STUDY SYNOPSIS

Sponsor: BIAL - Portela & Ca, S.A. **Finished Product:** BIA 2-093 **Active ingredient:** Eslicarbazepine acetate (ESL) (BIA 2-093)	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 as therapy in subjects with fibromyalgia: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial

Investigator and study centres:

The coordinating investigators of this multicentre study were Michael Späth, MD, PhD, and Jaime Branco, MD, PhD.

Subjects were screened in 84 centres in 16 European countries (Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Ukraine and United Kingdom).

Clinical Phase: II/therapeutic exploratory

Study duration and dates:

The duration per subject was 17 weeks (up to 2-week Baseline Period, 1-week Titration Period, 12-week Maintenance Period, 2-week safety Follow-up Period). The duration of the study overall was approximately 14 months (first subject in: 21APR2009 to last subject out: 02SEP2010).

Objectives:

The primary objective of the study was to assess the efficacy of eslicarbazepine acetate (ESL) as therapy in subjects with fibromyalgia (FMS).

The secondary objective of this study was to assess the safety and tolerability of ESL in subjects with FMS.

Methodology:

This was a double-blind, randomised, placebo-controlled, parallel-group, multicentre, multinational, Phase II study in 528 subjects with pain due to FMS. Subjects were randomised in a 1:1:1:1 ratio to receive placebo, ESL 400 mg once daily (QD), ESL 800 mg QD or ESL 1200 mg QD. The study was carried out as follows:

Screening Visit (Visit [V] 1): After completing screening procedures at V1, eligible subjects began the 2-week Baseline Period.

Baseline Period (2 weeks): Subjects discontinued taking prohibited medications on V1 (beginning of washout period). Subjects were tapered off of discontinued medications. Washout was completed by Day -7 (7 days before V2). Subjects refrained from taking any pain medications and other prohibited medications (except rescue medication) throughout the study. During the Baseline Period, subjects used the subject diary to complete the diary pain assessment on a 0-10 numeric pain rating scale (NPRS) and to record information on rescue medication daily on awakening.

Titration Period (1 week): Upon completing the Baseline Period, subjects returned to the study centre for V2 (Randomisation Visit, Day 1). At V2, subjects, who had completed at least 4 subject diary pain

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assessments satisfactorily within the past 7 days, had an average pain score that was ≥4 and ≤9 and continued to meet all study entry criteria, were randomly assigned to 1 of the 4 treatment groups. During the 1-week Titration Period, subjects randomised to the ESL 400 mg QD and the ESL 800 mg QD treatment groups received ESL 400 mg QD; and subjects randomised to the ESL 1200 mg QD treatment group received ESL 600 mg QD; subjects assigned to placebo treatment received placebo QD.

Maintenance Period (12 weeks): Starting at V3, subjects assigned to treatment with ESL received their full dosage regimens QD; subjects assigned to placebo treatment received placebo QD. During the Maintenance Period, subjects had visits every 4 weeks.

Follow-up Period (2 weeks): Approximately 2 weeks after taking the last dose of study medication, subjects returned to the study centre for the Follow-up Visit and underwent the end-of-study evaluations.

Number of subjects:

480 subjects planned, 800 screened, and 528 randomised and treated: 131 in the placebo group, 130 in the ESL 400 mg QD group, 135 in the ESL 800 mg QD group and 132 in the ESL 1200 mg QD group. 386 subjects completed the study.

Diagnosis and main criteria for inclusion:

Subjects were included in the study if they met all of the following inclusion criteria:

<u>At V1:</u>

1. Subject was male or female, 18 years of age or older (according to Amendment #1 for Czech Republic [24MAR2009]: 18 to 65 years of age).
2. Subject was able and willing to provide written informed consent to participate in the study after having the opportunity to review the Subject Information Sheet and Informed Consent Form.
3. Subject met the American College of Rheumatology (ACR) 1990 diagnostic criteria for FMS (widespread pain for at least 3 months and pain in at least 11 of 18 tender points) (according to Amendment #1 for Czech Republic [24MAR2009]: And the subject's current FMS treatment was either inefficacious or had intolerable side effects).
4. Subject was willing and able to understand and comply with all study requirements, in the judgment of the investigator.
5. Subject had negative results on the urine test for drugs of abuse at V1 (Screening Visit), except for medications/drugs reported by the subject at the Screening Visit.
6. Subject used of allowable non-pharmacological therapies had been stable for at least 4 weeks prior to V1 (Screening Visit) and was maintained at the stable regimen throughout the study.
7. Female subject was surgically sterile (i.e. bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or at least 2 years post-menopausal or, if of childbearing potential, she was sexually abstinent or agreed to use a medically acceptable non-hormonal method of contraception. (Addendum according to Amendment #1 for Czech Republic [24MAR2009]: However, their intake was not forbidden throughout the study.) (Addendum according to Amendment #1 for Spain [19JAN2009] and for United Kingdom [24MAR2009]: Male subject was sexually abstinent or agreed to use reliable contraceptive methods (i.e. double-barrier method: 1 male barrier [male condom] plus 1 female

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barrier method [female condom, spermicide or intrauterine device]. This was mandatory even for sexually active men who had been sterilised.)

At V2 (randomisation):

8. Subject had negative urine test for drugs of abuse.
9. Subject had completed at V2 at least 4 subject diary pain assessments satisfactorily within the past 7 days and the average pain score was ≥4 and ≤9.

In addition, the following were exclusion criteria:

At V1:

1. Subject had a known hypersensitivity to ESL or to other carboxamide derivatives (e.g. oxcarbazepine, carbamazepine) or to any of the excipients.
2. Subject had a history of or current active malignancy except for the following: basal cell carcinoma which had been treated; and malignancies that were successfully treated and had no recurrence within 5 years before V1 (Screening Visit).
3. Subject had a severe hepatic, renal, respiratory, hematologic or immunologic illness, unstable cardiovascular disease or any other medical or psychiatric condition that, in the judgment of the investigator, made the subject inappropriate for entry into this study.
4. Subject had a second or third-degree atrioventricular blockade not corrected with a pacemaker or any other clinically significant abnormality in the 12-lead ECG as determined by the investigator.
5. Subject had a history of illicit drug or alcohol abuse within 2 years before V1 (Screening Visit).
6. Subject had received an investigational drug (or a medical device) within 3 months of Screening or was currently participating in another study of an investigational drug (or a medical device).
7. Subject was pregnant or nursing.
8. Subject was an employee of the investigator or study centre, with direct involvement in the proposed study or other studies under the direction of that investigator or study centre or was a family member of the employees or the investigator.
9. Subject had any of the following: an inflammatory muscle or rheumatologic disease other than FMS; multiple sclerosis; active infections; untreated endocrine disorders; uncontrolled hypo- or hyper-thyroidism of any type.
10. Subjects whose pain was not due primarily to FMS.
11. Subject underwent tender point injection within 30 days before V1 (Screening Visit) and/or subject was unwilling to refrain from tender point injection throughout the study.
12. Subject had a white blood cell (WBC) count $<2.5 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, Na^+ <125 mmol/L or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 × the upper limit of normal at V1 (Screening Visit) or any other clinically relevant laboratory abnormality that, in the investigator's opinion, could compromise the subject's safety.
13. Subject had abnormal values for antinuclear antibody (ANA >1/160) or rheumatoid factor (RF >15 IU/mL) at V1 (Screening Visit). After approval of the global amendment in respective countries, the

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limit for ANA was changed to ≥1/160.

14. Subject had abnormal Westergren erythrocyte sedimentation rate (ESR) at V1 (Screening Visit) (ESR >40 mm/h).
15. Subject had creatinine clearance (CL_{Cr}) lower than 60 mL/min at Screening.
16. Subject had a MADRS total score ≥35 or a score of 4 to 6 on question 10 of the MADRS at V1 (Screening Visit).
17. Subject used prohibited concomitant medications during the 2-week Baseline Period or used fluoxetine during the 30 days before V1 (Screening Visit).
18. Subject used opiates every day for the 30 days before V1 (Screening Visit) for the control of pain related to FMS.

At V2:

19. Subject had a MADRS total score ≥35 or a score of 4 to 6 on question 10 of the MADRS.

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

ESL was supplied in 400-mg (batch numbers #080084 and #080612) and 600-mg (batch number #080613) tablets and was administered QD by oral route.

Reference therapy:

Placebo tablets matching the 400-mg and 600-mg (batch numbers #080075 and #080611) tablets were administered QD by oral route.

Duration of treatment:

Subjects were treated with either active study medication (i.e. ESL) or placebo for 13 weeks. The study consisted of a 2-week Baseline Period, a 1-week Titration Period (active treatment or placebo) and a 12-week Maintenance Period (active treatment or placebo).

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from baseline to endpoint in mean pain (assessed by the NPRS) recorded in a subject's diary upon awakening each morning. There were 2 key secondary efficacy variables, namely the 30% responder rate at endpoint, defined as the proportion of subjects with a reduction of endpoint mean pain by at least 30% with respect to baseline and the Patient Global Impression of Change (PGIC), rated on a 7-point categorical scale.

Other secondary efficacy variables based on the pain scores were 50% responder rates at endpoint, 30% and 50% responder rates mean pain intensity per week, the overall impact of FMS as assessed by the Fibromyalgia Impact Questionnaire (FIQ), Clinician Global Impression of Change (CGIC), depression as assessed by the Montgomery Åsberg Depression Rating Scale (MADRS), tender point count, sleep interference as assessed by the Medical Outcome Study (MOS) Sleep Scale, quality of life as assessed by the Short Form-36 Health Survey (SF-36) and intake of rescue medication.

Safety: Safety was evaluated based on adverse events (AEs), standard laboratory safety data (haematology, biochemistry), 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate) and physical examination (including a brief neurological examination).

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Statistical methods:

Analysis populations: Primary and secondary efficacy analyses were conducted on the full analysis set (FAS) which consisted of all randomised subjects who received at least 1 dose of study medication and with at least 1 post-randomisation rating of 24-h-average pain and on the per-protocol (PP) set which consisted of all subjects in the FAS who had completed the Maintenance Period and who did not have any protocol deviation (e.g. poor compliance, diaries not properly filled) in a sufficiently serious manner to warrant data (but not subject) exclusion. Safety analyses were performed on the safety set, defined as all randomised subjects who received at least 1 dose of study medication.

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 1 of the ESL treatment groups. Primary comparisons, which were performed using the FAS, evaluated the effect in each of the ESL groups versus placebo. The change from baseline to endpoint in mean pain was analysed using an analysis of covariance (ANCOVA) with treatment and region as fixed effects and baseline mean pain as a covariate. Generally, regions were equal to countries but in order to have a sufficient number of subjects in each region, some countries were pooled to regions. The primary hypothesis was tested using 3 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. If not otherwise specified, p-values generated in any secondary efficacy analyses were not adjusted for multiple comparisons as these p-values were seen as purely descriptive measures and should not be interpreted inferentially.

Safety analysis: Safety variables were analysed using summary statistics.

Demographics and baseline characteristics:

The demographic characteristics at screening were similar between the 4 treatment groups, except for gender. The majority of subjects were Caucasian and female. Mean age per treatment group ranged from 47.7 to 48.2 years, the proportion of males from 5.3% to 12.3%, and the mean body mass index from 26.8 kg/m^2 to 27.8 kg/m^2. The disease characteristics at screening were similar between the 4 treatment groups. The mean duration of FMS ranged between 39.5 and 44.1 months. The most common (with >80% of subjects in any treatment group) ongoing FMS symptoms were fatigue and sleep disturbance.

Efficacy results:

Overall, no ESL treatment group showed a consistent pattern of improved efficacy relative to placebo. After 13 weeks of treatment, no statistically significant difference between the 3 ESL groups and placebo was seen for the primary efficacy variable after an ANCOVA for the FAS. Sensitivity analysis revealed no statistically significant differences between ESL treatment groups and the placebo group for the PP set and the randomised set. When a baseline by treatment interaction or a region by treatment interaction were included in the ANCOVA model, there were again no statistically significant differences between ESL treatment groups and the placebo group for the FAS and the PP set.

The primary analysis was repeated using an unadjusted statistical analysis. There were also no statistically significant differences between ESL treatment groups and placebo for the FAS and the PP set after Van Elteren's test. There was no statistically significant difference between the ESL groups and the placebo group in the change of mean pain after adjusting the endpoint value for intake of rescue medication.

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Two key secondary variables were analysed. (1) The percentage of responders at endpoint, defined as proportion of subjects with at least 30% reduction in endpoint mean pain with respect to baseline mean pain, was not statistically significantly different between the ESL groups compared to the placebo group. (2) There were no statistically significant differences in the PGIC assessment between the ESL groups and the placebo group.

Other secondary efficacy variables showed that:

- There were no meaningful differences between placebo and ESL groups in mean pain per week in the Maintenance Period or in the Titration Period. Nor were there meaningful differences between placebo and the ESL groups in the average pain per day by period.
- There were no statistically significant differences between placebo and ESL groups in weekly responder rates for subjects with at least 30% or 50% reduction in mean pain and there was no difference between ESL groups and placebo for subjects with at least 50% reduction in mean pain at endpoint.
- There was no statistically significant difference between the ESL groups compared to the placebo group for the FIQ scores.
- There were no meaningful differences between placebo and the ESL groups in the SF-36 total score. Only 1 of the subscales (physical functioning) showed a difference between an ESL group (ESL 400 mg QD) and placebo (p=0.0167, no adjustment for multiplicity).
- For the MOS Sleep Scale, there was a greater reduction in the Sleep Problems Index II 9 items index in the ESL 1200 mg QD group compared to the placebo group (p=0.0432) and in the Sleep Disturbance Subscore in the ESL 800 mg QD group (p=0.0211) and in the ESL 1200 mg QD group (p=0.0045) compared to the placebo group. A multiplicity correction was not performed.
- There were no statistically significant differences between placebo and the ESL groups for the MADRS total score or the CGIC assessment.
- There was no statistically significant difference between placebo and the ESL groups for the number of painful tender points.
- The median intake of rescue medication in the Baseline and Titration Period was higher in the ESL groups than the placebo group. In the Maintenance Period the median intake of rescue medication was higher in the ESL 800 mg QD and ESL 1200 mg QD group but lower in the ESL 400 mg QD group compared to placebo. The majority of subjects (>88%) in any treatment group started rescue medication on their first day on study treatment.

Safety results:

The mean treatment durations of the Maintenance Period were 64.7 days (ESL 1200 mg), 69.8 days (ESL 800 mg), 73.0 days (ESL 400 mg) and 73.6 days (Placebo). Overall, 73.5% of the subjects completed the Maintenance Period, with the highest proportion in the placebo group (80.2%) and the lowest proportion (63.6%) in the ESL 1200 mg group (400 mg ESL: 75.4%, 800 mg ESL: 74.8%).

There was generally a higher incidence of TEAEs, possibly related TEAEs, and TEAEs leading to discontinuation in the ESL treatment groups compared to the placebo group, with the highest incidence usually in the ESL 1200 mg QD group. The most commonly reported TEAEs were those known to be

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common to this class of drug, namely nervous system and gastrointestinal disorders, as summarised below:

- For all TEAEs, the incidence was highest in the ESL 1200 mg QD group (70.5%) followed by the ESL 800 mg QD group (68.1%), the ESL 400 mg QD group (66.2%), and the placebo group (57.3%). More subjects in the 1200 mg QD group (47.0%) had TEAEs possibly related to the study drug compared to the ESL 800 mg QD group (45.2%), the ESL 400 mg QD group (36.9%) and the placebo group (28.2%). The incidence of TEAEs leading to discontinuation was highest in the ESL 1200 mg QD group (28.0%) followed by the ESL 800 mg QD group (18.5%), the ESL 400 mg QD group (11.5%), and the placebo group (7.6%).
- The most commonly reported TEAEs were headache (placebo: 12.2%; range over ESL groups: 13.8% to 18.9%), nausea (placebo: 7.6%; range over ESL groups: 7.7% to 15.9%) and dizziness (placebo: 4.6%; range over ESL groups: 5.2% to 11.4%). The TEAE gamma-glutamyl transferase (GGT) increased occurred in 0 placebo subjects but in 4.6% to 7.6% of ESL subjects.
- The most commonly reported TEAEs considered at least possibly related to study medication were nausea (placebo: 5.3%; range over ESL groups: 6.9% to 12.9%), headache (placebo: 6.9%; range over ESL groups: 7.7% to 11.4%) and dizziness (placebo: 4.6%; range over ESL groups: 3.8% to 10.6%). The ESL 1200 mg QD group had the highest incidence of these events. GGT increased occurred in none of the placebo-treated subjects but in all ESL groups some subjects showed an increase (range: 4.6% to 6.8%).
- There were few serious adverse events (SAEs) occurring in the study and these did not show a dose relationship to ESL: the highest incidence was in the ESL 800 mg QD group (4.4%) and the lowest in the ESL 1200 mg QD group (0.8%). One death occurred in the ESL 800 mg QD group (suicide).
- There were few TEAEs leading to discontinuation that occurred in more than 4% of subjects in any treatment group: nausea (placebo: 0.8%; ESL 400 mg QD: 1.5%; ESL 800 mg QD: 5.2%; ESL 1200 mg QD: 9.1%), headache (placebo: 0%; ESL 400 mg QD: 2.3%; ESL 800 mg QD: 5.2%; ESL 1200 mg QD: 6.8%) and dizziness (placebo: 0.8%; ESL 400 mg QD: 0%; ESL 800 mg QD: 0.7%; ESL 1200 mg QD: 6.1%). The highest incidence was seen in the ESL 1200 mg QD group.

For 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. Only the GGT increased values were considered clinically relevant and were seen at V4 and V6/EDV. The highest incidence was reported for the ESL 800 mg QD group and the ESL 1200 mg QD group.

Summary:

Treatment with ESL did not improve the clinical condition of FMS subjects compared to placebo treatment. The safety profile of the ESL treatment was typical for this drug class, with an increased incidence of TEAEs compared to placebo, particularly for the highest dose of ESL 1200 mg QD. Further studies are necessary to elucidate the optimal dose regimen of ESL to treat FMS.

Date of final report:

27 January 2012