STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], SA **Product:** Zebinix®/Exalief® **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 subjects with painful diabetic neuropathy: a double-blind, double-dummy, randomised, placebo-controlled, parallel-group, multicentre clinical trial

Study centres:

62 centres in 11 countries (Austria, Croatia, Czech Republic, Germany, Hungary, Poland, Portugal, Romania, Russia, Slovakia, and Ukraine).

Study period:	**Clinical Phase:**
Date first subject enrolled: 06 Nov 2007 Date last subject completed: 18 Nov 2008	II

Objectives:

Primary objective: to assess the efficacy of ESL as therapy for subjects with painful diabetic neuropathy.

Secondary objectives: to assess the safety, tolerability, and the potential for drug-drug pharmacokinetic interactions of ESL in subjects with painful diabetic neuropathy.

Methodology:

This 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 subjects 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, subjects 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, subjects were treated with half of the daily dose of their assigned treatment group. During the 12-week maintenance period, subjects received their daily dose if they had normal renal function. If subjects had a creatinine clearance between 30 and 60 mL/min, they were to receive half of the assigned dose. Subjects with a creatinine clearance below 30 mL/min were not enrolled in this study.

At the end of the 12-week maintenance period, subjects 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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Number of subjects:

Planned: 540 subjects (90 in each of the 6 treatment groups).
Randomised and treated: 557.
Analyzed for efficacy (modified intention-to-treat [Mod. ITT]): 554.
Analyzed for efficacy (per-protocol [PP]): 403.
Analyzed for safety: 557.

Diagnosis and main criteria for inclusion:

- Men and women 18 years of age or older.
- 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 supplied as 400 mg (batch number 70311, 70594, 70595, 70597), 600 mg (batch number 70322) and 800 mg (batch number 70301, 70585, 70586, 70588, 70589, 70590) tablets.

Using appropriate combinations of the ESL 400 mg, 600 mg, and 800 mg tablet strengths, and placebo tablets to maintain the double-dummy study design, ESL was administered orally during the maintenance period at a dose of 400 mg BID, 800 mg QD, 600 mg BID, 1200 mg QD, or 800 mg BID. If subjects had a creatinine clearance between 30 and 60 mL/min, they received half of the assigned dose.

Duration of treatment:

ESL or placebo was administered during the 1-week titration period and the 12-week maintenance period.

Reference therapy dose and mode of administration, batch number:

Placebo tablets matching either the ESL 400 mg and 600 mg tablets (batch number 70328, 70329, 70593, 70841) or the ESL 800 mg tablet (batch number 70299, 70300) were administered orally. Placebo was administered either as a control treatment, or together with ESL to maintain the double-dummy study design.

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Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from baseline to endpoint in mean pain (NRPS). Endpoint mean pain was defined as the mean of the last 4 available pain scores in the last 7 days of the treatment period. Likewise, baseline mean pain was defined as the mean of the last 4 available pain scores in the last 7 days of the baseline period.

Secondary efficacy variables based on the NRPS pain scores were responder rates (reduction in endpoint mean pain by at least 30% or at least 50% with respect to baseline), mean pain per week in the maintenance period, mean pain in the titration period, and average mean pain per day. Other secondary efficacy variables were: pain assessed via the sensory portion of the Short-Form McGill Pain Questionnaire (SF-MPQ), Patient's Global Impression of Change (PGIC), Clinician's Global Impression of Change (CGIC), mechanical (dynamic, static, and pinprick) and thermal (hot and cold) allodynia (evoked pain) assessed by the allodynia severity rating, assessment of sleep disturbance by the Chronic Pain Sleep Inventory (CPSI), and use of rescue medication.

Safety: Adverse events (AEs), standard laboratory safety data (haematology, biochemistry), vital signs (blood pressure, heart rate), physical and neurological examinations, 12-lead electrocardiogram (ECG).

Pharmacokinetics: Plasma concentrations of ESL and anti-diabetic drugs.

Quality of life: Quality of Life Index – Short-Form (36-item) Health Survey Questionnaire (SF-36).

Statistical methods:

Efficacy analysis: The primary alternative hypothesis was that the change from baseline to endpoint in mean pain for subjects treated with ESL was different from that for subjects treated with placebo in at least one of the ESL treatment groups. Primary comparisons, which were performed using the Mod. ITT set, evaluated the effect in each of the ESL groups versus placebo. (The Mod. ITT set was defined as the set of all randomised subjects with at least 1 study medication intake and at least 1 post-randomisation rating of 24-h average pain.)

The change from baseline to endpoint in mean pain was analyzed using an analysis of covariance (ANCOVA) with treatment, region and dosage group (half or full dose depending on the subject's creatinine clearance evaluated at Visit [V] 1) as fixed effects and baseline mean pain as a covariate. The primary hypothesis was tested using 5 two-sided tests at an overall significance level of 0.05. Due to the multiple comparisons, an adjustment of the significance level for each single test was performed via Dunnett's procedure.

Responder rates were compared with the pairwise Cochran-Mantel-Haenszel (CMH) tests stratified by region. Summary statistics were presented for the mean pain per week, mean pain in the titration period and the average pain per day. Time to onset of therapeutic pain was summarized using Kaplan-Meier estimates. The other secondary variables were summarized descriptively and analyzed by an ANCOVA or stratified CMH test, whichever was applicable.

Safety analysis: Safety variables were analyzed using summary statistics.

Quality of life analysis: Absolute values of the multi-item sub-scales and the absolute and relative changes from baseline were analyzed using summary statistics. Changes from baseline were also analyzed by an ANCOVA model with region and gender as fixed effects and the baseline value of the respective sub-scale as a covariate.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

After 12 weeks of treatment, although decreases in the least-squares (LS) mean for pain were larger in the ESL groups than in the placebo group, no statistically significant difference between the 5 ESL groups and placebo was seen in the primary analysis, i.e. the ANCOVA of change in the Mod. ITT set for the difference between endpoint mean pain and baseline mean pain, based on an assessment of pain intensity on an 11-point (0 – 10) NRPS as recorded in the subject diary. When the ESL groups were pooled by total daily dose, the difference between the ESL 800 mg/day dose and placebo for the change in mean pain from baseline to endpoint was statistically significant (p=0.0379).

Responder rates at V6 or early discontinuation visit (EDV) showed that the proportion of ESL subjects with a reduction in mean pain was greater than in the placebo group (between 5.1% and 17.7% greater for a reduction of at least 30% and between 5.2% and 13.8% greater for a reduction of at least 50%); the difference to placebo was only statistically significant for the ESL 400 mg BID group for a reduction of at least 30%. None of the other secondary efficacy variables showed a difference between placebo and any of the ESL treatment groups for changes between baseline and V6/EDV.

SAFETY RESULTS:

The most commonly reported treatment-emergent adverse events (TEAEs) in this study were those known to be common to this class of drug, namely nervous system and gastrointestinal disorders. TEAEs occurred most frequently in the ESL 1200 mg QD and the ESL 800 mg BID group, ranging from 32.3% of subjects in the placebo group to between 38.0% (ESL 800 mg QD) and 51.8% (ESL 1200 mg QD) of subjects in the ESL treatment groups, and can be summarized as follows:

- The most commonly reported TEAEs were vomiting, dizziness and nausea in up to 12% of subjects in the ESL 800 BID group, but otherwise in between 1% and 8% of subjects in the other treatment groups.
- At least possibly related TEAEs were reported by 19.8% in subjects of the placebo group, and between 22.8% and 38.0% in subjects of the ESL treatment groups.
- The incidence of severe TEAEs was <12% in any treatment group with the highest incidence in the ESL 800 mg BID (9.0%) and 1200 mg QD (11.8%) groups.
- A total of 79 subjects discontinued the study prematurely due to the occurrence of a TEAE: 6.3% of the placebo group, and between 8.7% and 24.0% of the ESL treatment groups.

For laboratory parameters, vital signs, and ECG parameters, there were few clinically relevant findings. For the majority of the laboratory analytes measured there were very few subjects with shifts to either below or above normal levels and who reported any clinically significant laboratory abnormalities.

QUALITY OF LIFE RESULTS:

There were no major changes in mean scores of the SF-36 Health Survey from V2 to V6 or EDV during the study.

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CONCLUSIONS: Although decreases in the LS mean for pain as measured by the NRPS were larger in the ESL groups than in the placebo group after 12 weeks of treatment, the only statistically significant difference was between the pooled ESL 800 mg/day group and placebo. The safety profile of the ESL 1200 mg QD and ESL 800 mg BID dose was less favourable than the other treatment regimens. Further studies are necessary to elucidate the optimal dose regimen of ESL to reduce neuropathic pain.		
Date of final report: 17 November 2009		