZ-CR/OL ESL group).

For nearly all laboratory parameters, no relevant changes over time or differences between groups were observed. Exceptions were observed in the proportion of subjects with high gamma-glutamyltransferase (GGT) (which increased in the DB ESL/OL ESL group [from 21.9% at OL baseline to 28.2% at OL EOS], but decreased in the DB CBZ-CR/OL ESL group [from 49.5% at OL baseline to 16.3% at OL EOS]), and high cholesterol (total) (which decreased in both groups, but more substantially decreased in the DB CBZ-CR/OL ESL group). However, as these changes were not corroborated by similar changes in other laboratory parameters, or by hepatic dysfunction (for GGT), no clinically meaningful conclusions from these changes can be made. No subject in the OL SAF discontinued the IMP due to GGT or any hepatic-related laboratory changes.

The majority of subjects in both groups had sodium values >130 mEq/L throughout the study (93.6% in the DB ESL/OL ESL group vs. 92.8% in the DB CBZ-CR/OL ESL group). A sodium decrease of >10 mEq/L from OL baseline was observed in 1 subject (0.9%) in the DB ESL/OL ESL group and 5 subjects (5.2%) in the DB CBZ-CR/OL ESL group. Sodium levels ≤125 mEq/L were observed in no more than 3 subjects (≤3.1%) in either group. One subject in each group discontinued the IMP due to hyponatraemia.

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*
There were no clinically meaningful changes over time or differences between groups in vital signs, neurological examinations, or ECGs. Suicidal ideation was reported via the C-SSRS for 1 subject in the DB ESL/OL ESL group only. Other than 1 subject in each group who actually showed improvement in suicidal ideation at OL endpoint, there were no suicide-related events. Throughout the OL extension study, no relevant changes in mean scores over time or differences between groups were observed for any of the Bond-Lader factors of alertness, calmness, or contentedness.		
Conclusions: This study has demonstrated that the efficacy, safety, and tolerability of ESL monotherapy observed in the initial Phase 3 study was sustained during long-term treatment in subjects initially treated with ESL and in those who transitioned from CBZ-CR monotherapy treatment.		
Date of final report: 08-Apr-2019		