STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], SA **Product:** BIA 2-093 **Active ingredient:** Eslicarbazepine acetate	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of study:

Efficacy and safety of Eslicarbazepine acetate (BIA 2-093, ESL) as therapy for patients with painful diabetic neuropathy: 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: 62 centres in 11 countries (Austria, Croatia, Czech Republic, Germany, Hungary, Poland, Portugal, Romania, Russia, Slovakia, and Ukraine).

Open-label extension: 29 centres in nine countries (Austria, Croatia, Germany, Hungary, Poland, Romania, Russia, Slovakia, and Ukraine)

Study period (open-label extension):	**Clinical Phase:**
Date first patient enrolled: 06JUN2008 Date last patient completed: 25MAR2010	II

Objectives:

Objective for the open-label extension: to assess the safety and tolerability of ESL during chronic use in patients with painful diabetic neuropathy over a 1-year open-label extension.

Secondary objectives: not defined.

Methodology:

Double-blind part was a randomised, double-blind, double-dummy, placebo-controlled, multicentre, parallel-group, dose finding, Phase II clinical study. A 2-week baseline period was followed by a 1-week titration period, a 12-week maintenance period, and 2-week safety follow-up period.

During the 2-week baseline period, current neuropathic pain drug therapy was discontinued and patients had to be free of any medication that could affect efficacy (except authorized rescue medication) for 2 weeks before start of double-blind study treatment. In case of unbearable pain, this drug-free period could be reduced, but had to be at least 7 days.

At the end of the baseline period, patients were randomly assigned in a 1:1:1:1:1:1 ratio to 1 of the following 6 double-blind treatment groups: placebo, ESL 400 mg twice daily (BID), ESL 800 mg once daily (QD), ESL 600 mg BID, ESL 1200 mg QD, or ESL 800 mg BID. During the 1-week titration period, patients were treated with half of the daily dose of their assigned treatment group. During the 12-week maintenance period, patients received their daily dose if they had normal renal function. If patients had a creatinine clearance between 30 and 60 mL/min, they were to receive half of the assigned dose. Patients with a creatinine clearance below 30 mL/min were not enrolled in this study.

At the end of the 12-week maintenance period, patients underwent the end-of-study examinations and were followed-up for safety for 2 weeks or were to start an open-label treatment with ESL.

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Methodology:

The **open-label extension** first visit (OL1) was planned to occur 4 weeks after Visit V6 and the following visits were to take place at least at 12 weeks intervals (OL2, OL3, OL4, OL5). Between V6 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 V6 (end of study examination 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 open-label extension 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 38 patients of 159 started the treatment with ESL without interruption. The median time to treatment initiation was 95.0 days with the maximum time interval of 248.0 days.

Number of patients:

Planned: there was no sample size estimation for open-label extension of the study.
Enrolled set: 159 patients.
Analysed for safety: 159 patients in the safety set.
Analysed for efficacy:
154 patients in the intention-to-treat (ITT) set,
38 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 at least 18 years old; diagnosis of diabetes mellitus type 1 or 2; pain attributed to diabetic neuropathy for more than 1 year prior to enrolment; stable glycaemic control: (total glycated haemoglobin A_{1c} [HbA_{1c}] level ≤11% at screening); completion of at least 4 daily diary entries during the week preceding randomisation; a minimum average daily pain score of 4 on the numeric rating pain scale (NRPS) in the last 4 diary entries before randomisation.

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

ESL was administered orally and supplied as tablets of 400 mg (for Slovakia batch number 060156-L, for other countries lot numbers: PD286M-001, PD286M-002, PD286M-003) or tablets of 600 mg (for Slovakia batch number 060157-L, for other countries lot number 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, 1200 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.

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Duration of treatment:

Double-blind part: ESL or placebo was administered during the 1-week titration period and the 12-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 analysed using summary statistics.

Safety analysis: Safety variables were analysed using summary statistics.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

During the open-label extension period, pain changes from baseline seen in the double-blind phase were maintained throughout 1-year 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 3.7 (2.04), which was comparable with the mean score at the end of the double-blind period 3.7 (2.07). Mean pain scores remained relatively low and stable over 12 months, ranging from 3.5 (2.47) at OL2 to 2.9 (2.10) at OL5. At the endpoint of the open-label extension period (missing values inputted via LOCF), mean pain score was 3.2 (2.22).

The largest change in mean (SD) pain score from the double-blind baseline was at visit OL4 where the absolute change was -3.5 (2.28). At the endpoint of the open-label extension period the mean absolute change was -3.1 (2.50) from the double-blind baseline and -0.6 (2.04) from the OL1, corresponding to decreases of -49.5% and -15.3%, respectively. In the planned ITT set, at the beginning of the extension phase (visit OL1), the mean (SD) pain score was 3.3 (2.08), which was comparable with the mean score at the end of the double-blind treatment 3.3 (1.99). The largest change in mean (SD) pain score from the double-blind baseline was at Visit OL3 where the absolute change was -4.4 (2.30). At the endpoint of the open-label extension period the absolute change from the double-blind baseline was -2.9 (2.77) and -0.1 (2.44) from the OL1, corresponding to decreases of -47.4% and -2.4%, 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 66% to 84% in the ITT set and 79% to 90% in the planned ITT set. At the double-blind baseline there were 8% of such patients in the ITT set and 11% of patients in the planned ITT set.

At the endpoint of the open-label extension the ≥30% and ≥50% responder rate in the ITT set was 71.4% and 56.5%, corresponding to an increase from the double-blind endpoint of 25% and 32%, respectively. In the planned ITT set the ≥30% and ≥50% responder rate at the end of the open-label extension was 63.2% and 52.6%, 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.

Quality of life was assessed by the SF-36 Health survey questionnaire. At the last open-label extension period assessment mean scores of all subscales comparing to the double-blind baseline scores increased. The largest relative changes were recorded in bodily pain and vitality.

SAFETY RESULTS:

Mean (SD) duration of treatment during the open-label study extension with ESL was 328.7±90.0 days. The mean (SD) daily dose of ESL calculated for the entire open-label extension period in the safety set was 848.9±300.0 mg and the median daily dose was 792.3 mg, ranging between the stipulated minimum and maximum doses of 400 mg and 1548 mg.

During the open-label extension period the incidence of treatment emergent AEs (TEAEs) in the safety set (n=159) was 59.1%. A total of 94 patients reported 294 TEAEs. During the study the most commonly affected System Organ Classes were: nervous system disorders (17.4% of patients), metabolism and nutrition disorders (15.1%), infections and infestations (15.1%), gastrointestinal disorders (14.5%), musculoskeletal and connective tissue disorders (11.9%), vascular disorders (11.3%) and investigations (10.7%). The most frequent individual TEAEs reported for ≥5% of patients were hyperglycaemia and hypertension, reported for 5.7% patients each, and dizziness and somnolence, reported for 5.0% patients

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each.

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 majority of TEAEs were assessed as mild or moderate. In total, 18 severe TEAEs were reported by 6.9% of patients.

The incidence of at least possibly related TEAEs was 23.9%, with the most frequent being somnolence (4.4%), diarrhoea (3.8%) and gamma-glutamyltransferase increased (2.5%).

No deaths occurred during the open-label extension. Overall 16 patients (10.1%) experienced 25 serious TEAEs (TESAEs) all of them were assessed as unlikely or not related to study treatment. Twelve patients (7.5%) prematurely discontinued from the study due to 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 6 subjects (3.9%) had a sodium value <130 mmol/L during the study. The minimum sodium value observed was 126 mmol/L. Two subjects had hyponatraemia reported as adverse event.

Two of 14 abnormal ECGs assessed by the investigators as being clinically significant had new abnormalities that were not documented in medical history or during double-blind part of the study. These abnormalities were extrasystole and right bundle branch block; and complete left bundle branch block and delay of AV conduction.

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, changes in pain observed at the end of the double-blind phase were maintained throughout the 1-year study duration.

Date of final report:

24 February 2011