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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Name of Active Ingredient: Eslicarbazepine Acetate	Page:	
TITLE OF STUDY: Extension study to investigate the efficacy, safety, and tolerability of eslicarbazepine acetate (BIA 2-093) in the recurrence prevention of bipolar I disorder		
INVESTIGATOR(S) AND STUDY CENTER(S): This was a multicenter study. Approximately 60 centers in Europe, South America, and South Africa enrolled patients in this study. A list of investigators is provided in Appendix 16.1.4.		
STUDY DATES: From 27 Mar 2006 to 15 Jun-2007		
PHASE OF DEVELOPMENT: II		
OBJECTIVES: Primary: to evaluate the dose-dependent efficacy of BIA 2-093 administered at once-daily doses of 300 mg, 900 mg, and 1800 mg in the recurrence prevention of bipolar I disorder. Secondary: to evaluate the safety and tolerability of BIA 2-093 administered at once-daily doses of 300 mg, 900 mg, and 1800 mg as maintenance treatment in patients with bipolar I disorder.		
METHODOLOGY: This was an extension study consisting of 2 parts. In Part I, all participants received open-label treatment with BIA 2-093 900 mg once daily for 2 weeks. Part II followed a double-blind, parallel-group design in which participants were randomly assigned to treatment with BIA 2-093 300 mg, 900 mg, or 1800 mg once daily. Patients stable in remission continued double-blind therapy until approximately 6 months after the last patient entered Part II. The occurrence of a new manic/depressive episode was considered a treatment failure, and the patient was discontinued from the study. At the end of Part II, 6 months after last patient enrolled and after no longer than approximately 15 months, if patients were still in remission and the investigational product was well-tolerated, patients had the option to enter long-term open-label treatment at the same dosage as used in Part II until a new episode occurred, until marketing was authorized, or until clinical development of BIA 2-093 in the recurrence prevention indication was discontinued. If patients did not enter long-term treatment, an established recurrence prevention medication was prescribed, and BIA 2-093 was tapered off (patients assigned to 1800 mg had the daily dose decreased to 900 mg for 6 days; those assigned to 900 mg or 300 mg received placebo for 6 days).		
NUMBER OF PATIENTS: Approximately 160 patients (about 53 per treatment group) who responded to treatment after a 3-week treatment period from 2 Phase II studies in acute mania (approximately 80 patients from Protocol SCO/BIA-2093-203 and 80 patients from Protocol PRA/BIA-2093-204) were planned. A total of 104 patients (77 patients from Protocol SCO/BIA-2093-203 and 27 patients from Protocol PRA/BIA 2093-204) were enrolled.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Patients must have had a diagnosis of bipolar I disorder and must have: signed the ICF, completed the 3-week treatment period in Protocol SCO/BIA-2093-203 or Protocol PRA/BIA-2093-204, and responded to treatment (i.e., ≥ 50% improvement in the Young Mania Rating Scale [YMRS] total score or a YMRS total score < 12); for women of childbearing potential, patients must have presented a serum pregnancy test consistent with a non-gravid state and used double-barrier contraception throughout the study.		
TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, and BATCH NUMBER: BIA 2-093 was available as 300 (batch #050080-L) and 900 mg tablets (batch #050071-L). Study medication was administered orally, once daily in the evening.		

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DURATION OF TREATMENT: Treatment duration in Part I, was 2 weeks. Treatment duration in Part II was approximately 6 months for the last patient enrolled; assuming a 9-month enrollment period, maximum individual participation in Part II was up to 15 months, plus a post-study visit (PSV).

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, and BATCH NUMBER: Placebo tablets matching the 300 mg and 900 mg active substance tablets were supplied; the batch numbers were batch #050079-L and batch #050070-L, respectively

CRITERIA FOR EVALUATION:
Efficacy: Efficacy assessments included Clinical Global Impressions - Bipolar Version (CGI-BP), YMRS, Montgomery-Asberg Depression Rating Scale (MADRS), Patient Life Charts (diaries), need for hospitalization, and treatment retention.

Primary endpoint: The proportion of patients who showed no worsening according to CGI-BP scale over Part II.

Secondary endpoints: The proportion of patients who developed manic or depressive symptomatology; the proportion of patients who required hospitalization for a bipolar episode; the proportion of patients who remained on treatment; and mood fluctuations as recorded in patient diaries (patient life charts).

Safety: Safety assessments included adverse events (AEs), clinical laboratory tests (hematology, biochemistry, and coagulation), vital signs, 12-lead electrocardiogram (ECG), and eslicarbazepine plasma levels.

STATISTICAL METHODS:
Primary variable: The proportion of patients who showed no worsening according to the CGI-BP scale over Part II was compared between treatments groups using the Cochran-Mantel-Haenszel (CMH) test stratified by region. To reduce statistical bias, intent-to-treat (ITT) and per-protocol (PP) patients with 'no worsening' must have had at least 2 post-baseline assessments in Part II (excluding early discontinuation visit [EDV] and PSV assessments) to be included in this analysis. However, ITT and PP patients who worsened were included in the analysis even if they had only 1 post-baseline assessment.

Secondary variables: The proportion of patients who developed manic symptomatology, defined as a YMRS total score of 15 or greater, was analyzed using the CMH test stratified by region. The actual and change from baseline in YMRS total score was summarized descriptively by treatment group and visit. The last observation for YMRS total score was analyzed using analysis of covariance (ANCOVA) modeling for baseline YMRS total score, region, and treatment. The treatment-region interaction was also assessed separately. Summaries of actual score and change from baseline are provided for each item.
The proportion of patients who developed depressive symptomatology (defined as a MADRS score of 18 or greater) was analyzed using the CMH test stratified by region.

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Summaries of actual score for each CGI-BP measurement (severity of illness, change from preceding phase and change from worst phase of illness) are provided for mania, depression, and overall bipolar illness at each visit by treatment group. CGI-BP was analyzed using a CMH test instead of ANCOVA due to the ordinal nature of the data. The last observed value for severity of illness, overall bipolar illness of CGI-BP, was analyzed using a CMH stratified by region.
Summaries of total MADRS score are provided by treatment group and visit. The last observation for MADRS total score was analyzed using ANCOVA modeling for baseline MADRS total score, region, and treatment. The treatment-region interaction was assessed separately.
The proportion of patients who remained on treatment was analyzed using a CMH test stratified by region. Only patients who completed the 6-month double-blind period were considered to have remained on treatment.

The time to withdrawal was analyzed by Cox proportional hazards model. Patients who completed the study were considered censored at the time of their last visit.
The highest and lowest mood states, collected in the diary card, were summarized. The mean score for each patient was calculated for intervals of 28 calendar days and used in the analysis. Treatment comparisons were made using an ANCOVA model for each time interval; modeling for baseline is the mean score of the open-label period, region, and treatment.

The safety population was used to summarize the safety data. Adverse events were coded using the Medical Dictionary for Regulatory Activities (Version 9.0). Summary tables and listings are provided, grouped by system organ class (SOC) and preferred term (PT), for patients who died and for patients with serious AEs. Shift tables are provided for laboratory values and vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) outside clinically significant limits. The number and percentage of patients with laboratory values and vital signs outside clinically significant limits are summarized. The 12-lead ECG parameters are summarized by treatment group and visit.

SUMMARY OF RESULTS AND CONCLUSIONS:

Efficacy: The primary efficacy analysis assessed the proportion of patients who showed no worsening, according to the CGI-BP scale over Part II. In the ITT population, in the BIA 2-093 300 mg, 900 mg, and 1800 mg groups, 26 (76.5%), 14 (56.0%), and 16 (61.5%) patients, respectively, showed no worsening according the CGI-BP scale. The results were not statistically significant.

The secondary efficacy analyses assessed the proportion of patients who developed manic symptomatology, defined as YMRS total score of 15 or greater.

In the ITT population, in the BIA 2-093 300 mg, 900 mg, and 1800 mg groups, 3 (8.8%), 4 (16.0%), and 5 (19.2%) patients had total YMRS scores ≥ 15 , and 5 (14.7%), 0, and 3 (11.5%) patients in those groups had total MADRS scores ≥ 18. Results were not statistically significant.

The highest mood states were collected in the diary cards and summarized. The mean score for each patient was calculated for intervals of 28 calendar days and used in the analysis. Treatment comparisons were made using an ANCOVA model for each time interval, modeling for baseline is the mean score of the open-label period, region and treatment. Statistically significant differences were seen in highest mood states between the open-label period and the double-blind period in the ITT population at weeks 1-4 and overall.

No other statistically significant differences occurred between groups in the secondary efficacy analyses.

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Safety: During the open-label period, 42 AEs were reported in 20 patients (19.2%). During the double-blind period, 14 patients in the 300 mg group (40%) reported 27 AEs, 14 patients in the 900 mg group (53.8%) reported 25 AEs, and 18 patients in the 1800 mg group (69.2%) reported 42 AEs. During the open-label period 1 patient reported 1 SAE. During the double-blind period, 2 patients in the 300 mg group (5.7%), 5 patients in the 900 mg group (19.2%), and 3 patients in the 1800 mg group (11.5%) reported 1 SAE. One patient committed suicide during the 28 day follow-up period. The relationship to study drug was assessed as "not related."

The most commonly reported AEs during the open-label period included infections and infestations (8, 7.7%) and gastrointestinal disorders (6, 5.8%). The most commonly reported AEs during the double-blind period included psychiatric disorders (14, 16.1%), infections and infestations (11, 12.6%), investigations (10, 11.5%), gastrointestinal disorders (9, 10.3%), general disorders and administration site conditions (5, 5.7%), and injury, poisoning, and procedural complications (5, 5.7%).

In the 300 mg group, 4 patients (11.4%) experienced mild AEs (11.4%), 7 (20%) experienced moderate AEs, and 3 (8.6%) experienced severe AEs. In the 900 mg group, 4 patients (15.4%) experienced mild AEs, 9 (34.6%) experienced moderate AEs, and 1 (3.8%) experienced a severe AE. In the 1800 mg group, 5 patients (19.2%) experienced mild AEs, 12 (46.2%) experienced moderate AE's, and 1 (3.8%) experienced a severe AE.

Overall, 17 patients (19.5%) experienced AEs that were related to study treatment. These included 7 patients in the 300 mg group (20%), 6 patients in the 900 mg group (23.1%), and 4 patients in the 1800 mg group (15.4%). AEs that occurred in more than 5% of patients overall included psychiatric disorders (9 patients, 10.3%) and investigations (5 patients, 5.7%).

Overall, AEs led to discontinuation for 14 patients (16.1%). Five discontinuations occurred in the 300 mg group (14.3%), 7 in the 900 mg group 26.9%), and 2 in the 1800 mg group (7.7%). The only AEs that led to discontinuation in more than 5% of patients overall were psychiatric disorders.

Serious AEs occurred in 10 patients (11.5%) overall. Two patients in the 300 mg group (5.7%), 5 patients in the 900 mg group (19.2%), and 3 patients in the 1800 mg group (11.5%) experience SAEs.

Three patients in the 300 mg group (8.6%), 3 patients in the 900 mg group (11.5%), and 1 patient in the 1800 mg group (3.8%) withdrew because of AEs.

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CONCLUSIONS: This was a phase II extension study to investigate the efficacy, safety, and tolerability of BIA 2-093 in the recurrence prevention of bipolar I disorder. The primary objective of this study was to evaluate the dose-dependent efficacy of BIA 2-093 administered at once-daily doses of 300 mg, 900 mg, and 1800 mg, and the secondary objective was to evaluate the safety and tolerability of BIA 2-093 administered at once-daily doses of 300 mg, 900 mg, and 1800 mg, as maintenance treatment in patients with bipolar I disorder.

The proportion of patients who showed no worsening according to the CGI-BP scale over Part II was not statistically significant.

The proportion of patients who showed manic/depressive symptomatology was not statistically significantly different between dosage groups for total YMRS scores or total MADRS scores.

No statistically significant differences were observed between the different dosage groups for lowest mood scores by weeks during the double-blind period. Differences between dosage groups for highest mood scores were statistically significant at weeks 1 through 4 p=0.006) and overall (p=0.016).

No statistically significant differences were observed between dosage groups for YMRS-analysis of total score-last observed value, MADRS-analysis of total score-last observed value, analysis of severity of illness, overall bipolar illness-last observed value or analysis of time to withdrawal.

The duration of study drug exposure was shortest in the BIA 2-093 1800 mg group and longest in the 300 mg group.

During the double-blind period, more patients in the BIA 2-093 1800 mg group reported AEs (18, 69.2%) than the 300 mg (14, 40%) or 900 mg (14, 53.8%) groups. Overall, the 1800 mg group had more AEs in almost all SOCs except psychiatric disorders, which were highest for the 300 mg group (7, 20%) vs. the 900 mg group (4, 15.4%) and the 1800 mg group (3, 11.5%).

More patients reported severe AEs in the 300 mg (3 patients, 8.6%) group than in the 900 mg (1 patient, 3.8%) or 1800 mg (1 patient, 3.8%) groups.

The numbers of patients who experienced study treatment-related AEs were not dramatically different for the 3 treatment groups, ranging from 4 (15.4%) in the 1800 mg group to 6 (23.1%) in the 900 mg group and 7 (20%) in the 300 mg group, nor were the numbers of patients who experienced SAEs in the 3 dosage groups (2, 5.7% in the 300 mg group; 5, 19.2% in the 900 mg group; and 3, 11.5% in the 1800 mg group).

Overall, no safety differences were noted between the 3 dosage groups. The 1800 mg group had more AEs than the lower dosage groups, but the 1800 mg group had no more AEs related to study treatment or that led to discontinuation or withdrawal than the lower dosage groups.

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