## 2. SYNOPSIS

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| Name of Sponsor/Company:<br>BIAL – Portela & C[a], SA | Individual Study Table<br>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, randomized, placebo-controlled, parallel-group, multicenter clinical trial

Note that the design features described in the title refer to Part I of the study; this report is about Part II, which is an open-label extension of Part I.

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 for Part I. Patients from 42 sites in 12 countries continued in Part II. A complete list of principal investigators is provided in Appendix 16.1.4.

STUDY DATES (Part II): From: 02 February 2005 To: 29 January 2008

PHASE OF DEVELOPMENT: III

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.

Secondary objectives for Part II were as follows: (1) to assess the maintenance of therapeutic effects of ESL over a 1-year open-label period; (2) to assess the drug–drug pharmacokinetic interactions between ESL and concomitant anti-epileptic drugs (AEDs) over a 1-year open-label period; and (3) to assess the health-related quality of life and depressive symptoms over a 1-year open-label period.

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 3 ESL dose levels (400 mg, 800 mg, or 1200 mg) 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 granted or clinical development is discontinued.

This clinical trial report presents results from Part II. Part I results are presented in a separate report.

NUMBER OF PATIENTS: There was no sample size estimate for Part II. Of the 327 patients who completed Part I, 325 were enrolled in Part II.

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.

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TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER: Eslicarbazepine acetate was supplied as scored 800-mg (batch numbers 040122-L, 050007-L, 050052-L, 050053-L, 060179-L, and 070301) tablets for daily oral administration.

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: Not applicable.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy endpoints were as follows: seizure frequency and reduction in seizure frequency during Part II; proportion of responders (i.e., patients with a ≥ 50% reduction in seizure frequency); proportion of seizure-free patients (100% seizure reduction); seizure frequency by seizure type; number of days with seizure during Part II (standardized to a "per 4 weeks" unit); treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]); and Quality of Life in Epilepsy–31 inventory (QOLIE-31) and Montgomery Asberg Depression Rating Scale (MADRS) at the end of Part II compared to the Part I baseline. All seizure frequency measures are standardized to a "frequency per 4 weeks" unit, and change in frequency is as compared with Part I baseline results.

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

STATISTICAL METHODS: The ITT population included all patients with at least 1 dose of ESL during Part II and at least 1 seizure frequency assessment during Part II. The PP population included patients in the ITT population who completed the 1-year open-label period of the study with no major protocol violations. All efficacy variables were analyzed for the ITT and PP populations. For efficacy analyses, data from beyond 1 year after the start of Part II were excluded. For efficacy analyses based on the ITT population, the last observation carried forward method was used.

Seizure frequency measures were based on standardized seizure frequency per 4 weeks, and were calculated for the 4-week period after the first Part II dose, in 12-week intervals starting with Week 5 of Part II, and for Part II overall. Analyses of change from baseline used results from the 8-week baseline period between Visits 1 and 2 during Part I of the study.

Part II data are analyzed without distinction based on actual ESL dose taken. Only pre-Part II AEs and treatment-emergent AEs that started within the first 4 weeks of Part II are summarized by Part I treatment group.

SUMMARY OF RESULTS AND CONCLUSIONS:

Exposure: The mean daily dose of ESL throughout the 1-year treatment period was 890 ± 192 mg (median 800 mg; Table 14.1-4.2.1). Most patients (82%) used 2 or more concomitant antiepileptic drugs (AEDs), and 18% used 1 concomitant AED (Table 14.1-3.3.1). The most commonly used concomitant AEDs were carbamazepine (by 58% of patients), valproic acid (22%), lamotrigine (22%), levetiracetam (17%), and clobazam (17%; Table 14.1-3.1.2).

Efficacy: The primary objective of Part II is to evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over a 1-year open-label period. However, efficacy endpoints were also evaluated:

- The baseline median seizure frequency was 8.4, and the median relative reduction in seizure frequency

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was 32.1% during the first 4 weeks (median seizure frequency was 6.0), ranged from 37.2 to 39.3% during subsequent 12-week periods, and was 36.7% overall (ITT population; Table 14.2-1.1.1).

- The median numbers of days with seizures per 4 weeks was 6.4 at baseline, 5.0 during Weeks 1-4 in Part II, ranged from 3.7-4.3 during subsequent 12-week periods, and was 4.1 for Part II overall (ITT population, Table 14.2-1.6.1).
- The proportion of responders was 36.6% in Weeks 1-4, ranged from 38.2 to 41.5% during subsequent 12-week periods, and was 37.2% during Part II overall (ITT population, Table 14.2-2.1). The proportion of seizure-free patients was 12.0% in Weeks 1-4, ranged from 4.6 to 10.8% during subsequent 12-week periods, and was 2.5% during Part II overall (ITT population, Table 14.2-2.1).
- Improvements from baseline in health-related outcomes (quality of life as measured by QOLIE-31 and depressive symptoms as measured by MADRS) were statistically significant for both the ITT and PP population in the overall or total scores and in several of the individual domains.

The results that have been observed during shorter study periods appear to continue when the duration of ESL treatment is increased.

Safety: Treatment-emergent AEs were reported by 83% of patients. Treatment-emergent AEs occurring in at least 5% of patients were dizziness (27%), headache (16%), somnolence (12%), decreased diastolic blood pressure (9%), abnormal coordination (9%), diplopia (9%), vomiting (7%), nausea (7%), nasopharyngitis (6%), diarrhea (6%), back pain (5%), and blurred vision (5%). Discontinuations because of AEs were reported for 37 patients (11.4%).

The proportion of Part I placebo patients who experienced treatment-emergent AEs during the first 4 weeks of Part II treatment with ESL 800 mg (53.2%) was similar to the proportions observed in Part I in the 400 and 800 mg ESL groups (47.0% and 51.3%, respectively), and greater than the proportion in the 1200 mg ESL group (30.9%; Table 14.3.1-1.1). The types of AEs that were common within the first 4 weeks of treatment did not differ from those that were common and had onsets later in the study.

Among the 270 patients who experienced treatment-emergent AEs, most experienced AEs at a maximum severity of mild to moderate (82%; Table 14.3.1-1.3). Among frequently occurring adverse events, most instances of dizziness, somnolence, abnormal coordination, diplopia, nausea, and blurred vision were considered at least possibly related to the study medication; 10 of 28 instances of decreased diastolic blood pressure were considered at least possibly related to the study medication (Table 14.3.1-1.4). Aside from the decreased diastolic blood pressure, no trends suggesting changes in blood pressure, heart rate, weight, ECG, and laboratory parameters were observed.

Serious adverse events (SAEs) affected 28 patients overall (8.6%), 12 SAEs were considered at least possibly related to the study medication, and most SAEs were reported to have resolved (Listing 14.3.2-2; Table 14.3.1-1.6). Treatment-emergent AEs that led to discontinuation of study treatment were reported for 37 patients (11.4%), most events were considered related to the study medication, and the AE that most frequently led to discontinuation was dizziness (Table 14.3.1-1.5). Three patients died; 2 deaths were not related to the study medication, and 1 death was considered possibly related.

This extension study of treatment with ESL (titrated to an efficacy or safety endpoint) for 1 year did not reveal notable differences in the safety profile compared to that previously observed in Part I of the study, with the exception of mostly mild decreases in diastolic blood pressure.

CONCLUSIONS: The median relative reduction in seizure frequency per 4 weeks was 36.7% overall in Part II, and the proportion of responders was 37.2% overall. With the exception of decreased diastolic blood pressure, which was notably more frequent in Part II than in Part I, no new safety trends emerged in the year-long study.

The reductions in seizure frequency observed in Parts I and II were similar. The results from Part I of the study suggested that 800 mg ESL provided a favorable balance of efficacy and safety, and the results of Part II, which show statistically significant improvements in patient quality of life and depressive symptoms,

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| provide further support for the optimal balance between benefit and risk of treatment with 800 mg ESL for patients and their physicians seeking effective seizure control. | | |
| DATE OF REPORT: 15 September 2008 | | |