1. SYNOPSIS

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

Title:
A phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical study of eslicarbazepine acetate in diabetic neuropathic pain.

Coordinating investigator:
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Study site(s):
Fifty nine (59) sites in 10 countries (Argentina, Austria, Chile, Germany, India, Israel, Mexico, Russia, South Africa, and United Kingdom) participated in the study.

Publication reference:
None.

Study period:	**Clinical phase**:
Date of first admission: 2010.12.06 Date of last visit: 2012.04.24	III

OBJECTIVES:
Primary objective:
The primary objective of this study was to assess the efficacy of eslicarbazepine acetate (ESL) as therapy in subjects with diabetic neuropathic pain (DNP) 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 DNP 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 open label (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 DPN. 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 had 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 unblended interim analysis to

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evaluate 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 DNP 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: 468 subjects (117 in each of the treatment groups).
Randomised: 332 subjects.
Analysed for efficacy (interim analysis population):
- FAS (full analysis set): 277 subjects;
- CTS (completed treatment set): 140 subjects.

Analysed for safety (double blind): 332 subjects.
Analysed for safety (open-label): 195 subjects.

Diagnosis and main criteria for inclusion:
- Male and female outpatients aged 18 years or older.
- Diagnosis of Type 1 or Type 2 diabetes mellitus.
- Pain due to bilateral peripheral polyneuropathy caused by Type 1 or Type 2 diabetes mellitus. Daily pain present for at least 6 months and should have begun in the feet with relatively symmetrical onset.
- Diagnosis of DNP confirmed by a score of at least 3 on the investigator-rated Part B of the Michigan Neuropathy Screening Instrument at Visit 1 (Screening).
- Stable glycaemic control, as assessed by the investigator, and have glycosylated haemoglobin proportion of less than or equal to 11% before randomization.
- 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 DNP during the previous 24 hours.
- Daily eDiaries completed for at least 70% of the 7 to 10 days between Visit 2 and Visit 3.

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 and 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 were used.
During the OL phase, ESL was supplied as divisible tablets of 800 mg (batch number

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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 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

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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 AEs, potentially related AEs, SAEs, AEs leading to discontinuation of study treatment and AEs 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 117 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 2.3 units. Based on the same assumptions, approximately 65 subjects per treatment group were needed so the statistical power of the interim analysis was above 65%. 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 66% and 68% (calculations by means of nQuery Advisor® 7.0).

SUMMARY – CONCLUSIONS (ANALYSED POPULATION)

A total of 527 subjects were screened for eligibility to participate in the study. A total of 332 subjects were randomized to study treatment. The analysis sets were as follows:

- Safety population: 82 subjects PLC; 83 subjects ESL 800mg; 83 subjects ESL 1200mg; 84 subjects ESL 1600mg.
- Interim analysis population:
  - FAS population: 71 subjects PLC; 68 subjects ESL 800mg; 67 subjects ESL 1200mg; 71 subjects ESL 1600mg.
  - CTS population: 41 subjects PLC; 32 subjects ESL 800mg; 37 subjects ESL 1200mg; 30 subjects ESL 1600mg.
- Safety OL population: 197 subjects

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EFFICACY RESULTS (interim analysis):

At the efficacy interim endpoint (mean treatment duration 80.2 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 -0.60 points in the pain scale, considerably below the assumed treatment effect of -1.1 (ESL 800 mg -0.60, 95% CI: [-1.34,0.14], p=0.1391; ESL 1200 mg +0.23, 95% CI: [-0.51,0.96], p=0.8034; ESL 1600 mg -0.43, 95% CI: [-1.16,0.30], p=0.3726). Results for the CTS population confirmed the FAS analysis. For the CTS the largest treatment group difference was -0.86 for ESL 1600mg (95% CI: [-1.93, 0.20], p=0.1427).

SAFETY RESULTS:

- More than half of subjects in each treatment group experienced at least 1 AE during the DB period (53.7% placebo versus 69.9% ESL 800 mg, 61.4% ESL 1200 mg and 69.0% ESL 1600 mg). During the OL period 47.7% of the subjects experienced at least one AE.
- The most common AEs occuring in higher frequency in the ESL groups compared to placebo were nausea (9.2% vs. 4.9%), hyponatremia (7.2% vs 0%), vertigo (6.8% vs. 0%), somnolence (6.0% vs. 0%), dizziness (5.6% vs. 0%), headache (5.6% vs. 4.9%), hypertension (5.2% vs. 2.4%) and vomiting (4.8% vs 0%). A dose proportionality trend was seen for the incidences of vertigo, vomiting, hypertension and hyponatremia. Only one case of diplopia was reported (ESL 1600 mg). The incidence of these events was lower in the OL period: nausea and dizziness were the most common AEs affecting up to 6.1% of the subjects.
- Subjects in the placebo group (11.0%) had fewer AEs that were reported as potentially related to study drug compared to subjects in the active treatment groups (31.3% ESL 800 mg, 33.7% ESL 1200 mg and 38.1% ESL 1600). During the OL period, at least possible related AEs were reported by 21.8% of the subjects.
- The majority of AEs were of mild or moderate intensity across the 4 treatment groups. The incidence of severe AEs was higher for the ESL 1600 mg group, but for the ESL 1200 mg and 800 mg groups was lower than placebo (6.1% placebo, 6.0% ESL 800 mg, 6.0% ESL 1200 mg and 10.7% ESL 1600 mg). AEs reported as severe affecting ≥2% subjects in any treatment group were nausea and vertigo. During the OL period severe AEs were reported by 6.1% of the subjects. The only severe AE reported for more than one subject was headache (n=2).
- Discontinuations 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 with increasing ESL dose (9.8% placebo, 19.3% ESL 800 mg, 20.5% ESL 1200 mg and 28.6% ESL 1600 mg). During the OL period 7.1% of the subjects discontinued due to AEs.
- Overall a small proportion of subjects experienced at least one SAE. In the DB period more subjects reported SAEs in the placebo (7.3%) and ESL 1600 mg (6.0%) groups compared to the ESL 1200 mg (3.6%) and ESL 800 mg (1.2%) groups; there were no

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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 5.6% of the subjects.

- There was 1 death during the all study duration: cardiac arrest/ventricular tachycardia. The event occurred while on treatment with double-blind ESL 1600 mg and was considered possibly related to study drug by the investigator.
- Aside the above-mentioned fatal event, there were 3 cases of cardio-cerebrovascular SAEs reported as at least possible related to study drug: a myocardial infarction, a supraventricular tachycardia and an accelerated hypertension/cerebrovascular accident. The events occurred while on treatment with DB ESL 1600 mg.
- Rash was reported by 1.2% in the placebo group, 2.4% in the ESL 800 mg group and 1.2% in the ESL 1600 mg group (including rash, rash papular). No rash was reported in the ESL 1200 mg group, but there was 1 case of dermatitis allergic (SAE) assessed by the investigator as possible related to study drug. During the OL period rash was reported by 1% of the subjects.
- The incidence of hyponatremia reported as AE (including hyponatremia and blood sodium decreased) was higher than observed in other ESL trials. Cases occurred only in the active treatment groups and increased with increasing dose: 2.4% of subjects in ESL 800 mg, 8.4% of subjects in ESL 1200 mg and 11.9% of subjects in ESL 1600 mg. In the OL period hyponatremia was reported for 3.0% 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 levels in ESL treatment groups compared to the placebo group.
- No clinically important changes were observed in aminotransferases levels. There was one case of transient clinically important elevation of bilirubin during OL treatment with ESL 800 mg and one case of jaundice in the placebo group. 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 2.4% of subjects in ESL 800 mg, 3.6% of subjects in ESL 1200 mg and 3.6% of subjects in ESL 1600 mg, compared to no cases in placebo. Similar trend was seen in the incidence of subjects who exhibited post baseline chloride levels <90 mEq/L. During the OL period, sodium level <125 mEq/L occurred in 2.0% of the subjects.
- There were no noticeable differences in all physical and neurological examinations between active and placebo groups during the study.
- 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.
- For ECG parameters there were few findings considered clinically relevant with no noticeable differences between active and placebo groups.

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• No differences between subjects in the placebo group and subjects in the active treatment groups were observed for any of the C-SSRS parameters. More importantly, treatment with ESL did not appear to have any effect on suicidality.		
PHARMACOKINETIC RESULTS: Plasma concentrations of eslicarbazepine increased with increasing dose in the overall analysis.		
Date of report: 2014.01.24		