STUDY SYNOPSIS

Sponsor: BIAL - Portela & C[a], S.A. **Product**: BIA 2-093 **Active ingredient:** Eslicarbazepine acetate (ESL) (BIA 2-093)	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 as preventive therapy for subjects with migraine: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial		
Investigators and study centres: The coordinating investigators of this multicentre study were Volker Limmroth, MD, PhD, and José Pereira Monteiro, MD, PhD. Subjects were screened in 61 centres in 13 countries (Austria, Bulgaria, Czech Republic, Germany, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Spain, and Ukraine).		
Study period: Date first subject screened: 15 Apr 2009 Date last subject completed study: 14 Jun 2010		**Clinical phase:** II/therapeutic exploratory
Objectives: The primary objective was to assess the efficacy of ESL as a preventive therapy for subjects with migraine with and without aura. The secondary objective was to assess the safety and tolerability of ESL in subjects with migraine.		
Methodology: This was a multinational, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of multiple doses of ESL as prophylactic treatment in subjects with migraine with or without aura. Subjects were randomised in a 1:1:1 ratio to receive placebo, ESL 800 mg/day once daily (QD), or ESL 1200 mg/day QD. The study consisted of a Screening Period of 2 to 4 weeks, a 4-week placebo Baseline Period, a 2-week Titration Period, a 12-week Maintenance Period, and a 4-week Follow-up Period. During the entire study the subjects had a diary to document the occurrence, duration, and intensity of headaches, the occurrence or not of aura and its nature, as well as other related symptoms, and the use of study medication and acute medication.		
Number of subjects (total and analysed): Planned: 515 subjects. Screened: 518. Enrolled: 452. Randomised and treated: 410 (136 in the placebo group, 135 in the ESL 800 mg QD group, and 139 in the ESL 1200 mg QD group). Completers for efficacy (Visit [V] 1-V7 performed): 355.		

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Diagnosis and main criteria for inclusion:

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

- Women or men, 18 years of age or older (according to Amendment #1 for Czech Republic [24 Mar 2009]: 18 to 65 years of age).
- Diagnosis (established prior to 50 years of age) of migraine headaches for at least 1 year, and a well-documented history of migraine headaches with or without aura according to the criteria of the International Headache Society for at least 3 months (according to Amendment #1 for Czech Republic [24 Mar 2009]: for at least 3 months with at least 3 migraine attacks per month in each of these 3 months).
- At least 2 (according to Amendment #1 for Czech Republic [24 Mar 2009]: at least 3) (and no more than 10) well-defined migraine headache attacks per month, with at least 24 h of freedom from headaches and other symptoms of migraine between attacks.
- Able to distinguish the migraine headache attacks from other types of common headaches (tension-type headaches, sinus-related headaches, etc.).
- Not taking any prophylactic migraine therapies for at least 2 weeks prior to Baseline Visit (V2). Flunarizine had to be discontinued at least 4 weeks prior to V2.

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

ESL was supplied in 400-mg (batch numbers 080084 and 080612) and 600-mg (batch number 080613) tablets and was administered with a dose of 800 or 1200 mg QD in the evening by the oral route.

Reference therapy:

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

Duration of treatment:

Subjects were treated with either active study medication (i.e. ESL) or placebo for a period of up to 18 weeks in total: a 4-week Baseline Period (placebo only), a 2-week Titration Period (active treatment or placebo), and a 12-week Maintenance Period (active treatment or placebo). Hence, the double-blind Treatment Period was 14 weeks (a 2-week Titration Period [active treatment or placebo], and a 12-week Maintenance Period [active treatment or placebo]).

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Criteria for evaluation:

Efficacy: The primary efficacy variable was the absolute change from baseline in the frequency of migraine attacks standardised to 4 weeks in the Maintenance Period. There had to be a minimum of 24 h of freedom from headache, pain, and symptoms of migraine between attacks recorded in the subject diary to be considered as more than 1 attack of migraine for statistical analysis.

In addition, there was 1 key secondary efficacy variable:

- Percentage of responders: A responder was defined as a subject who experienced a reduction from baseline of at least 50% in the standardised frequency of migraine attacks during the last 4 weeks of the Maintenance Period. Subjects prematurely discontinuing the study at any timepoint prior to follow-up were considered as non-responders irrespective of their frequency of migraine attacks.

The exploratory secondary efficacy variables were:

- Standardised frequency of migraine attacks per period for the Baseline, Titration, Maintenance, and Follow-up Period.
- Change from baseline in the standardised frequency of migraine attacks per period for the Titration and the Follow-up Period.
- Standardised frequency of migraine attacks and change from baseline during the first, second, and third 4-week periods of the Maintenance Period.
- Standardised frequency of migraine attacks and change from baseline during the last 4 weeks of the Maintenance Period.
- Relative change in standardised frequency of migraine attacks from the Baseline Period to the Maintenance Period.
- Responder rate during the whole Maintenance Period.
- Responder rate during the first, second, and third 4-week periods of the Maintenance Period.
- Proportion of subjects who were migraine-free during the Maintenance Period.
- Standardised frequency of migraine attacks by aura type during the Maintenance Period and corresponding change from baseline.
- Standardised frequency of migraine attacks by intensity of nausea, vomiting, sensitivity to light, and sensitivity to noise during the Maintenance Period and corresponding change from baseline.
- Number of headache days in the Baseline, the Titration, and the Maintenance Period, and in the last 4 weeks of the Maintenance Period.
- Change from baseline in the number of headache days in the Titration Period, the Maintenance Period, and in the last 4 weeks of the Maintenance Period.
- Treatment retention time (days) during the Titration or Maintenance Period.
- Average and worst pain intensity of migraine attacks in the Baseline, Titration, and Maintenance Period, and in the last 4 weeks of the Maintenance Period.
- Change from baseline in average and worst pain intensity of migraine attacks in the Titration Period, Maintenance Period, and in the last 4 weeks of the Maintenance Period.
- Number of days with intake of acute migraine medication in the Baseline Period, Titration Period, and Maintenance Period, and in the last 4 weeks of the Maintenance Period.

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- Exacerbations of migraine attacks during the Follow-up Period.

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

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 (i.e. ESL or placebo, post baseline) and who had at least 1 day of migraine headache evaluation after randomisation; and on the per-protocol (PP) set which consisted of all subjects in the FAS who had completed the Maintenance Period, who did not have any protocol deviation (e.g. poor compliance with study medication, subject diaries not properly filled) in a sufficiently serious manner to warrant data (but not subject) exclusion. The primary analyses were also repeated on the randomised set, i.e. subjects randomised to study medication irrespective of whether they received study medication or not. A sensitivity analysis of the primary variable was also performed in the FAS. Safety analysis was performed on the safety set. The safety set was defined as all randomised subjects who received at least 1 dose of study medication (i.e. ESL or placebo, post baseline).

Efficacy analysis: Analysis of the primary efficacy variable was performed using an analysis of covariance (ANCOVA) model with the fixed factors treatment and region and with the standardised frequency of migraine attacks during the Baseline Period as 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. In the first step, a p-value was calculated for an overall ANCOVA model testing the null hypothesis that all treatment groups showed the same mean change from baseline in the standardised frequency of migraine attacks. If this p-value was significant at the 5% level (2-sided test), pairwise comparisons were conducted to compare each of the 2 ESL treatment groups to placebo. According to the closed testing principle the significance level of 5% (2-sided) was used for these pairwise comparisons without comprising the overall significance level of 5%.

Safety analysis: Safety variables were analysed using summary statistics.

Demographics and baseline characteristics:

The demographic characteristics at screening were similar between the 3 treatment groups. The mean age over the treatment groups ranged from 41.6 to 42.3 years. The proportion of male subjects ranged from 11.0% to 20.1%, and the mean body mass index from 24.4 kg/m^2 to 25.1 kg/m^2. All subjects were Caucasian.

Efficacy results:

There was no statistically significant difference between placebo and any of the ESL treatment groups for the primary efficacy variable, i.e. the absolute change from baseline in the frequency of migraine attacks standardised to 4 weeks in the Maintenance Period, as recorded in the subject diary.

As secondary efficacy variables, the primary analysis was repeated in different analysis populations and using several sensitivity analyses. Again, there were no statistically significant differences between ESL treatment groups and placebo for the randomised set, for the PP set, for the sensitivity analysis with different handling of withdrawals or without imputation of missing values, for the sensitivity analysis

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with additional baseline-by-treatment interaction, and for the sensitivity analysis with additional region-by-treatment interaction.

As a key secondary efficacy variable, the proportion of subjects with a reduction of at least 50% in the standardised frequency of migraine attacks during the last 4 weeks of the Maintenance Period was defined. Here, ESL treatment groups showed higher responder rates compared to the placebo group in the FAS. This difference was statistically significant for the ESL 800 mg QD group (p=0.0307). For the PP set, both the ESL 800 mg QD group (p=0.0101) and the ESL 1200 mg QD group (p=0.0370) showed a statistically significantly higher proportion of subjects with a reduction of at least 50% in the standardised frequency of migraine attacks during the last 4 weeks of the Maintenance Period compared to the placebo group.

The key secondary efficacy variable was also analysed exploratively using a logistic regression modelling response as a function of region, treatment, and baseline migraine frequency for the FAS. Countries were pooled to regions as follows: Austria/Germany, Italy/Spain/Portugal, Lithuania/Russia/Ukraine, and Romania/Slovakia. For the remaining countries, i.e. Bulgaria, Czech Republic, and Poland, region was equal to country. Neither treatment nor the standardised migraine frequency of the Baseline Period showed statistically significant differences as covariates. However, for treatment as a covariate, the odds ratio (95% confidence interval) for the ESL 800 mg QD group was 1.82 (1.07, 3.09) and for the ESL 1200 mg QD group it was 1.55 (0.91, 2.65) indicating that the responder rate was numerically 1.5 to 2 times higher for ESL treatment compared to placebo. When using region as a covariate, there was an overall significant effect (p=0.0001). The comparison of all regions to Germany/Austria showed that the odds for being a responder was about 2 to 3 times larger in Lithuania/Russia/Ukraine, Romania/Slovakia, Bulgaria, and Poland compared to Germany/Austria and about half as large in Italy/Spain/Portugal and Czech Republic compared to Germany/Austria. The difference of odds ratios was statistically significant for Lithuania/Russia/Ukraine, Romania/Slovakia, and Bulgaria vs. Germany/Austria.

The least squares (LS) mean decreases in change from baseline in the standardised frequency of migraine attacks during the first, the second, and the third 4-week period of the Maintenance Period were generally greater in the ESL groups than in the placebo group in the FAS, but there were no statistically significant differences between ESL groups and the placebo group.

The change from baseline in the number of headache days standardised per 4 weeks during the whole Maintenance Period and during the last 4 weeks of the Maintenance Period was generally numerically greater in the ESL groups compared to the placebo group in the FAS. However, there was no statistically significant difference between ESL groups and the placebo group.

The change from baseline in the average intensity and worst intensity of migraine attacks measured by the visual analogue scale during the Titration Period, the Maintenance Period, and the last 4 weeks of the Maintenance Period was numerically more pronounced in the placebo group compared to the ESL groups in the FAS.

The change from baseline in the number of days requiring acute medication taken by the subjects during the Maintenance Period and the last 4 weeks of the Maintenance Period was numerically more pronounced in the ESL groups compared to the placebo group in the FAS and the PP set.

Most of the other secondary efficacy variables showed numerically better efficacy for the ESL groups compared to the placebo group.

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Safety results:

Generally, there was a higher incidence of treatment-emergent adverse events (TEAEs) in the ESL treatment groups compared to placebo and the incidence tended to be highest in the ESL 1200 mg QD group (53.2%) compared to the ESL 800 mg QD group (50.4%) and the placebo group (36.0%). More subjects in the 1200 mg QD group (38.1%) had TEAEs possibly related to the study medication compared to the ESL 800 mg QD group (23.7%) and the placebo group (14.7%). More subjects in the 1200 mg QD group had TEAEs leading to discontinuation (9.4%) or dose reduction (18.7%) compared to the ESL 800 mg QD group (5.2% and 5.9%) and the placebo group (2.2% and 0.7%). The most commonly reported TEAEs are those known to be common to this class of drug, namely nervous system and gastrointestinal disorders:

- The most commonly reported TEAEs were dizziness, somnolence, vertigo, and nausea; the incidence of these events was generally highest in the ESL 1200 mg QD group. Tension headache and status migrainosus were more common in the ESL treatment groups compared to placebo.
- The most commonly reported TEAEs considered at least possibly related to study medication were dizziness, somnolence, vertigo, and nausea. The ESL 1200 mg QD group had the highest incidence of these events.
- There were few serious adverse events occurring in the study with the highest incidence in the ESL 1200 mg QD group (2.9%; ventricular arrhythmia, viral infection, status migrainosus, and adjustment disorder) compared to the ESL 800 mg QD group (0.7%; status migrainosus) and the placebo group (0.7%; viral infection). No deaths occurred in the study.
- There were few TEAEs leading to discontinuation that occurred in more than 1 subject in any treatment group: migraine (placebo: 0.7% of subjects; ESL 800 mg QD: 0%; ESL 1200 mg QD: 1.4%); somnolence (placebo: 0%; ESL 800 mg QD: 0.7%; ESL 1200 mg QD: 1.4%); nausea (placebo: 1.5%; ESL 800 mg QD: 0%; ESL 1200 mg QD: 0%); and dizziness (placebo: 0%; ESL 800 mg QD: 0%; ESL 1200 mg QD: 1.4%).

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.

Summary:

There was no statistically significant difference between the ESL groups and placebo in change from baseline in the frequency of migraine attacks standardised to 4 weeks in the Maintenance Period in both the FAS (primary efficacy variable) and the PP set (secondary efficacy variable). However, numerically higher decreases in the LS mean were seen in the ESL groups compared to the placebo group after 12 weeks of treatment.

For the key secondary efficacy variable, the proportion of responders during the last 4 weeks of the Maintenance Period, ESL 800 mg QD showed higher responder rates compared to the placebo group in the FAS (p=0.0307) and the PP set (p=0.0101).

The safety profile of the ESL 1200 mg QD and ESL 800 mg QD dose was less favourable compared to placebo. Further studies are necessary to elucidate the optimal dose regimen of ESL to prevent migraine.

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Date of final report: 27 January 2012		