2. SYNOPSIS

Name of Sponsor/Company: BIAL – Portela & C[a], SA	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

TITLE OF STUDY: Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial

INVESTIGATORS AND STUDY CENTERS: The coordinating investigators in this multicenter study were António Gil-Nagel, and José Lopes-Lima. A complete list of principal investigators is provided in Appendix 16.1.4. Patients were screened at 39 sites in 3 countries.

STUDY DATES: from: 14 Dec 2004 to: 19 Jan 2007

PHASE OF DEVELOPMENT: III

OBJECTIVES: The primary objective was to evaluate the efficacy of eslicarbazepine acetate (ESL) administered once daily at 1200 mg or 800 mg, compared with placebo as adjunctive therapy in patients with refractory partial epilepsy over a 12-week maintenance period.

Secondary objectives were as follows: (1) to evaluate the safety and tolerability of ESL given once daily at doses of 1200 and 800 mg in comparison to placebo over a 12-week maintenance period preceded by a 2-week titration period, and followed by a 4-week tapering-off period; (2) to evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over a 1-year open-label period; (3) to assess the maintenance of therapeutic effects of ESL over a 12-week maintenance period preceded by a 2-week titration period and followed by a 4-week tapering-off period, and over a 1-year open-label period; (4) to assess the drug–drug pharmacokinetic interactions between ESL and concomitant anti-epileptic drugs (AEDs) during the double-blind and open-label periods of the study; and (5) to assess the health-related quality of life and depressive symptoms during the double-blind and open-label parts of the study.

METHODOLOGY: This was a phase III, 2-part multicenter study.

Part I was an 26-week parallel-group, randomized, placebo-controlled design consisting of an 8-week baseline period, a 2-week double-blinded titration period, 12-week maintenance period, and a 4-week tapering-off period. After completing the baseline period, patients were randomized in a 1:1:1 ratio to 1 of the 2 ESL daily dose levels (1200 or 800 mg) or placebo.

Part II was a 1-year open-label extension for patients who had completed Part I. Starting at 800 mg/day, the dosage could be titrated at 400 mg intervals down to a minimum of 400 mg/day or up to a maximum of 1200 mg/day. Patients who completed Part II could participate in a study extension and continue treatment with ESL until marketing authorization is obtained or clinical development is discontinued, with visits scheduled at the discretion of the investigator but at least every 6 months.

This clinical trial report presents results from Part I. Part II results will be presented in a separate CSR

NUMBER OF PATIENTS: 252 patients were planned. Of 330 patients screened, 253 were randomized.

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Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female patients at least 18 years old with a documented diagnosis of simple partial or complex partial seizures with or without secondary generalization since at least 12 months before screening, who were receiving 1 to 2 AEDs in a stable dose regimen since at least 2 months before screening, had at least 4 partial-onset seizures in each 4-week half of the baseline period, had signed the informed consent form, had diaries satisfactorily completed by the patient or his/her caregiver, and for women of childbearing capability, had a negative pregnancy test, agreed to remain abstinent or use acceptable contraception, and presented a serum β-hCG test consistent with a non-gravid state. Patients taking felbamate or oxcarbazepine or who had taken these medications within 1 month before screening, patients with more than occasional use of benzodiazepines (unless used chronically as an AED), and patients with known hypersensitivity to carbamazepine, oxcarbazepine, or chemically related substances were excluded.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER: Eslicarbazepine acetate was supplied in 400 and 600 mg tablets for Part I, and scored 800 mg tablets for Part II. Batch numbers used were 040120 L (400 mg tablets) and 040121-L (600 mg tablets).

DURATION OF TREATMENT: The duration of Part I was 26 weeks, including the 8-week baseline period. The duration of Part II was 1 year. The optional study extension, for subjects completing Part 2, can continue until marketing authorization is obtained or clinical development is discontinued.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION AND BATCH NUMBER: Placebo tablets matching the 400 and 600 mg active substance tablets were supplied. Batch number: 040119-L.

CRITERIA FOR EVALUATION:
Efficacy: The primary efficacy endpoint was seizure frequency over the 12-week maintenance period in Part I of the study, standardized to a "frequency per 4 weeks" unit.

Secondary efficacy endpoints were as follows: proportion of responders (i.e., patients with a ≥ 50% reduction in seizure frequency during the 12-week maintenance period compared with the 8-week baseline period); seizure frequency per week for each week of the baseline, titration, maintenance, and tapering-off periods; distribution of seizure reduction (< 50%, 50–75%, or > 75% seizure reduction); proportion of seizure-free patients (100% seizure reduction); proportion of patients with a 25% or greater exacerbation in seizure frequency compared to baseline; seizure frequency by seizure type; seizure frequency as a function of BIA 2-194 plasma levels at Visit 5; treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]) during Part I of the study; proportion of patients remaining on treatment for the duration of Part I of the study; clinical global impressions (CGIs); responses to the Quality of Life in Epilepsy–31 inventory (QOLIE-31); and symptoms of depression (based on the Montgomery Asberg Depression Rating Scale [MADRS]).

Safety: Safety endpoints included AEs, clinical laboratory tests (hematology, coagulation, biochemistry, and thyroid function, urinalysis), vital signs and weight, electrocardiogram, blood trough levels of concomitant AEDs, and withdrawal and/or rebound effect during the tapering-off period.

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Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

STATISTICAL METHODS: The intent-to-treat (ITT) population included all randomized patients with at least one dose of investigational product and at least one post-baseline seizure frequency assessment. The per protocol (PP) population included patients in the ITT population who completed the 12-week maintenance period with no major protocol violations. All primary and secondary efficacy variables were analyzed for the ITT and PP) populations. The primary efficacy analysis was based on the ITT population. Efficacy analyses were performed chiefly using data collected over the 12 week maintenance period in Part I of the study. Where possible, 2 additional sets of secondary analyses were performed on the same variables, but using data collected over the 12 week maintenance and 2 week titration periods for the first set and the 12 week maintenance, 2 week titration, and 4 week tapering-off periods for the second set.

The primary efficacy variable was the natural log transformation of the seizure frequency per 4 weeks. Seizure frequency was compared between each active treatment group and the placebo group using an ANCOVA that models seizure frequency as a function of baseline seizure frequency and treatment. Secondary analyses were performed similarly.

A Cochran-Mantel-Haenszel test stratified by region using the analysis of variance statistic for ordinal data was used to compare each active treatment group to placebo for measures including: proportion of patients classified as responders (a $\geq$ 50% reduction in standardized seizure frequency per 4 weeks relative to baseline); proportion of seizure-free patients (100% reduction in seizure frequency); and distribution of seizure reduction (the number and proportion of patients with a seizure reduction of $<$ 50%, $\geq$ 50–75%, or $>$ 75%).

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Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

SUMMARY OF RESULTS AND CONCLUSIONS:

Efficacy: The primary efficacy analysis was an ANCOVA that assessed reduction in seizure frequency per 4 weeks for the ITT population during the 12 week maintenance period. The difference in seizure frequency per 4 weeks compared to placebo was statistically significant for both the ESL 800 mg and ESL 1200 mg groups ($p < 0.05$) and the LS mean difference to placebo increased in a dose-dependent manner (-1.6 and -1.9 in the ESL 800 mg and ESL 1200 mg groups, respectively).

ANCOVA Analysis for Seizure Frequency per 4 Weeks over the 12-Week Maintenance Period* (ITT Population)

Parameter	Placebo (N=84)	ESL 800 mg (N=77)	ESL 1200 mg (N=97)
Seizure Frequency per 4 weeks			
N	79	80	69
LS Mean	7.3	5.7	5.5
95% CI for Mean	(6.3, 8.5)	(4.9, 6.7)	(4.6, 6.5)
LS Mean Difference to Placebo		-1.6	-1.9
P-value		0.048	0.021

ANCOVA Analysis for Seizure Frequency per 4 Weeks over the 2-Week Titration and 12-Week Maintenance Periods* (ITT Population)

Parameter	Placebo (N=84)	ESL 800 mg (N=77)	ESL 1200 mg (N=97)
Seizure Frequency per 4 weeks			
N	84	84	77
LS Mean	8.0	6.2	6.1
95% CI for Mean	(7.0,9.1)	(5.4,7.2)	(5.3,7.1)
LS Mean Difference to Placebo		-1.8	-1.8
P-value		0.025	0.020

* ANCOVA model: treatment as factor and log-transformed baseline seizure frequency as covariate. Model was based on log-transformed seizure frequencies. Estimates from the ANCOVA model were back transformed using the exponential function. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

Supportive analyses on the primary endpoint included median relative reduction in seizure frequency in the ITT population, ANCOVA analysis for seizure frequency per 4 weeks over the 12 week maintenance period for the PP population, and over the 2 week titration and 12 week maintenance period and the 2 week titration, 12 week maintenance period and 4 week tapering off period for the ITT and PP populations.

- Median relative reduction in seizure frequency per 4 weeks during the 12 week maintenance period in the ITT population was greater in the ESL 1200 mg and ESL 800 mg groups (41.9% and 37.9%, respectively) than in the placebo group (17.0%).
- ANCOVA analysis for seizure frequency per 4 weeks during the 2 week titration and 12 week maintenance periods (Table 11-6 and Table 14.2-2.2.2) indicated that the treatment groups were statistically significantly different from those in the placebo group ($p < 0.05$) and the LS mean difference compared to placebo was the same in both groups (-1.8).
- In the PP population, ANCOVA analysis for seizure frequency per 4 weeks over the 12 week maintenance period and the 2 week titration and 12 week maintenance periods revealed no statistically significant difference between treatment and placebo groups, which is most likely due to a low sample size for the PP population compared with that of the ITT population (133 vs. 245 patients, respectively). The LS mean difference to placebo was greater in the ESL 1200 mg group than in the ESL 800 mg

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Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

group (-1.6 versus -1.2, respectively; Table 14.2 2.2.8).

Secondary efficacy endpoints included the responder's rate (proportion of patients with a ≥ 50% decrease in seizure frequency) and seizure freedom (proportion of patients with 100% decrease in seizure frequency) in the ITT and PP populations over the 12-week maintenance period. In the ITT population, the responder rate was comparable between the ESL 800 mg and ESL 1200 mg groups (34.5 and 37.7%, respectively). The proportion of patients in the ESL 1200 mg group with a decrease in seizure frequency was statistically significantly different from that of the placebo group ($p = 0.008$), but not in the ESL 800 mg group (Table 11-8). Similarly, in the PP population, the responder rate was 29.8 and 45.7% in the ESL 800 mg and ESL 1200 mg groups, respectively; and the seizure frequency reduction in the ESL 1200 mg group was statistically significantly different from the placebo group ($p = 0.031$; Table 14.2-3.1.4). Statistical analyses in this study were not powered to determine responder's rate in the ITT and PP populations.

Seizure freedom was greater in the ESL 800 mg and ESL 1200 mg groups than in the placebo group but difference did not attain statistical significance (Table 14.2-3.2.1, Table 14.2-3.2.4, and Table 11-9).

Safety: Overall, the incidence of AEs was notably higher in the active treatment groups, with 61.3% in the ESL 1200 mg group, 52.9% in the ESL 800 mg group, and 39.1% in the placebo group (Table 12-2). The most common AEs overall included dizziness, somnolence, and headache (19.4, 11.9, and 9.1%, respectively; Table 12-3) and the maximum intensity of each was more commonly mild or moderate than severe (Table 12-5). These have also been the most commonly reported events in prior studies with ESL and their incidence increased with increasing ESL dose, with the exception of headache, for which the incidence was higher in the placebo group.

Only 1 patient, in the ESL 1200 mg group, experienced 1 serious adverse event (SAE) of severe treatment-related cerebellar syndrome; as a result, the patient withdrew consent, and was reported to have recovered.

Across treatment groups, there was no apparent trend in changes to body weight, blood pressure, ECG, or laboratory parameters.

The frequency of discontinuations resulting from treatment-emergent AEs increased slightly with each increasing ESL dose, with 6 patients in the placebo group (6.9%), 7 patients (8.2%) in the ESL 800 mg group, and 9 patients (11.3%) in the ESL 1200 mg group (Table 12-10 and Table 14.3.1-1.5).

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Name of Finished Product: Not assigned	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

Summary of Adverse Events (Safety Population)

Number (%) of patients	Placebo (N=87)	ESL 800 mg (N=85)	ESL 1200 mg (N=80)
With one or more AEs	34 (39.1)	45 (52.9)	49 (61.3)
With no AEs	66 (60.9)	55 (47.1)	51 (38.7)
With drug-related AEs*	23 (26.4)	35 (41.2)	41 (51.3)
With serious AEs	0 (0.0)	0 (0.0)	1 (1.3)
With serious drug-related AEs*	0 (0.0)	0 (0.0)	1 (1.3)
Discontinued due to AEs	6 (6.9)	7 (8.2)	10 (12.5)
Discontinued due to drug-related AEs*	6 (6.9)	7 (8.2)	10 (12.5)
Discontinued due to serious AEs*	0 (0.0)	0 (0.0)	1 (1.3)
Discontinued due to serious drug-related AEs*	0 (0.0)	0 (0.0)	1 (1.3)

* Determined by the investigator to be possibly, probably, or definitely drug related.

Cross-reference: Table 14.3.1-1.1, Table 14.3.1-1.5, Table 14.3.1-1.6, Table 14.3.1-1.7, Listing 14.3.2-1, and Listing 14.3.2-2.

Conclusions: This was a double-blind, randomized, placebo-controlled, parallel-group, multi-center study, which included an 8 week baseline period to establish pre-treatment seizure frequency, a 2 week titration period, a 12 week maintenance period, and a 4 week tapering-off period. The purpose of this study was to determine the efficacy of ESL as adjunctive therapy in the treatment of refractory partial seizures.

Analysis of the primary efficacy endpoint (reduction in seizure frequency per 4 weeks for the ITT population during the 12 week maintenance period) revealed that treatment with ESL 800 mg and ESL 1200 was statistically significant less than in patients taking placebo ($p < 0.05$).

The primary endpoint was supported by analysis of the median relative reduction in seizure frequency in the ITT population per 4 weeks during the 12 week maintenance period, which revealed that seizure frequency was greater in the ESL 800 mg and ESL 1200 mg groups (37.9% and 41.9%, respectively) than in the placebo group (17.0%). In addition, the ANCOVA for seizure frequency in the ITT population during the 2 week titration and 12 week maintenance period revealed that both treatment groups were statistically significantly less than the placebo group ($p < 0.05$).

Over one-third (≥ 34.5%) of the patients in the treatment groups experienced a response rate ≥ 50% during the 12 week maintenance period revealed compared to 22.7% of the patients in the placebo group and complete freedom from seizures (100% reduction in seizure frequency) occurred at a higher rate in the ESL 800 and ESL 1200 mg groups than in the placebo group (4.8% and 3.9%, respectively, versus 1.2%).

The incidence of treatment-emergent AEs was low in patients treated with ESL and the type and severity of these AEs was consistent with those most commonly experienced by patients previously treated with ESL. Only 1 SAE was experienced by any patient on study and no trends in laboratory or vital sign measurements were observed.

Treatment with a daily dose of ESL 800 mg or 1200 mg as an adjunct treatment for refractory partial seizures affords patients a safe an effective treatment to reduce seizure frequency.

DATE OF REPORT: 14 Jun 2007