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.
Note that the design features mentioned in the title refer to Part I of the study; Part II is an open-label extension of Part I.</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 II):
11 JAN 2005 – 04 JAN 2007</td><td>Phase of development:
III / therapeutic confirmatory</td></tr>
<tr><td colspan="3">Objectives:
The primary objective for Part II of the study was to evaluate the safety and tolerability of eslicarbazepine acetate (ESL, BIA 2-093) at doses titrated to an efficacy or safety endpoint over a 1-year open-label period.
The secondary objectives were (a) to assess the maintenance of therapeutic effects of ESL over a 1-year open-label period; (b) to assess the drug-drug pharmacokinetic interactions between ESL and concomitant anti-epileptic drugs (AEDs) over a 1-year open-label period; (c) to assess the health-related quality-of-life and depressive symptoms over a 1-year open-label period.</td></tr>
<tr><td colspan="3">Methodology:
This was a phase III 2-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 one 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 report presents results from Part II. Part I results are presented in a separate report.</td></tr>
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Number of patients (planned and analysed):
Planned: For Part II there was no sample size estimation; analysed: 314 patients (safety population); 312 patients in intention-to-treat (ITT) population; 237 patients in per-protocol (PP) population.

Diagnosis and main criteria for inclusion:
Part II: Completion of study Part I and willing to continue into study Part II.
Part I: 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 as scored 800 mg tablets (batch numbers #040122-L, #050007-L, #050052-L, #050053-L); 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: Not applicable

Criteria for evaluation:
Efficacy variables (for Part II): Seizure frequency reduction over Part II in relation to the baseline period of Part I (seizure frequency was standardised to a "frequency per 4 weeks" basis); proportion of responders (patients with a 50% or greater reduction in seizure frequency); proportion of seizure-free patients (100% seizure reduction); seizure frequency over Part II (seizure frequency will be standardised to a "frequency per 4 weeks" basis); seizure frequency by seizure type; number of days with seizure over Part II, standardised to a "number of days with seizure per 4 weeks"; treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]) in Part II of the study; Quality of Life in Epilepsy Inventory-31 (QOLIE-31) at the end of Part II (Visit 11 or early discontinuation visit [EDV]) in relation to the baseline (Visit 2); Montgomery Asberg Depression Rating Scale (MADRS) at the end of Part II (Visit 11 or EDV) in relation to the baseline (Visit 2).

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Safety variables (for Part II): AEs; clinical laboratory tests (haematology, coagulation, biochemistry, thyroid function, and urinalysis); vital signs and body weight; electrocardiogram (ECG); blood trough levels of concomitant AEDs.

Statistical methods:
Presentation of results regardless of dose administered; calculation of descriptive statistics (by periods or visits); GEE (Generalized Estimating Equations) method to analyse the non-standardised seizure frequency over the 1-year period (counted by period) as a function of baseline seizure frequency, number of concomitant AEDs, and time after baseline; t-test to compare the difference between questionnaire scores at Visit 2 and last assessment; Cochran-Mantel-Haenszel test to analyse AE incidence during the first 4 weeks after the first intake of ESL in Part II depending on treatment allocation in Part I.

Summary of Results and Conclusions:
Efficacy results:
ESL decreased seizure frequency markedly, and the effect was sustained over the 1-year treatment period. The mean relative change in seizure frequency from baseline during the first 4 weeks of Part II was -31.6% (95% confidence interval: -37.8%, -25.3%) in the ITT population and -33.7% (-40.4%, -27.1%) in the PP population. Subsequently, the relative change in seizure frequency remained stable or became even more marked as treatment duration increased, ranging from -37.5% (-43.5%, -31.5%) in Weeks 5-16 to -40.6% (-47.0%, -34.2%) in Weeks 41-52 in the ITT population, and from -43.4% (-49.0%, -37.9%) to -48.8% (-54.6%, -42.9%) in the PP population. In the ITT population, the median relative reduction in seizure frequency was 39.2% in Weeks 1-4, 47.6% in Weeks 5-16, 49.8% in Weeks 17-28, 52.1% in Weeks 29-40, and 56.3% in Weeks 41-52; in the PP population, the median relative reduction was 43.7%, 51.1%, 57.6%, 56.8% and 62.7%, respectively.

The responder rate during Weeks 1-4 was 41.0% in the ITT population and 43.0% in the PP population. Subsequently, the responder rate per 12-week interval increased slightly over time, from 48.1% (Weeks 5-16) to 53.2% (Weeks 41-52) in the ITT population and from 51.9% to 59.9% in the PP population.

The proportion of seizure-free patients during Weeks 1-4 was 12.5% in the ITT population and 11.0% in the PP population. Subsequently, the proportion of seizure-free patients per 12-week interval increased over time, from 8.7% (Weeks 5-16) to 12.5% (Weeks 41-52) in the ITT population and from 6.3% to 11.0% in the PP population.

The mean (median) number of days with seizures in the baseline period was 8.0 (5.9) in the ITT population and 8.2 (5.9) in the PP population. During the first 4 weeks of Part II, the number of days with seizures decreased to 5.2 (3.9) in the ITT population and 5.1 (3.9) in the PP population. Subsequently, the number of days with seizures ranged between 4.9 (3.3) and 4.6 (3.0) in the ITT population and between 4.7 (3.0) and 4.3 (2.6) in the PP population.

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Statistically significant improvements were found in health-related outcomes (quality of life, as assessed by QOLIE-31, and depressive symptoms, as assessed by MADRS). In the ITT population, QOLIE-31 scores at last assessment (Part II completion or early discontinuation) showed a mean absolute increase (i.e., improvement) from baseline of 4.9 ($p<0.0001$) in overall quality of life, 5.8 ($p<0.0001$) in seizure worry, 1.6 (n.s.) in emotional well-being, 2.7 ($p<0.05$) in energy fatigue, 2.9 ($p<0.05$) in cognitive functioning, 7.9 ($p<0.0001$) in medication effects, 4.6 ($p<0.01$) in social function, and 3.8 ($p<0.0001$) in overall score. In the PP population, mean absolute improvement was 6.5 ($p<0.0001$) in overall quality of life, 6.9 ($p<0.0001$) in seizure worry, 2.9 ($p<0.01$) in emotional well-being, 4.0 ($p<0.001$) in energy fatigue, 3.7 ($p<0.01$) in cognitive functioning, 8.9 ($p<0.0001$) in medication effects, 5.6 ($p<0.001$) in social function, and 4.9 ($p<0.0001$) in overall score. The improvement was statistically significant for all QOLIE-31 subscales in the PP population and for all subscales except emotional well-being in the ITT population. In the ITT population, the mean relative improvement in QOLIE-31 scores between baseline and last assessment was 15.7% in overall quality of life, 51.4% in seizure worry, 7.1% in emotional well-being, 16.3% in energy fatigue, 15.0% in cognitive functioning, 33.1% in medication effects, 35.7% in social function, and 11.5% in overall score. In the PP population, the mean relative improvement was 18.9% in overall quality of life, 58.6% in seizure worry, 9.7% in emotional well-being, 20.0% in energy fatigue, 18.0% in cognitive functioning, 33.8% in medication effects, 40.9% in social function, and 14.2% in overall score.

The mean MADRS total score was 9.5 at baseline and 7.2 at the last assessment in the ITT population and 9.6 and 7.1, respectively, in the PP population. Mean absolute decrease (i.e., improvement) in the MADRS total score was 2.0 ($p<0.0001$) in the ITT population and 2.3 ($p<0.0001$) in the PP population. In the ITT population, MADRS subscale scores at last assessment showed a mean decrease from baseline of 0.3 ($p=0.0001$) in apparent sadness, 0.2 ($p<0.01$) in reported sadness, 0.3 ($p<0.001$) in inner tension, 0.1 (n.s.) in reduced sleep, 0.1 (n.s.) in reduced appetite, 0.3 ($p<0.0001$) in concentration difficulties, 0.2 ($p<0.001$) in lassitude, 0.2 ($p<0.01$) in inability to feel, 0.1 ($p<0.05$) in pessimistic thoughts, and 0.1 (n.s.) in suicidal thoughts. In the PP population, mean absolute improvement was 0.3 ($p<0.0001$) in apparent sadness, 0.2 ($p<0.01$) in reported sadness, 0.3 ($p<0.0001$) in inner tension, 0.1 (n.s.) in reduced sleep, 0.1 (n.s.) in reduced appetite, 0.4 ($p<0.0001$) in concentration difficulties, 0.3 ($p<0.001$) in lassitude, 0.2 ($p<0.01$) in inability to feel, 0.2 ($p<0.01$) in pessimistic thoughts, and 0.1 (n.s.) in suicidal thoughts. The improvement attained statistical significance in most MADRS subscales (all but reduced sleep, reduced appetite and suicidal thoughts) in both the ITT and PP populations. In the ITT population, the mean relative improvement in MADRS subscale scores between baseline and last assessment was 34.3% in apparent sadness, 39.7% in reported sadness, 31.0% in inner tension, 48.1% in reduced sleep, 56.9% in reduced appetite, 30.1% in concentration difficulties, 37.8% in lassitude, 38.3% in inability to

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feel, 26.3% in pessimistic thoughts, and 56.4% in suicidal thoughts. In the PP population, mean relative improvement was 38.3% in apparent sadness, 41.0% in reported sadness, 34.1% in inner tension, 52.8% in reduced sleep, 61.8% in reduced appetite, 33.1% in concentration difficulties, 38.7% in lassitude, 35.0% in inability to feel, 30.8% in pessimistic thoughts, and 60.0% in suicidal thoughts.

Safety results:

A total of 314 patients (38.7±11.9 years, range: 19-76 years, 51.9% males / 48.1% females) received at least one dose of ESL during study Part II; 265 (84.4%) patients were exposed to ESL treatment for ≥6 months and 155 (49.4%) patients for ≥12 months. The mean±standard deviation (SD) duration of treatment with ESL was 337.1±128.3 days (median = 364 days). Some patients continued treatment with ESL after the end of the planned one-year open-label extension: 113 (36.0%) completed 365-448 days of treatment, 31 (9.9%) patients completed 449-532 days, and 11 (3.5%) patients completed 533-616 days. Overall, the safety population was exposed to 92.9 kg of ESL for 289.8 patient-years. Overall, the mean±SD daily dose of ESL was 876.7±189.22 mg (median = 800 mg; range = 400-1600 mg).

According to the protocol, patients were to receive 800 mg (400 mg, in Hungarian sites) once daily during Weeks 1-4 of Part II. Thereafter, they could be up- or down-titrated in 400 mg steps according to clinical response. The mean±SD dose used during Weeks 1-4 was 775.4±127.1 mg; in Weeks 5-16, the daily dose was increased to 863.4±194.5 mg, and remained stable during the remaining treatment period (Weeks 17-28 = 896.7±223.8 mg; Weeks 29-40 = 898.9±234.1 mg; Weeks 41-52 = 892.5±234.1 mg). In agreement with the protocol, doses of concomitant AEDs were kept stable during Part II: overall, the mean daily dose during Part II was 898.4±379.6 mg for carbamazepine, 1309.4±1672.4 mg for valproic acid, and 328.7±221.7 mg for lamotrigine.

In the safety population, 160 (51.0%) patients reported at least one treatment-emergent adverse event (TEAE). The most frequently reported TEAEs were headache and dizziness (in 10.2% each), diplopia (5.4%), and nasopharyngitis (5.1%). The incidence of TEAEs was higher during the initial weeks of treatment. TEAEs were generally of mild to moderate severity: 119 patients (37.9%) were affected by mild TEAEs, 78 patients (24.8%) by moderate TEAEs, and 9 patients (2.9%) by severe TEAEs. A total of 11 patients (3.5%) experienced at least one TEAE leading to premature discontinuation from the study. One patient died during Part II due to drowning.

Regarding the laboratory, vital signs and 12-lead ECG results, there were a few clinically relevant individual findings which, however, were not markedly more frequently observed under treatment with ESL than at the respective baseline. In general, there were no major mean changes of quantitative safety parameters during Part II.

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Conclusion:

ESL, in mean once-daily doses of approximately 880 mg (median = 800 mg), proved to be well tolerated and to markedly and sustainedly decrease seizure frequency over a 1-year open-label treatment period. Health-related quality-of-life, as assessed by QOLIE-31, and depressive symptoms, as assessed by MADRS, showed statistically significant improvements.

Date of the report: 30 June 2007