STUDY SYNOPSIS

Sponsor: BIAL – Portela & Ca, S.A. **Finished Product:** BIA 2-093 **Active ingredient:** Eslicarbazepine acetate	Individual Study Table Referring to Part XX of the Dossier Volume: Page:	*(For National Authority Use only)*
Title of study: Efficacy and safety of Eslicarbazepine acetate (BIA 2–093) as therapy for subjects with post–herpetic neuralgia: a double–blind, double–dummy, randomised, placebo–controlled, parallel–group, multicentre clinical trial. Note: the design features mentioned in the title refer to the double-blind part of the study.		
Study centres: Double-blind part: 87 centres in 14 countries (Austria, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Lithuania, Poland, Portugal, Romania, Slovakia, Russia and Ukraine). Open-label extension: 43 centres in 11 countries (Austria, Bulgaria, Croatia, Germany, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, and Ukraine).		
Study period (open-label extension): Date first patient enrolled: 25 June 2008 Date last patient completed: 19 May 2010		Clinical Phase: II
Objectives: <u>Objective for the open-label extension</u>: to assess the safety and tolerability of Eslicarbazepine acetate (ESL) during chronic use in patients with post–herpetic neuralgia.		
Methodology: **Double-blind part** was a multinational, randomised, double–blind, double–dummy, placebo–controlled, parallel–group, Phase II clinical trial with 567 randomized patients with post-herpetic neuralgia. The study started with a baseline period of 14 days in which patients must have been free of any medication that could affect efficacy (except authorized rescue medication). In case of unbearable pain, this drug free period might have been reduced, but must have been at least 7 days. At the end of the baseline period, eligible patients were randomly assigned in a proportion of 1:1:1:1:1:1 to one of the following 6 treatment groups: ESL 400 mg twice–daily (BID), ESL 800 mg once–daily (QD), ESL 600 mg BID, ESL 1200 mg QD, ESL 800 mg BID or placebo. During the 1-week titration period, patients were treated with half of the assigned daily dose. During the 8–week maintenance period, patients received their full daily dose if they presented normal renal function. If patients had a creatinine clearance between 30 and 60 mL/min, they received half of the assigned dose, and patients with a creatinine clearance below 30 mL/min were not enrolled in this study. At the end of the 8-week maintenance period, patients underwent the end-of-study examinations and were followed-up for 2 weeks, in which they could receive their pre-study treatment or any other treatment for post-herpetic neuralgia or they entered an open–label treatment with ESL.		

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The **open-label** (OL) **extension** first visit (OL1) was planned to occur 4 weeks after Visit 5 and the following visits were to take place at least at 12 weeks intervals (OL2, OL3, OL4, OL5). Between Visit 5 and OL1 the investigator had to contact the patient and to decide if a change of daily dose and/or regimen was necessary or not. Treatment of all patients was to start at Visit 5 (end of study medication of double-blind part) with 400 mg once daily for 1 week. After that, based on individual response and tolerability the daily dose might be increased up to a maximum daily dose of 1600 mg at 400 mg steps. Daily doses up to 1200 mg could be administered once-daily or divided into two doses. Daily dose of 1600 mg had to be divided in two doses of 800 mg each. An open-label follow-up visit had to occur at 1 month after completion or premature discontinuation from the open-label extension.

Not all patients started the OL immediately after the double-blind part. The open-label extension was not planned in the initial protocol and the approval dates were only obtained after the double-blind part was finalized for some patients. Therefore some patients had an interruption between the end of the double-blind part and the start of the open-label part. As the treatment interruption could have an effect in the outcomes, analysis was conducted for all patients (ITT set) and for patients without interruption (planned ITT set). Patients without interruption were defined as patients without treatment interruption or at most two days without treatment since the last intake in the double-blind part. Only 39 patients of 151 started the treatment with ESL without interruption. The median time to treatment initiation was 37.0 days with the maximum time interval of 258.0 days.

Number of patients:

Planned: there was no sample size estimation for open-label extension of the study.
Enrolled: 151 patients.
Analysed for safety: 151 patients in the safety set.
Analysed for efficacy:
138 patients in the intention-to-treat (ITT) set,
37 patients in the intention-to-treat set-as planned (planned ITT) set.

Diagnosis and main criteria for inclusion:

Open-label extension: completion of double-blind part of the study and willingness to continue in the open-label extension.

Double-blind part:

- Men and women 18 years of age or older.
- Previous diagnosis of herpes zoster.
- Post–herpetic neuralgia and neuropathic pain present for more than 3 months after healing of the herpes zoster skin rash.
- Completion of at least 4 daily diary entries during the week preceding randomisation.
- A minimum average daily pain score of 4 on the NRPS in the last 4 diary entries before randomisation.

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

ESL was administered orally and supplied as tablets of 400 mg (batch numbers PD286M-001, PD286M-002, PD286M-003) and 600 mg (batch numbers PD287M-001).

Using appropriate combinations of the ESL 400 mg or 600 mg tablet strengths the following ESL dosing was allowed during the open-label extension: 400 mg QD, 400 mg BID, 600 mg BID, 800 mg QD and 800 mg BID. The start dose was 400 mg QD and then based on individual response and tolerability might be increased up to a maximum daily dose of 1600 mg at 400 mg steps.

Duration of treatment:

Double-blind part: ESL or placebo was administered during the 1–week titration period and the 8–week maintenance period.

The duration of treatment in the open-label extension was 1 year.

Reference therapy dose and mode of administration, batch number:

Not applicable.

Criteria for evaluation:

Efficacy (for open-label extension): The change in pain compared to Visit OL1 was calculated to assess the long-term treatment effect during the open-label extension using Numeric Rating Pain Scale (NRPS). Other efficacy variables based on NRPS: categorized pain at double-blind baseline, double-blind endpoint and each open-label extension visit; responder rates (reduction in endpoint pain with respect to double-blind baseline mean pain by at least 30% or 50%). Time to withdrawal due to lack of efficacy or adverse events. Patient's Global Impression of Change (PGIC), Clinician's Global Impression of Change (CGIC), Quality of Life Index – Short-Form (36-item) Health Survey Questionnaire (SF-36).

Safety (for open-label extension): Extent of exposure, adverse events (AEs), laboratory safety data (haematology, biochemistry), vital signs (blood pressure, heart rate), 12-lead electrocardiogram (ECG).

Statistical methods:

Efficacy analysis: The efficacy analyses of the open-label extension were performed using descriptive statistics. The distribution of the time to withdrawal due to lack of efficacy or adverse event was descriptively summarized using Kaplan-Meier estimation. Absolute values of the 8 multi-item subscales (transformed scores) of the SF-36 Health Survey and the absolute and relative changes from double-blind baseline by subscale were analyzed using summary statistics.

Safety analysis: Safety variables were analyzed using summary statistics.

Summary – Conclusions

Efficacy results:

During the open-label extension period, pain changes from baseline seen in the double-blind phase were not only maintained for 1-year, but additional pain score reduction was observed as assessed by patients using NRPS. In the ITT set at the beginning of the extension phase (visit OL1), the mean (SD) pain score was 4.3 (2.08), which was comparable with the mean score at the end of the double-blind period: 4.1 (2.55). Mean pain scores were gradually decreasing during all open-label period: from 3.4 (2.23) at OL2

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to 2.3 (2.13) at OL5. At the endpoint of the open-label extension period (missing values inputted via LOCF), mean pain score was 3.0 (2.63). The largest change in mean pain score from the double-blind baseline was at Visit OL5 where the absolute change was -3.9 (2.29). At the endpoint of the open-label extension period the mean absolute change was -3.3 (2.68) from the double-blind baseline, and -1.3 (2.01) from the OL1, corresponding to decreases of -53.0% and -30.6%, respectively. In the planned ITT set at the beginning of the extension phase (visit OL1), the mean (SD) pain score was 4.1 (1.93), which was comparable with the mean score at the end of the double-blind treatment 4.3 (2.41). The largest change in mean (SD) pain score from the double-blind baseline was at visit OL5 where the absolute change was -3.7 (2.26). At the endpoint of the open-label extension the absolute change from the double-blind baseline was -2.6 (3.00) and -0.5 (2.43) from the OL1, corresponding to decreases of -41.7% and -12.3%, respectively.

The prevalent pain intensity during the open-label extension period was categorized as being mild. The number of patients feeling no or mild pain was within ranges of 58% to 85% in the ITT set and 61% to 84% in the planned ITT set. At the double-blind baseline there were only 10.1% of such patients in the ITT set and 10.8% of patients in the planned ITT set.

At the endpoint of the open-label extension the ≥30% and ≥50% responder rate was 75.4% and 64.5%, corresponding to an increase from the double-blind endpoint of 37% and 75%, respectively (ITT set). In the planned ITT set the ≥30% and ≥50% responder rate at the end of the open-label extension was 67.6% and 51.4%, respectively. At the end of the open-label extension period the majority of patients and clinicians indicated at least minimal improvement in pain comparing to the double-blind baseline. Overall there were no differences in the PGIC and CGIC scores between the end of the double-blind part and at the endpoint of the open-label extension period.

Quality of life was assessed by the SF-36 Health survey questionnaire. At the last open-label extension period assessment, comparing to the double-blind baseline, largest improvements were observed for bodily pain (87% and 46.3%, ITT and planned ITT sets, respectively). Magnitude of changes was smaller for the other subscales ranging from 13.1% to 35.9% in the ITT set, while in the planned ITT set scores remained relatively unchanged (-3.1% to 16.6%).

Safety results:

Mean (SD) duration of treatment during the open-label study extension with ESL was 295.9±118.24 days. The mean (SD) daily dose of ESL calculated for the entire open-label extension period in the safety set was 744.5±283.94 mg and the median daily dose was 769.2 mg, ranging between the minimum and maximum doses of 400 mg and 1561.8 mg.

During the open-label extension of the study 86 patients (57.0%) experienced at least one treatment-emergent adverse event (TEAE). The SOCs most commonly affected during the open-label extension of the study were nervous system disorders (17.9% of patients), infections and infestations (14.6%) and gastrointestinal disorders (13.2%). The most frequent individual TEAEs were dizziness (6.6% of patients), headache (5.3%), followed by cystitis, hypertension, nasopharyngitis and nausea each reported for 3.3%.

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During the first four weeks of open-label extension the incidence of TEAEs in patients treated with placebo in the double-blind part who entered open-label without or with short interruption was not relevantly different from that in patients treated with different ESL doses.
The incidence of at least possibly related TEAEs was 27.8% (80 TEAEs were reported for 42 patients), with the most frequent being dizziness (6.0% of patients), nausea (3.3%), fatigue (2.6%) and vertigo (2.6%).
The majority of reported TEAEs were of mild or moderate intensity. In total 18 severe TEAEs were reported for 12 patients (7.9%).
In total, 14 patients (9.3%) experienced 16 serious TEAEs (TESAEs), all of them were assessed by the investigators as not or unlikely related to study treatment. One patient died due to severe pneumonia, assessed as not related to study treatment. According to sponsor's judgment two of these TESAEs: hyponatraemia and suicide attempt were considered possibly related to treatment with ESL. Overall 17 patients (11.3%) discontinued the study prematurely due to 25 TEAEs. Frequency of individual TESAEs or TEAEs leading to discontinuation was low and the vast majority of such TEAEs were reported for only one patient.
No relevant changes occurred in mean and median values for laboratory variables or vital signs over time. A total of six patients (4.3%) had a sodium value <130 mmol/L during the open-label extension of the study. The minimum sodium value observed was 124 mmol/L. Two patients had hyponatraemia reported as treatment emergent adverse events.
For laboratory parameters, vital signs, and ECG parameters, the incidence of clinically relevant findings was low.

Conclusions:

During the 1-year open label administration of Eslicarbazepine acetate there were no new significant safety or tolerance issues observed. For the subjects who entered the open-label extension, pain changes from baseline seen in the double-blind phase were not only maintained, but additional pain score reduction was observed throughout the 1-year study duration.

Date of final report:

26 April 2011