STUDY SYNOPSIS

Sponsor: BIAL – Portela & Ca, S.A. **Finished Product:** Zebinix®/Exalief® **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.

Study centres:

87 centres in 14 countries (Austria, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Lithuania, Poland, Portugal, Romania, Slovakia, Russia and Ukraine).

Study period:	Clinical Phase:
Date first subject enrolled: 06 November 2007 Date last subject completed: 19 January 2009	II

Objectives:

Primary objective: to assess the efficacy of eslicarbazepine acetate (ESL) as therapy for subjects with post–herpetic neuralgia.

Secondary objectives: to assess the safety and tolerability of ESL in subjects with post–herpetic neuralgia.

Methodology:

This was a multicenter, randomised, double–blind, double–dummy, placebo–controlled, parallel–group, dose finding, Phase II clinical trial. An up to 2–week baseline was followed by a 1–week titration period, an 8–week maintenance period, and a 2–week safety follow–up period.

During the 2–week baseline period, current post–herpetic neuralgia drug therapy was discontinued and subjects had to be free of any medication that could affect efficacy (except not prohibited concomitant medication and 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 8–week maintenance period, subjects received their complete daily dose if they had normal renal function. If subjects had a creatinine clearance between 30 and 60 mL/min, they received half of the assigned dose, and subjects with a creatinine clearance below 30 mL/min were not enrolled in this study.

At the end of the 8–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: 567.
Analysed for efficacy (modified intention–to–treat): 561.
Analysed for efficacy (per–protocol): 396.
Analysed for safety: 567.

Diagnosis and main criteria for inclusion:

- 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.

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

ESL was supplied as 400 mg (batch numbers 070331, 070331, 070331, 070594, 070594, 070595, 070595, 070597, 080084), 600 mg (batch numbers 070332, 070332, 070332, 070332, 070332, 080093, 080094) and 800 mg (batch numbers 070301, 070301, 070301, 070589, 070588, 070586, 070589, 070596, 070590, 070596, 080066) tablets.

Using appropriate combinations of the ESL 400, 600, 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 8–week maintenance period.

Reference therapy dose and mode of administration, batch number:

Placebo tablets matching either the ESL 400 mg and 600 mg (batch numbers 070328, 070328, 070328, 070328, 070328, 070841, 070329, 070841, 080074, 080075) or the ESL 800 mg (batch numbers 070299, 070299, 070299, 070299, 070299, 070299, 080299) tablets 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 (numeric rating pain scale [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 prior to randomisation.

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 Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), the mechanical (static, dynamic and pinprick) and thermal 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), 12–lead electrocardiogram (ECG), vital signs (blood pressure, heart rate), physical and neurological examinations.

Quality of life: Quality of Life Index–Short Form 36 Health Survey (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 modified intention–to–treat (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 one 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 analysed 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 analysed by an ANCOVA or stratified CMH test, whichever was applicable.

Safety analysis: Safety variables were analysed using summary statistics.

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

Summary – Conclusions

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Demographic and baseline characteristics:

The demographic characteristics at screening were similar between the 6 treatment groups. The mean age per treatment group ranged from 65.4 to 68.0 years. The proportion of male subjects ranged from 28.9% to 52.7% (with the lowest number of males in the 2 highest ESL dose groups), and the mean body mass index (BMI) from 27.0 kg/m2 to 28.3 kg/m2. All subjects were Caucasian.

Efficacy results:

The primary efficacy variable was the change from baseline to endpoint in mean pain measured with the NRPS. Although the mean change in pain was greater in the ESL groups than in the placebo group, there was no statistically significant difference between placebo and any of the ESL treatment groups in the Mod. ITT set. However, for the per protocol (PP) set the difference for the reduction in pain in the ESL 800 mg BID group (LS mean change: - 2.75) compared to placebo (LS mean change: –1.64) was statistically significant (p=0.0277). For the pooled daily doses, no statistically significant differences were seen for the mean change in pain between placebo and the 3 daily doses in the Mod. ITT set, but in the completer set, in which subjects who had discontinued early were excluded from the analysis, the larger decrease in pain in the ESL 1600 mg/day was statistically significant compared to placebo (p=0.0334).

This tendency for greater improvement with the ESL 800 mg BID group was seen consistently for several of the secondary variables. The improvements compared to placebo were statistically significant for mean pain per week from Week 2 through Week 7 ($p<0.02$ at each time point), subject self–assessed pain using the PGIC at V5 (p=0.0370), clinician assessed pain using the CGIC at V5 (p=0.0373) and intake of rescue medication (p=0.0069). In addition, 30% of ESL 800 mg BID subjects did not take rescue medication compared to only 10% of placebo subjects.

Statistically significant differences in secondary efficacy variables were also seen in lower dose ESL treatment groups compared to placebo. These were the shorter onset of the therapeutic effect in the ESL 400 mg BID (p=0.0112) and the ESL 800 mg QD (p=0.0349) groups, and the later start to the first intake of rescue medication in the ESL 400 mg BID (p=0.0209), ESL 600 mg BID (p=0.0284), and the ESL 1200mg QD (p=0.0235) groups. None of the other secondary efficacy variables showed a difference between placebo and any of the ESL treatment groups.

Safety results:

Common AEs included dizziness, somnolence, headache, nausea, and vertigo. Most AEs occurred at mild or moderate intensities. AEs and treatment–emergent adverse events (TEAEs) affected more subjects in the ESL treatment groups compared to the placebo group and were highest in the ESL 800 mg BID treatment group. Discontinuations due to TEAEs were more prevalent in the ESL treatment groups compared to the placebo group and occurred most often in the ESL 800 mg BID treatment group.

Quality of life results:

In general, there were no major changes in mean scores of the SF–36 Health Survey from V2 to V5 or early discontinuation visit (EDV) in the Mod. ITT set. The only statistically significant difference seen was in the role–emotional subscale where the ESL 800 mg QD group had decreased role limitations due to emotional problems compared to the placebo group (p=0.0282).

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Conclusions: Overall, while slightly better efficacy was seen at most ESL doses compared to placebo, only the ESL 800 mg BID group showed a consistent pattern of statistically significant improved efficacy relative to placebo. The safety profile of the ESL treatment groups was less favourable than that of the placebo group, particularly in the highest ESL dose group, i.e. ESL 800 mg BID. Further studies are necessary to elucidate the optimal dose regimen of ESL to reduce post–herpetic neuralgia while minimising the safety risk.		
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