1. SYNOPSIS

Name of Sponsor/Company: BIAL – Portela & Cª S.A. **Name of finished product**: ESL tablets **Name of active ingredient**: Eslicarbazepine acetate	Individual Study Table referring to Part of Dossier Volume:	*(For authorities use only)*

Title:
A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Clinical Study of Eslicarbazepine Acetate in Post-Herpetic Neuralgia

Coordinating investigator:
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Study site(s):
Eighty nine (89) sites in 12 countries (Argentina, Austria, Chile, Czech Republic, Germany, India, Israel, Mexico, Poland, Russia, South Africa, and United Kingdom) participated in the study.

Publication reference:
None.

Study period:	**Clinical phase**:
Date of first admission: 2010.09.28 Date of last visit: 2012.04.23	III

OBJECTIVES:
Primary objective:
The primary objective of this study was to assess the efficacy of ESL as therapy in subjects with PHN over a 15-week treatment phase.
Secondary objective:
The secondary objective of this study was to assess the safety, tolerability, and pharmacokinetics of ESL in subjects with PHN over a 19-week treatment phase. It was also to evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over a 36-week OL phase and the maintenance of therapeutic effect of ESL over 32 weeks of OL ESL treatment at flexible doses.

Study design and methodology:
This was a multicenter, parallel-group, double-blind, randomized, placebo-controlled study of 3 ESL doses (800, 1200, or 1600 mg once-daily [OD]) compared with placebo for the treatment of PHN. Study duration was planned to be a 3-week titration phase, followed by a 12-week treatment maintenance phase and a 4-week follow-up phase (comprising 3-week tapering). Subjects had the option to enter a subsequent 36-week open label phase (32-week ESL treatment at flexible doses (between 800 and 1600 mg OD), followed by a 4 week follow-up phase (comprising a 3-week tapering)).

Signals of limited treatment effect have been identified by Sponsor's standard monitoring procedures of the accumulating available data. These signals were considered to deserve further evaluation to allow an understanding of the benefit of continuing treatment with ESL. Hence, recruitment was temporarily suspended and an unblinded interim analysis to evaluate

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the primary efficacy variable was performed by Accovion GmbH (Frankfurt, Germany). This analysis was not planned in the study protocol. Investigators, Authorities and Ethic Committees were informed on this decision. The analysis was performed in March 2012 and resulted in the decision to early terminate the trial as the treatment effect of ESL on PHN was of limited efficacy and unlikely to be clinically relevant.

As the study was prematurely halted, the planned analyses regarding efficacy outcomes were not performed. The efficacy analysis was restricted to the primary efficacy variable in the interim analysis population. Safety analyses were performed for the safety population as initially planned.

Number of subjects (planned and analyzed):
Planned: 392 subjects (98 in each treatment group).
Randomised: 242 subjects.
Analysed for efficacy (interim analysis population):

- FAS (full analysis set): 209 subjects;
- CTS (completed treatment set): 90 subjects.

Analysed for safety (double blind): 240 subjects.
Analysed for safety (open-label): 118 subjects.

Diagnosis and main criteria for inclusion:

- Male and female outpatients aged 18 years or older.
- Experiencing pain for at least 6 months after the healing of a herpes zoster skin rash. Subjects with PHN involving the trigeminal nerve must have medical documentation of a history of herpes zoster lesions, to avoid enrolling subjects with trigeminal neuralgia of mechanical etiology.
- A mean score between 4.0 and 9.0, inclusive, on the 24-hour average pain intensity assessment using the 11-point Numeric Rating Pain Scale (NRPS).
- A subject rated score at Visit 3 of 40 mm or more on a 100-mm visual analogue scale (VAS) for PHN during the previous 24 hours.
- Daily eDiaries completed for at least 70% of the 7 to 10 days between Visit 2 and Visit 3.
- If not used to treat PHN, subjects were permitted to take nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) if they were kept on a stable dose for 1 month prior to screening and were foreseen to remain stable throughout the study.

Test product, dose, administration route and batch numbers:
ESL was administered orally during the maintenance period at a dose of 800, 1200, or 1600 mg OD. During the double-blind part, ESL was supplied as tablets of 400 mg (batch numbers 100300/100301/100701) and 600 mg (batch numbers 100302, 100303 and 100702). To maintain the double-dummy study design during the 3-week titration phase plus the 12-week treatment maintenance phase and tapering-off, appropriate combinations of the 400 and 600 mg ESL tablet strengths, and placebo tablets (batch numbers 100299, 100699, and 100700)

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were used.
During the OL phase, ESL was supplied as divisible tablets of 800 mg (batch number 100306, 100305, and 110172). ESL was administered orally during the OL period at a dose between 800 and 1600 mg OD.

Duration of treatment:
ESL or placebo were to be administered during a 3-week titration period followed by a 12-week maintenance period and a 3-week tapering period. ESL was also to be administered during a 32-week OL period and a 3-week tapering period.

Reference therapy, dose, administration route:
Placebo tablets matching either the 400 or 600 mg ESL tablets were administered, either as a control treatment, or together with ESL to maintain the double-dummy study design.

CRITERIA FOR EVALUATION:
Efficacy: As the study was prematurely halted, the planned statistical analyses regarding efficacy outcomes were not performed. The efficacy analysis was restricted to the primary efficacy variable in the interim analysis population. The intended treatment period, starting on the day of the randomization and ending at the efficacy cut-off date (October 31, 2011), was the basis for the analysis. The primary efficacy variable was the difference between the mean values of 7 daily pain scores preceding the efficacy cut-off date (endpoint mean pain score), and before randomization (baseline mean pain score), respectively. The daily pain scores were based on the morning response to the 11-point Numeric Rating Pain Scale (NRPS) question relating to average pain intensity over the last 24 hours.

The following efficacy analysis sets were defined:

- the full analysis set (FAS) comprised all randomized subjects with mean pain score at baseline (before randomization) and mean score after randomization; subjects with less than 20 days of study medication were excluded from the dataset, except those that prematurely withdrew; this was the primary population used in the analysis.
- the completed treatment set (CTS) comprised all subjects from the FAS who had completed the double-blind part of the study by the cut-off date.

Safety: Adverse events (AEs), standard laboratory safety data (haematology, biochemistry), vital signs (blood pressure, heart rate), physical and brief neurological examinations, 12-lead electrocardiogram (ECG) and Columbia Suicide Severity Rating Scale (C-SSRS).

The safety population included all randomized subjects who received at least one dose of study treatment after randomization. All safety data is summarized for the safety population, separately for the double-blind and open-label periods.

STATISTICAL METHODS:
Efficacy: As the study was prematurely halted, the planned statistical analyses regarding efficacy outcomes were not performed. The efficacy analysis was restricted to the primary efficacy variable in the interim analysis population. The primary efficacy variable was the

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difference between the mean values of 7 daily pain scores preceding the efficacy cut-off date and before randomization, respectively. Descriptive statistics (number of subjects, mean, standard deviation, median, quartiles, min, max), box-whisker plots of mean pain scores at baseline, endpoint and change from baseline to endpoint were presented by treatment group and region and overall. An exploratory, non-confirmative statistical assessment of the primary efficacy variable was undertaken using an analysis of co-variance with fixed effects for treatment and region and mean pain score at baseline as a covariate. Comparisons between each ESL dose and placebo were made using Dunnett's adjustment for multiple comparisons within the family of hypotheses, and corresponding simultaneous 95%-confidence intervals of the differences between treatment groups were calculated. All statistical analysis were performed using SAS 9.2. Summaries of the efficacy data are presented by subject listings.

Safety: Summaries of TEAEs, potentially related TEAEs, treatment-emergent SAEs, TEAEs leading to discontinuation of study treatment and TEAEs leading to death were presented by treatment group. Physical and brief neurological examination, vital signs, body weight, ECG, clinical laboratory data and C-SSRS results were also summarized.

Pharmacokinetic analysis: ESL plasma concentrations were summarized descriptively by ESL treatment group.

Sample size calculations: The sample size estimation resulted in a sample size of 98 subjects per treatment group in order to achieve 90% power to detect a significant difference in change from baseline to endpoint mean pain between at least one ESL dose and placebo. The sample size estimation was based on an expected clinically relevant difference between ESL and placebo of 1.1 units in mean pain score relative to common standard deviation of 2.1 units. Based on the same assumptions, approximately 50 subjects per treatment group were needed so the statistical power of the interim analysis was above 60%. This would allow a judgment better than chance under the alternative hypothesis that at least one dose of ESL has a clinically relevant effect. Per the number of subjects included in the interim analysis (FAS population), the comparisons ESL vs. placebo have a power between 60% and 61% (calculations by means of nQuery Advisor® 7.0).

SUMMARY – CONCLUSIONS (ANALYSED POPULATION)

A total of 369 subjects were screened for eligibility to participate in the study. A total of 242 subjects were randomized to study treatment.

The analysis sets were:

- Safety population: 60 subjects PLC; 60 subjects ESL 800mg; 60 subjects ESL 1200mg; 60 subjects ESL 1600mg.
- Interim analysis population:
  - FAS population: 51 subjects PLC; 53 subjects ESL 800mg; 53 subjects ESL 1200mg; 52 subjects ESL 1600mg.

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- CTS population: 26 subjects PLC; 22 subjects ESL 800mg; 24 subjects ESL 1200mg; 18 subjects ESL 1600mg.
- OL safety population: 118 subjects

EFFICACY RESULTS (interim analysis): At the efficacy interim endpoint (mean treatment duration 71.6 days) no significant difference between the 3 ESL groups and placebo was seen for the change in mean pain scores from baseline. The differences between ESL groups and placebo were small and lower than assumed when the study was planned. The difference between ESL and placebo in the FAS population did not exceed -0.57 points in the pain scale, considerably below the assumed treatment effect of -1.1 (ESL 800 mg -0.17, 95% CI: [-1.00,0.66], p=0.932; ESL 1200 mg -0.57, 95% CI: [-1.41,0.28], p = 0.261; ESL 1600 mg -0.42, 95% CI: [-1.25,0.40], p=0.476). Results for the CTS population confirmed the FAS analysis. For the CTS the largest treatment group difference was -0.98 for ESL 1600mg (95% CI: [-2.26, 0.31], p=0.179).

SAFETY RESULTS:

- More than two-thirds of subjects in active treatment groups experienced at least 1 TEAE during the DB period, compared to less than half of placebo-treated subjects (68.3% ESL 800 mg, 66.7% ESL 1200 mg, 76.7% ESL 1600 mg versus 41.7% placebo). During the OL period 49.2% of the subjects experienced at least one TEAE.
- The most common TEAEs (>5%) occuring in higher frequency in the ESL groups compared to placebo were dizziness (13.9% vs. 0%), nausea (12.2% vs. 0%), headache (11.1% vs. 3.3%), hyponatremia (7.8% vs. 0%), vertigo (6.1% vs. 1.7%), and fatigue (5.6% vs. 1.7%). These events were more frequent in the 3 active treatments than in placebo and, overall, the incidences were noticeably higher in the ESL 1600 mg group. Only one case of diplopia was reported (ESL 1600 mg). The incidence of these events was lower in the OL period: dizziness, nausea and hyponatremia were the most common TEAEs affecting up to 11% of the subjects.
- Subjects in the placebo group (21.7%) had fewer TEAEs that were reported as potentially related to study drug compared to subjects in the active treatment groups (43.3% ESL 800 mg, 40.0% ESL 1200 mg and 56.7% ESL 1600). During the OL period, at least possible related TEAEs were reported by 33.1% of the subjects.
- The majority of TEAEs were of mild or moderate intensity across the 4 treatment groups. The incidence of severe TEAEs was higher for the 3 active treatment groups compared to placebo (6.7% placebo, 13.3% ESL 800 mg, 10.0% ESL 1200 mg and 18.3% ESL 1600 mg). TEAEs reported as severe affecting ≥2 subjects in any treatment group were nausea, dizziness, vomiting and fatigue. During the OL period severe TEAEs were reported by 4.2% of the subjects; no severe TEAE were reported for more than one subject.
- Discontinuation of study drug due to AEs were more frequent in the active treatment groups than in the placebo group, and the frequency of these discontinuations increased

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with increasing ESL dose (11.7% placebo, 25.0% ESL 800 mg, 26.7% ESL 1200 mg and 40.0% ESL 1600 mg). During the OL period 11.9% of the subjects discontinued due to TEAEs.

- In the DB period more subjects reported SAEs in the ESL 800 mg (6.7%) and ESL 1200 mg (10.0%) groups compared to the ESL 1600 mg (3.3%) and placebo groups (3.3%). There were no real discernible differences in the types of SAEs among the treatment groups and no dose-dependent trends emerged. During the OL period SAEs were reported by 1.7% of the subjects.
- No death cases occurred during the treatment period. One subject died in the screening period, before initiation of study treatment, with a respiratory tract infection.
- There were 3 cases of serious at least possible related cardiovascular events reported during the study: hypertensive crisis, ventricular extrasystoles and atrial fibrillation/syncope. All occurred in the DB ESL 1200 mg group.
- Rash was reported by 1.7% in the placebo group, 3.3% in the ESL 800 mg group, 6.7% in the ESL 1200 mg group and 5.0% in the ESL 1600 mg group (including rash, rash pruritic). During the OL period rash was reported by 1.7% of the subjects (rash and rash erythematous). There was 1 serious possible related cutaneous event (drug hypersensitivity) reported in the ESL 1600 mg treatment group.
- The incidence of hyponatremia reported as TEAE (including hyponatremia and blood sodium decreased) was higher than observed in other ESL trials: 8.3% of subjects in ESL 800 mg, 6.7% of subjects in ESL 1200 mg and 13.3% of subjects in ESL 1600 mg, compared to 1.7% in Placebo. In the OL period hyponatremia was reported for 10.2% of the subjects.
- For clinical laboratory data, in all post-baseline visits there was a higher proportion of subjects with decreased sodium and chloride levels and increased GGT in ESL treatment groups compared to the placebo group.
- The incidence of clinically important values of aminotransferases (ALT and AST) and bilirubin was low and similar between active and placebo groups across all study visits. There were 2 cases of clinically important elevation of ALT and AST, one in placebo and one in ESL 100 mg; and 1 case of clinically important bilirubin elevation in placebo compared to no cases in ESL treated subjects. Importantly, there were no cases meeting Hy's law criteria.
- For the measured hematological values there were no major differences between active and placebo groups either for shifts from baseline to below or above normal levels and the incidence of clinically relevant changes of such values.
- Clinically relevant sodium levels, defined as a sodium level <125 mEq/L, occurred in 5.0% of subjects in ESL 800 mg, 1.6% of subjects in ESL 1200 mg and 3.3% of subjects in ESL 1600 mg, compared to no cases in placebo. During the OL period, sodium level <125 mEq/L occurred in 6.8% of the subjects.

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- Overall, the means and mean changes from baseline for vital signs and body weight were not substantially different across visits for the placebo and active treatment groups.
- There were no noticeable differences in all physical and neurological examinations between active and placebo groups during the study.
- For ECG parameters there were few findings considered clinically relevant, with no noticeable differences between active and placebo groups.
- No differences between subjects in the placebo group and subjects in the active treatment groups were observed for any of the C-SSRS parameters. There was one single report of suicidal ideation with specific plan and intent to commit suicide (ESL 1200 mg group). No suicidal preparatory acts, behaviors or attempts were reported post-baseline.

PHARMACOKINETIC RESULTS: Plasma concentrations of eslicarbazepine increased with increasing dose in the overall analysis.

Date of report: 2013.12.27