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 (ESL)	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 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 António Gil-Nagel, and José Lopes-Lima. A complete list of principal investigators is provided in Appendix 16.1.4. Patients were screened at 39 sites in 3 countries (Portugal, Spain, and Mexico). In total 253 patients were randomized. Of these, 197 patients completed Part I of the study and 194 patients entered Part II of the study.
STUDY DATES (Part II): from 21 June 2005 to 22 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 multicenter study. Part I was an 26-week parallel-group, randomized, placebo-controlled design consisting of an 8-week baseline period, a 2-week double-blinded titration period, 12-week maintenance period, and a 4-week tapering-off period. After completing the baseline period, patients were randomized in a 1:1:1 ratio to 1 of the 2 ESL daily dose levels (1200 or 800 mg) or placebo. Part II was a 1-year open-label extension for patients who had completed Part I. Starting at 800 mg once daily, the dosage could be titrated at 400 mg intervals down to a minimum of 400 mg once daily or up to a maximum of 1200 mg once daily. 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 study report presents results from Part II. Results from Part I were presented in a separate report.
NUMBER OF PATIENTS: There was no sample size estimate for Part II. Of the 197 patients who completed Part I of the study, 194 patients entered Part II of the study.

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 (ESL)	Page:	

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Part I: Male and female patients at least 18 years old with a documented diagnosis of simple partial or complex partial seizures with or without secondary generalization 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 signed the informed consent form, had diaries satisfactorily completed by the patient or his/her caregiver, and for women of childbearing capability, had a negative pregnancy test, agreed to remain abstinent or use acceptable contraception, and presented a serum beta-human chorionic gonadotropin test consistent with a non-gravid state. 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 used chronically as an AED), and patients with known hypersensitivity to carbamazepine, oxcarbazepine, or chemically related substances were excluded. Part II: Completed Part I and was willing to continue treatment in Part II.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER: Eslicarbazepine acetate (ESL) was supplied in 400 and 600 mg tablets for Part I, and scored 800 mg tablets for Part II. In Part I, tablet batch numbers included 040120 L (400 mg tablets) and 040121-L (600 mg tablets). In Part II, tablet batch numbers included 050007-L, 050052-L, 050053-L, and 060179-L (scored 800 mg tablets).

DURATION OF TREATMENT: The duration of Part I was 26 weeks, including the 8-week baseline period. The duration of Part II was 1 year. The optional study extension period, 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: In Part I, placebo tablets matching the 400 and 600 mg active substance tablets were supplied and the batch number was 040119-L. In Part II, no placebo tablets were supplied.

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 $\geq$ 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, blood trough levels of concomitant AEDs for patients in Part I and II, and withdrawal and/or rebound effect during the tapering-off period (Part I, only).

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 (ESL)	Page:	

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 1-year open-label period (i.e., who had a Visit 11 assessment or participated for at least 1 year) with no major protocol violations. Primary efficacy analysis was based on the ITT population. Seizure frequency measures were based on standardized seizure frequency per 4 weeks, and were calculated for the first 4-week period after the first dose in Part II, 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 (Part II):

Exposure: The mean daily dose of ESL throughout the 1-year treatment was 917±179 mg (median=800 mg; range: 400-1500 mg; Table 14.1-4.2.1). Most patients (72%) used two concomitant antiepileptic drugs (AEDs); 24% used 1 concomitant AED. The most commonly used concomitant AEDs were carbamazepine (used by 56% of patients), valproic acid (32%), levetiracetam (20%), topiramate (17%), phenytoin (16%), and lamotrigine (12%; Table 14.1-3.1.1).

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 6.5, and the median relative reduction in seizure frequency was 47.5% during the first 4 weeks, ranged from 53.5 and 57.5% during subsequent 12-week periods, and was 53.4% overall (ITT population, Table 11-3 and Table 14.2-1.1.1).
- The median numbers of days with seizures per 4 weeks was 5.6 at baseline, 3.0 during Weeks 1-4 in Part II, ranged from 2.3-2.7 during subsequent 12-week periods, and was 2.6 for Part II overall (ITT population, Table 14.2-1.6.1).
- The proportion of responders was 45.5% in Weeks 1-4, ranged from 52.4 to 55.5% during subsequent 12-week periods, and was 52.9% during Part II overall (ITT population, Table 14.2-2.1). The proportion of seizure-free patients was 13.6% in Weeks 1-4, ranged from 5.8 to 17.8% during subsequent 12-week periods, and was 2.6% during Part II overall (ITT population, Table 14.2-2.1).
- The mean baseline (Day 1 of Part I) QOLIE-31 overall score in the ITT population was 56.3, and the mean change from baseline at the last observed value was 6.7 (Table 14.2-4.8.2). In all domains tested, the change from baseline to last observed value (early discontinuation of end of 1-year treatment) was considered a statistically significantly improvement (p values ranged from < 0.0001 to 0.0028).
- The mean baseline (Day 1 of Part I) MADRS score in the ITT population was 10.4, and the mean change from baseline at the last observed value (early discontinuation or end of 1-year treatment) was -2.6 (p = 0.0001; Table 14.2-5.11.2). Improvements considered statistically significant included concentration difficulties, pessimistic thoughts, apparent sadness, and inability to feel (p values ranged from < 0.0001 to 0.063).

Results observed during shorter study periods appear to continue with an increased duration of ESL treatment.

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 (ESL)	Page:	

Safety:

Treatment-emergent AEs were reported by 58% of patients. Those occurring in more than 3 patients were dizziness (17%), somnolence (10%), headache (9%), vomiting (6%), influenza (5%), nausea (4%), blurred vision (4%), diarrhea (3%), urinary tract infection (3%), anxiety (2%), diplopia (2%), and pyrexia (2%).

The proportion of Part I placebo patients who experienced AEs during the first 4 weeks of treatment (23.1%) was similar to the proportion in the Part I 800 mg ESL group (21.7%) and greater than the proportion in the Part I 1200 ESL group (16.7%; Table 14.3.1-1.1). The most common AEs within the first 4 weeks of treatment were also common and had onsets later in the study.

Treatment-emergent AEs were of mild to moderate severity in 87% of patients who experienced treatment-emergent AEs (Table 12-5, Table 14.3.1-1.3). Among frequently occurring AEs, most instances of dizziness and somnolence were considered at least possibly related to the study medication (Table 14.3.1-1.4). No trends suggesting changes in blood pressure, heart rate, weight, electrocardiogram, and laboratory parameters were observed.

Thirteen treatment-emergent serious AEs (SAEs) were reported for 11 patients (5.7%); of these, 3 patients (1.5%) experienced SAEs in the SOC nervous system disorders, including cerebellar syndrome, status epilepticus, and transient ischemic attack (each, 1 patient). For most SAEs (11 of 13), patient outcome was reported as recovered or recovered with sequelae (Listing 14.3.2-2); 2 SAEs had an outcome of death. All SAEs occurred after the first 4 weeks of Part II treatment (Table 14.3.1-1.6.1 and Table 14.3.1-1.6.2). Five SAEs were considered at least possibly related to study medication: 2 events of moderate severity (suspected hepatitis and cerebellar syndrome) and 3 events considered severe (hyponatremia, epileptic status, and transitory ischemic attack); each event occurred only once (Listing 14.3.2-2; Table 14.3.1-1.6).

Two patients (1.0%) died during the study (Table 14.3.1-1.7); patient 611/70327 died as a result of astrocytoma tumor relapse (not related to treatment), and patient 703/70252 died as a result of severe status epilepticus, which was considered possibly related to study medication (Listing 14.3.2-3).

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.

CONCLUSIONS: The median relative reduction in seizure frequency per 4 weeks was 53.4% overall in Part II, and the proportion of responders was 52.9% overall. 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 or 1200 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, 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