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)***
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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.
Design features mentioned in the title refer to Part I of the study; Parts III and IV were open-label extensions.

Study Centres:
Patients were treated in 27 centres in total in Part III (in Austria, Germany, Czech Republic, Hungary, Poland, Romania, Russia, and Ukraine) and in 23 centres in total in Part IV (in Germany, Czech Republic, Hungary, Poland, Romania, Russia, and Ukraine)

Publication (Reference): none for Parts III or IV of the study

Study Period:	**Phase of Development:**
Part III: 17 October 2006 to 04 April 2008 Part IV: 31 January 2008 to 23 September 2011	III / therapeutic confirmatory

Objectives:
Part III:
The *primary objective* for Part III 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 second 1-year open-label period (following the 1-year open-label extension during Part II that followed Part I [26-week, double-blind, placebo-controlled period]). The *secondary objectives* were (a) to assess the maintenance of therapeutic effects of ESL over a second 1-year open-label period; (b) to assess the health-related quality-of-life and depressive symptoms over a second 1-year open-label period.
Part IV:
The *primary objective* for Part IV of the study was to evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over Part IV of the study (following Part III of the study). The *secondary objective* was to assess the maintenance of therapeutic effects of ESL over Part IV of the study.

Methodology:
This was a phase III 4-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 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. Part III was an additional 1-year open-label extension for patients who had completed Part II, had participated in the post-Part II study extension, which allowed patients to continue treatment with ESL, or had

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continued to take ESL in a compassionate use program. ESL starting doses were the same as received at the end of Part II, during post-Part II study extension, or under compassionate use, and could be titrated up or down at 400-mg intervals between 400 and 1200 mg once daily. Part IV was a study extension to allow patients to continue ESL treatment after the end of Part III until marketing authorisation or discontinuation of clinical development.
This report presents results from Part III and Part IV. Part I and Part II results are presented in separate reports.

Number of Patients (Planned and Analysed):
There was no sample size estimation for Parts III and IV. Patients analysed in Part III: 95 patients (safety population); 94 patients in the intention-to-treat (ITT) population; 82 patients in the per-protocol (PP) population. Patients analysed in Part IV: 71 patients (safety and ITT populations); 46 patients in the PP population.

Diagnosis and Main Criteria for Inclusion:
Part IV: Completion of study Part III, willing to continue into study Part IV.
Part III: Completion of study Part II, entered post-Part II study extension or continued to take ESL in a compassionate use program, and willing to continue into study Part III.
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 050053-L, 060179-L, 050052-L, 070301-L, 070587-L, 070591, 070588, 080066, 080481, 090722); 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. The duration of Part III was planned to be 1 year (some patients were treated for >1 year). The duration of Part IV was >3 years (patients could continue treatment with ESL until market availability).

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

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Criteria for Evaluation:

Efficacy variables:

Parts III and IV (only the first 60 weeks were evaluated for efficacy): seizure frequency reduction over Part III or IV 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 ≥50% reduction in seizure frequency); proportion of seizure-free patients (100% seizure reduction); seizure frequency over Part III or IV; seizure frequency by seizure type; number of days with seizure over Part III or IV.

Efficacy variables only assessed in Part III: treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]) in Part III of the study; Quality of Life in Epilepsy Inventory-31 (QOLIE-31) at the end of Part III (Visit 16 or early discontinuation visit [EDV]) in relation to the baseline (Visit 2); Montgomery Asberg Depression Rating Scale (MADRS) at the end of Part III (Visit 16 or EDV) in relation to the baseline (Visit 2).

Safety variables:

Parts III and IV: AEs; clinical laboratory tests (haematology and biochemistry; in Part III also: coagulation, thyroid function, and urinalysis); vital signs and body weight; electrocardiogram (ECG).

Safety variables only assessed in Part III: blood trough levels of concomitant AEDs.

Statistical Methods:

Presentation of results regardless of dose administered; calculation of descriptive statistics (by periods or visits); Generalised Estimating Equations method to analyse the non-standardised seizure frequency during Parts III and IV 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 during Part III.

Summary of Results and Conclusions:

Efficacy results (Part III):

ESL decreased seizure frequency with a sustained effect over the first 60 weeks of Part III that were analysed for efficacy. The overall mean relative change in seizure frequency from baseline during Part III was −61.8% (95% confidence interval [CI]: −68.2%; −55.4%) in the ITT population and −65.4% (−71.9%; −58.9%) in the PP population. During the first 12 weeks in Part III, seizure frequency in the ITT population was reduced by −61.4% (mean), compared to baseline. Subsequently, the relative change of seizure frequency remained stable, varying between −65.0% and −59.1%. The time course of seizure frequency reduction in the PP population was similar to the ITT population.

The responder rate overall was 63.8% in the ITT population and 69.5% in the PP population. During the first 12 weeks of ESL treatment it was 69.1% in the ITT population, increasing to 71.3% in the 12-week period between Week 25 and 36 and decreasing thereafter by approximately 10%. A similar time course was observed in the PP population.

Overall, the proportion of seizure-free patients during Part III was 8.5% in the ITT population

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and 9.8% in the PP population. Analysed by 12-week intervals, the proportion of seizure-free patients varied between 14.9% and 20.2% in the ITT population, and between 17.1% and 22.0% in the PP population. No clear trend over time could be discerned.

ESL treatment reduced the frequency of all types of seizures throughout the first 60 weeks of Part III that were analysed for efficacy, with similar results for the ITT and PP populations. In the ITT population, the median frequency of simple partial seizures decreased compared to baseline from 7.0 to 2.2 seizures per 4 weeks, the frequency of complex partial seizures decreased from 5.0 to 1.7 per 4 weeks, and the frequency of partial evolving to secondarily generalised seizures decreased from 2.0 to 0.5 per 4 weeks.

The median number of days with seizure per 4 weeks in the baseline period was 6.4 in both the ITT population and the PP population, during Part III it decreased to 2.2 days per 4 weeks and 1.7 days, respectively. Analysed by 12-week intervals, the median numbers of days with seizure per 4 weeks remained stable during Part III, ranging between 1.3 and 2.0 in both the ITT and PP populations.

Relative to baseline of Part I, the questionnaires used in this study showed statistically significant improvements in quality of life (QOLIE-31) and depressive symptoms (MADRS) at the last assessment. The overall score reported for the QOLIE-31 and the individual scales overall quality of life and medication effects all had statistically significant mean increases at the last assessment in both the ITT and PP populations. Statistically significant improvements were reported for the total MADRS score as well as subscale scores for apparent and reported sadness, inner tension, reduced sleep, and inability to feel.

Efficacy results (Part IV):

ESL decreased seizure frequency with a sustained effect over the first 60 weeks of Part IV that were analysed for efficacy. The overall mean relative reduction in seizure frequency from baseline during Part IV was –64.1% (95% CI: –72.5%; –55.8%) in the ITT population and –67.1% (–77.2%; –57.1%) in the PP population. During the first 12 weeks in Part IV, seizure frequency in the ITT population was reduced by −63.9% (mean), compared to baseline. Subsequently, the relative change of seizure frequency varied between –55.3% and –59.8%. In the PP population, the mean relative change in seizure frequency was −64.0% during Week 1 to 12 and varied between −63.2% and −73.0% during subsequent 12-week intervals.

The overall responder rate was 70.4% in the ITT population and 71.7% in the PP population. The proportion of patients with a ≥50% reduction in seizure frequency in the ITT population was similar for all 12-week periods analysed in Part IV (between 70.4% and 73.2%). In the PP population, the proportion of responders increased from 67.4% between Week 1 and 12 to 76.1% between Week 49 and 60.

Overall, the proportion of seizure-free patients during Part IV was 12.7% in the ITT population and 15.2% in the PP population. Analysed by 12-week intervals, the proportion of seizure-free patients increased from 19.7% between Week 1 and 12 to 29.6% between Week 49 and 60 in the ITT population, and from 19.6% to 37.0% in the PP population.

ESL treatment reduced the frequency of all types of seizures throughout the first 60 weeks of

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Part IV that were analysed for efficacy, both in the ITT and PP populations. In the ITT population, the median frequency of simple partial seizures decreased compared to baseline from 5.3 to 1.5 seizures per 4 weeks, the median frequency of complex partial seizures decreased from 4.8 to 1.3 per 4 weeks, and the frequency of partial evolving to secondarily generalised seizures decreased from 2.0 to 0.5 per 4 weeks.

The median number of days with seizure per 4 weeks in the baseline period was 5.9 in the ITT population and 5.7 in the PP population, it decreased to 1.6 and 1.4 days per 4 weeks, respectively. Analysed by 12-week intervals, the median numbers of days with seizure per 4 weeks remained stable during Part IV, ranging between 1.3 and 2.0 days in the ITT and between 0.7 and 1.6 in the PP population.

Safety results (Part III):

The safety of ESL was evaluated in all 95 patients who received at least 1 dose of ESL during Part III of the study. A total of 92 patients (96.8%) were exposed to ESL for at least 6 months and 73 patients (76.8%) for at least 12 months during Part III of the study. The mean duration of treatment with ESL was 419.8 days, ranging between 93 and 556 days. Overall, the safety population was exposed to 36.0 kg of ESL for 109.2 patient-years. The median daily dose of ESL was 800 mg, ranging between the minimum and maximum doses of 400 mg and 1200 mg that were stipulated in the protocol. The mean daily dose remained stable at approximately 900 to 1000 mg.

All patients were treated with 1 or 2 concomitant AEDs during Part III, approximately 55% of patients were administered with 2 concomitant AEDs. Carbamazepine, valproic acid, and lamotrigine were the predominant concomitant AEDs, taken at Visit 12 by 57.9%, 32.6%, and 23.2% of patients, respectively. In agreement with the protocol, doses of concomitant AEDs remained stable during Part III.

Overall, there were no safety concerns with the use of ESL in patients with epilepsy. A total of 36 patients (37.9%) reported 82 treatment-emergent adverse events (TEAEs). The predominant system organ class (SOC) in which TEAEs were reported was nervous system disorders. The most frequent TEAEs were headache (in 14.7% of patients) and nasopharyngitis and dizziness (in 5.3% each). The incidence of TEAEs during periods of about 13 weeks ranged between 9.5% and 14.7% of patients, with a slight decrease over time. Most TEAEs were mild or moderate in intensity, 2 TEAEs were of severe intensity. Adverse drug reactions (ADRs), predominantly headache and dizziness, were experienced by 10 patients (10.5%).

One patient died during Part III due to a serious TEAE of brain oedema that occurred 38 days after the last intake of ESL and was considered unlikely to be related to study medication. Two other serious TEAEs (status epilepticus and exacerbation of chronic bronchitis) resolved. The event of status epilepticus, which had occurred 64 days after the last intake of ESL, was considered possibly related to study medication. In addition to the patient who died, 2 patients were discontinued from the study due to TEAEs (status epilepticus and acute psychosis).

There were a few clinically relevant individual findings for laboratory, vital signs, and ECG

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results, but these were not observed more frequently under treatment with ESL than at baseline. In general, there were no major mean changes of quantitative safety parameters during Part III.

Safety results (Part IV):

The safety of ESL was evaluated in all 71 patients who received at least 1 dose of ESL during Part IV of the study. A total of 68 patients (95.8%) were exposed to ESL for at least 6 months and 59 patients (83.1%) for at least 12 months during Part IV of the study. The mean duration of treatment with ESL was 645.0 days, ranging between 92 and 1325 days. Overall, the safety population was exposed to 43.8 kg of ESL for 125.4 patient-years. The median daily dose of ESL was 800 mg. Analysed by 12-week intervals, the mean daily dose of ESL ranged between 907.0 and 1076.9 mg.

All patients were treated with concomitant AEDs during Part IV of the study; 49.3% were treated with 2 concomitant AEDs, 28.2% with 1 AED, and 22.5% with 3, 4, or 5 AEDs. Carbamazepine, valproic acid, and lamotrigine were the predominant concomitant AEDs, taken by 57.7%, 32.4%, and 29.6% of patients, respectively.

Overall, there were no safety concerns with the use of ESL in patients with epilepsy. A total of 49 patients (69.0%) reported 178 TEAEs. The predominant SOC in which TEAEs were reported was nervous system disorders. The most frequent TEAEs were headache (in 15.5% of patients), nasopharyngitis (in 12.7% of patients), and convulsion (in 11.3% of patients). The overall incidence of TEAEs per period (periods of about 13 weeks) ranged between 18.3% and 26.8% of patients, during the final period covering the time after Day 366 (i.e. up to >2 years), 39.4% of patients had a TEAE. Most TEAEs were mild or moderate in intensity, 5 TEAEs were of severe intensity. ADRs, predominantly headache, convulsion, and dizziness, were experienced by 20 patients (28.2%).

One patient died during Part IV due to a serious TEAE of brain oedema that occurred 62 days after the last intake of ESL and was considered not related to study medication. Nine other patients experienced 10 other serious TEAEs, all of which resolved. Only 1 of the serious TEAEs (convulsion) was considered possibly related to study medication. Except for the patient who died, no other patients were discontinued from the study due to TEAEs.

There were no safety concerns regarding findings for laboratory, vital signs, and ECG results.

Conclusion:

ESL at median once daily doses of 800 mg proved to be well-tolerated and to decrease seizure frequency over additional treatment periods of 1 year and up to >3 years in Parts III and IV of the study. Depressive symptoms, as assessed by MADRS, showed statistically significant improvements during Part III (not assessed in Part IV).

Date of the Report: 05 January 2012