2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
BIAL – Portela & C[a], SA</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

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<tr><td>Name of Finished Product:
Not assigned</td></tr>
<tr><td>Name of Active Ingredient:
Eslicarbazepine acetate (BIA 2-093)</td></tr>
<tr><td colspan="3">Title of Study:
Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical study.</td></tr>
<tr><td colspan="3">Investigators and study centres:
The co-ordinating investigators in this multicentre study were:
Prof. Christian Elger
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Patients were screened in 40 centres in total (2 in Austria, 3 in Croatia, 5 in Czech Republic, 4 in Germany, 3 in Hungary, 3 in Lithuania, 8 in Poland, 2 in Romania, 5 in Russia, 1 in Switzerland and 4 in Ukraine).</td></tr>
<tr><td colspan="3">Publication (reference): none</td></tr>
<tr><td colspan="2">Study period (Part I):
15JUL2004 to 09NOV2005</td><td>Phase of development:
III / therapeutic confirmatory</td></tr>
<tr><td colspan="3">Objectives:
The primary objective was to evaluate the efficacy of eslicarbazepine acetate (ESL, BIA 2-093) administered 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.
The secondary objective were: (a) to evaluate the safety and tolerability of ESL at once daily 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 and followed by a 4-week tapering-off period; (b) to evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over a 1-year open-label period; (c) 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; (d) to assess the drug-drug pharmacokinetic interactions between ESL and concomitant anti-epileptic drugs (AEDs) over the double-blind and open-label parts of the study; and (e) to assess the health-related quality-of-life and depressive symptoms over the double-blind and open-label parts of the study.</td></tr>
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Methodology:
This was a phase III two-part study in multiple centres.
Part I was a 26-week parallel-group, randomised, placebo-controlled period (8 weeks single-blind placebo baseline, 2 weeks double-blind titration, 12 weeks maintenance, and 4 weeks tapering off). After completing the baseline period, patients were randomised 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.
This clinical trial report presents results from Part I. Part II results will be presented in a separate report.

Number of patients (planned and analysed):
Planned: 400 randomised patients; analysed for Part I: 468 patients screened, 402 randomised (safety population), 397 in intention-to-treat (ITT) population, and 343 in per-protocol (PP) population

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 generalisation 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 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 and mode of administration, batch number:
ESL was supplied in 400-mg (batch number #040029-L and #040120-L) and 800-mg (batch number #040030-L and #040122-L) tablets; once daily administration by oral route.

Duration of treatment:
The duration of Part I was 26 weeks: 8 weeks of placebo run-in, 2 weeks of dose titration, 12 weeks of maintenance and 4 weeks of tapering-off period. The duration of Part II was 1 year.

Reference therapy, dose and mode of administration, batch number:
Placebo tablets matching the 400-mg (batch number #040025-L) and 800-mg (batch number #040026-L and #040118-L) active substance tablets were supplied; once daily administration by oral route.

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Criteria for evaluation:

Efficacy variables:

The primary efficacy endpoint was seizure frequency over the 12-week maintenance period in Part I of the study, standardised 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% 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 Inventory-31 (QOLIE-31); and symptoms of depression (based on the Montgomery Asberg Depression Rating Scale [MADRS]).

Safety variables:

Safety endpoints included AEs, clinical laboratory tests (haematology, coagulation, biochemistry, thyroid function, and urinalysis), vital signs and weight, electrocardiogram, and blood trough levels of concomitant AEDs.

Statistical methods:

Seizure frequency was compared among the treatment groups by using an analysis of covariance (ANCOVA) that models seizure frequency as a function of baseline seizure frequency and treatment. Natural logarithm transformation was applied to standardised seizure frequency in order to conform to the assumptions of ANCOVA and to be consistent with sample size calculation. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.

The proportion of responders over the 12-week maintenance period was analysed by using a Cochran-Mantel-Haenszel (CMH) test. Continuous data were summarised by using descriptive statistics, i.e., number of patients, mean, standard deviation, median, and range (minimum and maximum). Categorical variables were summarised by using frequency (counts) and percentages. By-patient data listings were prepared in support of all statistical summary tables and for other case report form data, as appropriate. For testing the differences the following test were used: Least square means from the ANCOVA for each treatment group (adjusted for the covariates), least square means for differences between each active dose and placebo; Dunnett p-values and confidence intervals (CIs) for those differences were presented when ANCOVA or analysis of variance test were used.

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Summary of Results and Conclusions:

Efficacy results:

The primary efficacy analysis was an ANCOVA of log-transformed seizure frequency per 4 weeks that assessed reduction in seizure frequency per 4 weeks for the ITT population during the 12-week maintenance period: the difference to placebo was statistically significant for both the ESL 800 mg ($p = 0.0028$) and ESL 1200 mg ($p = 0.0003$) groups. The LS means of the logarithmised difference to placebo increased in a dose-dependent manner (-0.0812, -0.1869, and -0.2196 in the ESL 400 mg, ESL 800 mg, and ESL 1200 mg groups, respectively).

Supportively, the ANCOVAs of reduction in seizure frequency per 4 weeks for the PP population during the 12-week maintenance period and for the ITT and PP populations during the 2-week titration and 12-week maintenance periods showed results similar to those obtained with the primary efficacy analysis.

Median relative reduction in seizure frequency for the ITT population during the 12-week maintenance period was higher in the ESL 800 mg and ESL 1200 mg groups (36.1% and 45.3%, respectively) than in the ESL 400 mg and placebo groups (25.8% and 16.4%). In the ESL 1200 mg group and the ESL 800 mg group, the median number of seizures decreased notably during the first weeks of treatment and then remained unchanged over the 12-week maintenance period; seizure frequency reduction during the maintenance period was less stable in the ESL 400 mg group and transitory in the placebo group.

The responder rate was markedly higher in the ESL 1200 mg group (42.9%) and the ESL 800 mg group (33.7%) than in the placebo group (19.6%) ($p = 0.0004$ and 0.0246, respectively, according to CMH test, $p = 0.0009$ and 0.0359, respectively, according to Hochberg; ITT population). Results for the PP population were similar.

The proportions of patients who were classified as seizure-free were greater in the ESL 800 mg (4.1% and 3.5% in the ITT and the PP population, respectively) and ESL 1200 mg (8.2% and 5.6%, respectively) groups than in the ESL 400 mg and placebo groups; difference between ESL 1200 mg and placebo attained statistical significance ($p = 0.0426$) in the ITT population.

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

Parameter	Placebo (N=102)	ESL 400 mg (N=99)	ESL 800 mg (N=98)	ESL 1200 mg (N=98)
Seizure Frequency per 4 weeks				
N	99	97	94	94
LS Mean (back-transformed)	7.64	6.73	5.66	5.35
95% CI for Mean	(6.78,8.58)	(5.93,7.60)	(4.92,6.45)	(4.63,6.12)
LS Mean Logarithmised Difference to Placebo		-0.0812	-0.1869	-0.2196
P-value		0.3332	0.0028	0.0003

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

Parameter	Placebo (N=102)	ESL 400 mg (N=99)	ESL 800 mg (N=98)	ESL 1200 mg (N=98)
Seizure Frequency per 4 weeks				
N	102	99	98	98
LS Mean (back-transformed)	8.14	6.90	6.08	5.92
95% CI for Mean	(7.27,9.09)	(6.10,7.75)	(5.34,6.88)	(5.19,6.70)
LS Mean Logarithmised Difference to Placebo		-0.1084	-0.1860	-0.2027
P-value		0.1162	0.0020	0.0006

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

Safety results:

Both AEs in total and the predominant AEs occurred most frequently in the ESL 1200 mg group and the ESL 800 mg group. Treatment-emergent AEs (TEAEs) were reported by 60.8% of the patients in the ESL 1200 mg group, 50.0% in the ESL 800 mg group, 44.0% in the ESL 400 mg group and 31.4% in the placebo group. Nervous system disorders AEs prevailed. Dizziness occurred in 13.7% of the patients in the ESL 1200 mg group, 14.3% in the ESL 800 mg group, 4.0% in the ESL 400 mg group and 2.0% of the placebo group, headache in 10.8%, 9.2%, 5.0% and 5.9%, respectively, and somnolence in 9.8%, 9.2%, 6.0% and 2.0%, respectively. 40.2% of patients in the ESL 1200 mg group, 27.6% in the ESL 800 mg group, 19.0% in the ESL 400 mg group and 9.8% in the placebo group reported at least one adverse drug reaction (AE rated as definitely, probably, possibly related to treatment).

No relevant treatment-specific differences were found regarding the incidence of treatment-emergent serious AEs (TESAEs) and severe TEAEs. In total, 19 patients were affected by severe TEAEs. Vertigo was the only severe event reported twice: by one patient of the ESL 800 mg group (judged as unrelated to study treatment) and by one patient of the ESL 400 mg group (classified as definitely related to treatment and reason for premature discontinuation of the patient).

In total, 37 (9.2%) patients discontinued the participation in the study prematurely due to occurrence of an AE; the highest rate (20 patients, 19.6%) occurred in the ESL 1200 mg group. One patient from the placebo group died during the study (due to hypothermia).

Regarding the laboratory, vital signs and electrocardiogram parameters, there were a few clinically relevant individual findings which, however, did not preferentially occur in a particular treatment group and did not suggest an obvious relation to treatment. Mean changes of these parameters did not show relevant treatment-specific differences.

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Summary of Adverse Events (Safety Population)

Patients	Placebo (N=102) n (%)	ESL 400 mg (N=100) n (%)	ESL 800 mg (N=98) n (%)	ESL 1200 mg (N=102) n (%)	Total (N=402) n (%)
With one or more AEs	32 (31.4)	44 (44.0)	49 (50.0)	62 (60.8)	187 (46.5)
With no AEs	70 (68.6)	56 (56.0)	49 (50.0)	40 (39.2)	215 (53.5)
With drug-related AEs[#]	10 (9.8)	19 (19.0)	27 (27.6)	41 (40.2)	97 (24.1)
With SAEs	4 (3.9)	5 (5.0)	4 (4.1)	6 (5.9)	19 (4.7)
Discontinued due to AEs	4 (3.9)	4 (4.0)	9 (9.2)	20 (19.6)	37 (9.2)

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

Conclusion:

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. The safety profile of the ESL 800 mg dose level was more favourable than that of the ESL 1200 mg group and, therefore, the 800 mg dose might be preferred under risk/benefit considerations.

Date of the report: 28 June 2007