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 Elinor Ben-Menachem and Alberto Alain Gabbai. Patients were screened at 46 sites in 13 countries. A complete list of principal investigators is provided in Appendix 16.1.4.

STUDY DATES: From: 01 Sep 2004 To: 19 Dec 2006

PHASE OF DEVELOPMENT: III

OBJECTIVES: The primary objective was to evaluate the efficacy of eslicarbazepine acetate (ESL; BIA 2-093) given once daily at doses of 400 mg, 800 mg, and 1200 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 400 mg, 800 mg, and 1200 mg in comparison to placebo over a 12-week maintenance period preceded by a 2-week titration 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 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 study in multiple centers.

Part I was a 22-week parallel-group, randomized, placebo-controlled period (8 weeks baseline, 2 weeks double-blind titration, and 12 weeks maintenance). After completing the baseline period, patients were randomized in a 1:1:1:1 ratio to 1 of the 3 ESL dose levels or to placebo.

Part II was a 1-year open-label extension for patients who had completed Part I. The starting dose was 800 mg once daily and could be titrated up or down at 400-mg intervals between 400 and 1200 mg.

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 report.

NUMBER OF PATIENTS: 400 patients (100 patients per treatment group) were planned. Of 503 patients screened, 395 were randomized.

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:	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female patients at least 18 years old with a documented diagnosis of simple or complex partial seizures with or without secondary generalization since at least 12 months before screening, who were receiving 1 to 3 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 a negative pregnancy test (females of child-bearing potential), agreed to use acceptable contraception, and had signed the informed consent form. 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 use was chronic 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-mg (batch numbers 040029-L and 040120-L) and 800-mg (batch numbers 040030-L, 050007-L, and 050053-L) tablets for Part I, and in scored 800-mg tablets for Part II.

DURATION OF TREATMENT: The duration of Part I was 22 weeks, including the 8-week baseline period. The duration of Part II was 1 year. The optional study extension, for subjects completing Part II, 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-mg (batch numbers 040119-L and 040025-L) and 800-mg (batch numbers 040026-L and 050086-L) active substance tablets were supplied.

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, and maintenance 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% 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, thyroid function, and urinalysis), vital signs and weight, electrocardiogram, and blood trough levels of concomitant AEDs.

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

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:	

ITT and PP) populations. The primary efficacy analysis was based on the ITT population. Efficacy analyses were performed chiefly using data from the 12-week maintenance period in Part I of the study. Secondary analyses were also performed using data from the 2-week titration period along with the 12-week maintenance period.

The primary efficacy variable is the ln 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%, 50–75%, or > 75%).

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 compared to placebo was statistically significant for both the ESL 800 mg and ESL 1200 mg groups ($p \leq 0.002$). The LS mean difference to placebo increased in a dose-dependent manner (-1.1, -2.7, and -2.8 in the ESL 400 mg, ESL 800 mg, and ESL 1200 mg groups, respectively).

The main supportive analyses for the primary efficacy endpoint were as follows:

- Median relative reduction in seizure frequency for the ITT population during the 12-week maintenance period: reductions were essentially equal in the ESL 800 mg and ESL 1200 mg groups (32.6% and 32.9%), and greater than that in the ESL 400 mg and placebo groups (20.9% and 5.0%).
- ANCOVA of reduction in seizure frequency per 4 weeks for the PP population during the 12-week maintenance period: these results were similar to those obtained for the ITT population.
- ANCOVAs of reduction in seizure frequency per 4 weeks for the ITT and PP populations during the 2-week titration and 12-week maintenance periods: results in the ESL 800 mg and ESL 1200 mg groups were statistically significantly different from those in the placebo group ($p < 0.001$), and the LS mean difference to placebo was greater in the ESL 800 mg group than in the ESL 1200 mg group (-3.8 versus -3.5). Results for the PP population were similar, except that the LS mean difference to placebo was greater in the ESL 1200 mg group than in the ESL 800 mg group (-3.5 versus -3.2; Table 14.2-2.2.6).

The key secondary endpoints were responder rates and seizure freedom for the ITT and PP populations. In both populations, about one-third of patients in the ESL 800 mg and ESL 1200 mg groups were responders, compared to less than one-fifth of patients in the placebo and ESL 400 mg groups. The differences between the ESL 800 mg and ESL 1200 mg groups and the placebo group were statistically significant ($p \leq 0.005$). The proportions of patients who were classified as seizure-free were greater in the ESL 800 mg and ESL 1200 mg groups than in the ESL 400 mg and placebo groups. When data from the 2-week titration period were included, the number of seizure-free patients in the ESL 800 mg group (8 patients, 8.0%. $p = 0.019$) was twice that of ESL 1200 mg patients (4 patients, 4.1%; Table 14.2-3.2.2).

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:	

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

Parameter	Placebo (N=100)	ESL 400 mg (N=96)	ESL 800 mg (N=100)	ESL 1200 mg (N=97)
Seizure Frequency per 4 weeks				
n	99	95	88	85
LS Mean	9.8	8.7	7.1	7
95% CI for Mean	(8.7,11.1)	(7.7,9.9)	(6.2,8.2)	(6.0,8.1)
LS Mean Difference to Placebo		-1.1	-2.7	-2.8
P-value		0.423	0.002	0.001

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

Parameter	Placebo (N=100)	ESL 400 mg (N=96)	ESL 800 mg (N=100)	ESL 1200 mg (N=97)
Seizure Frequency per 4 weeks				
n	100	96	100	97
LS Mean	10.9	9.3	7.1	7.4
95% CI for Mean	(9.6,12.2)	(8.2,10.5)	(6.2,8.1)	(6.4,8.4)
LS Mean Difference to Placebo		-1.5	-3.8	-3.5
P-value		0.192	< 0.001	< 0.001

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.
Cross-reference: Table 14.2-2.2.1 and Table 14.2-2.2.2

Safety: As in prior studies with ESL, the most common AEs in this study were dizziness, somnolence, headache, and nausea. The incidence of these AEs increased with increasing ESL dose (Table 14.3.1-1.2) with the exception of somnolence, for which incidence was similar in the ESL 800 mg, ESL 400 mg, and placebo groups. These and other AEs occurred more frequently at mild and moderate intensities and were infrequently severe. The incidence of severe AEs increased with increasing ESL dose. Patients tended to experience AEs relatively early in the treatment. No trends suggesting changes in blood pressure, heart rate, weight, ECG, and laboratory parameters were observed.

Serious adverse events affected 12 patients overall (3.0%) in the active treatment groups only, but dose-dependent trends did not emerge (Table 14.3.1-1.6). Most events were reported to have resolved, and most were reported as possibly or probably related to the study medication. Discontinuations because of AEs increased with increasing ESL dose: 3 placebo patients (3.0%), 12 ESL 400 mg patients (12.5%), 19 ESL 800 mg patients (18.8%), and 26 ESL 1200 mg patients (26.5%; Table 14.3.1-1.5).

Overall, the incidence of AEs was approximately similar in the ESL 800 mg and ESL 1200 mg groups (83.2% versus 79.6% of patients). In the ESL 1200 mg group, however, the AEs were more likely to be severe, they were more likely to have a probable or definite relationship to the study medication, and they were more likely to lead to discontinuation of study treatments. The ESL 800 mg dose level therefore has a more favorable safety profile than the ESL 1200 mg dose level.

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:	

Summary of Adverse Events (Safety Population)

Patients	Placebo (N=100) n (%)	ESL 400 mg (N=96) n (%)	ESL 800 mg (N=101) n (%)	ESL 1200 mg (N=98) n (%)	Total (N=395) n (%)
With one or more AEs	68 (68.0)	75 (78.1)	84 (83.2)	78 (79.6)	305 (77.2)
With no AEs	32 (32.0)	21 (21.9)	17 (16.8)	20 (20.4)	90 (22.8)
With drug-related AEs[#]	39 (39.0)	56 (58.3)	72 (71.3)	73 (74.5)	240 (60.8)
With SAEs	0 (0.0)	4 (4.2)	6 (5.9)	2 (2.0)	12 (3.0)
With serious drug-related AEs[#]	0 (0.0)	3 (3.1)	3 (3.0)	2 (2.0)	8 (2.0)
Discontinued due to AEs	3 (3.0)	12 (12.5)	19 (18.8)	26 (26.5)	60 (15.2)
Discontinued due to drug-related AEs[#]	3 (3.0)	12 (12.5)	19 (18.8)	26 (26.5)	60 (15.2)
Discontinued due to SAEs	0 (0.0)	3 (3.1)	3 (3.0)	1 (1.0)	7 (1.8)
Discontinued due to serious drug-related AEs[#]	0 (0.0)	2 (2.1)	3 (3.0)	1 (1.0)	6 (1.5)

#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, and a 12-week maintenance period. The purpose of this study was to determine the efficacy of ESL as adjunctive therapy in the treatment of refractory partial seizures.

The primary efficacy endpoint was the reduction in seizure frequency per 4 weeks for the ITT population during the 12-week maintenance period: an ANCOVA revealed that the difference compared to placebo was statistically significant for both the ESL 800 mg and ESL 1200 mg groups. The efficacy of ESL 1200 mg and 800 mg was further supported by the median relative reduction for the ITT population and by seizure frequency reduction during the maintenance period in the PP population and during the titration and maintenance period for the ITT and PP populations. Key secondary endpoints also support the efficacy of ESL 1200 mg and 800 mg: about one-third of patients in the ESL 800 mg and ESL 1200 mg groups were responders (compared to less than one-fifth of patients in the placebo and ESL 400 mg groups) and the differences between each higher dose group and placebo were statistically significant; and more patients became seizure-free in the ESL 1200 mg and 800 mg groups than in the other groups.

Common AEs included dizziness, somnolence, and headache, and most AEs occurred at mild or moderate severities, and onset tended to be relatively soon after the start of treatment. Serious adverse events affected 12 patients (3.0%) in the active treatment groups only, and did not appear to occur in a dose-dependent manner. Discontinuations because of AEs occurred in a dose-dependent manner and were most prevalent in the ESL 1200 mg group.

The reductions in seizure frequency that occurred in the ESL 800 mg and ESL 1200 mg groups were statistically significantly different from the reductions that occurred in the placebo group. In both of these groups, about one-third of patients were considered responders and had clinically significant seizure reduction (> 50%). The safety profile of the ESL 800 mg dose level was more favorable than that of the ESL 1200 mg group. Treatment with ESL 800 mg appeared to offer the optimal balance of benefit and risk in this trial, and represents a potentially useful additional option for patients and their physicians seeking effective

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:	
seizure control.		
DATE OF REPORT: 14 Jun 2007		