2. SYNOPSIS

Name of Sponsor/Company: Bial - Portela & C[a], S.A.	Individual Study Table Referring to part of the Dossier	(for National Authority Use only)
Name of Finished Product: to be determined	Volume:	
Name of Active Ingredient: Eslicarbazepine acetate	Page:	

TITLE OF STUDY: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) in acute manic episodes associated with bipolar I disorder in a double-blind, fixed multiple dose, randomised, placebo-controlled, multicentre clinical trial.

INVESTIGATORS AND STUDY CENTERS: Investigators: Dr. Eduardo Amado Cattaneo, Dr. Gerardo Garcia Bonetto, Dr. Miguel Márquez, Dr. Carlos Morra, Dr. Daniel Mosca, Dr. Eduardo Kotlik, Prof. Dr. Goran Dodig, Dr. Pavo Filakovic, Prof. Vera Folnegovic Smalc, Dr. Neven Henigsberg, Dr. Mate Mihanovic, Prof. Tanja Franciskovic, Dr. Ante Gilic, Prof. Carllo Gagiano, Dr. Prema Laban, Dr. Lynette Nel, Dr. Paresh Ramjee, Dr. Jacobus Roux, Dr. Sergio Gloger, Dr. Rosario de Arce, Prof. Dr. Julio Bobes, Dr. Santiago Kassem, Dr. Tomás Palomo, Prof. Dr. Eduardo Vieta, and Dr. Carlos Gonzalez Borras.
Study centers: 25 study centers in Europe, South Africa and South America: 7 centers in Croatia, 6 centers in Spain, 6 centers in Argentina, 1 center in Chile and 5 centers in South Africa.

STUDY DATES: From: 28 Feb 2006 To: 13 Nov 2006

PHASE OF DEVELOPMENT: II

OBJECTIVES: The primary study objective was to evaluate the dose-dependent efficacy of eslicarbazepine acetate administered at doses of 600, 1200, and 1800 mg over a 3-week period, compared with placebo, as therapy in patients with acute mania. The secondary objectives of this study were to a) evaluate the safety and tolerability of eslicarbazepine acetate (BIA 2-093) administered at doses of 600, 1200, and 1800 mg compared with placebo, b) assess the duration to onset of action in the different dose groups, and c) monitor the appearance of depressive symptoms.

METHODOLOGY: This was a phase II, double-blind, fixed multiple dose, randomised, placebo-controlled, multicentre clinical trial in patients with a diagnosis of bipolar I disorder who experienced an acute manic (including mixed) episode. Patients who met the selection criteria at randomisation visit (V) (V2, Day 1) were randomised to 1 of 4 treatment groups: 600, 1200, or 1800 mg eslicarbazepine acetate, or placebo. Patients started the assigned treatment on Day 1 and were followed for up to 3 weeks. On Day 10, patients who showed no improvement were switched to open-label escape therapy with an established antimanic therapy. Patients could have been hospitalized at screening or at any time during the study at the investigator's discretion. Following randomisation (V2, Day 1), patients were assessed on Days 3, 7, 10, 14, 21, 28, and 56, after which they could either enter a recurrence prevention study, or the study drug could be tapered off and they could undergo follow-up assessments.

NUMBER OF PATIENTS: Planned: 160; due to a slow recruitment rate, study enrollment was terminated early and only 38 patients were randomised. Analyzed: 37 patients in the intent-to-treat (ITT) population and 38 patients in the safety population.

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CRITERIA FOR INCLUSION: Patients must have been/had the following: 18 years of age or older; Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for bipolar I disorder (i.e., 296.0, 296.4 or 296.6) and for current acute manic (including mixed) episode; Young Mania Rating Scale (YMRS) total score ≥ 20; symptoms of current manic episode starting within 2 weeks prior to randomisation (V2, Day 1); able to undergo a standard evaluation, including clinical interview, ratings, and laboratory studies; signed informed consent form; post-menopausal or otherwise incapable of becoming pregnant by reason of surgery or tubal ligation; in case of woman of childbearing potential, patient presents a serum pregnancy test consistent with a non-gravid state and will use double-barrier contraception until at least the post-study visit.

CRITERIA FOR EXCLUSION: Patients must not be/have the following: history of schizophrenia or schizoaffective disorder, psychotic features or rapid cycling; currently treated with carbamazepine or oxcarbazepine; history of unresponsiveness, intolerance or hypersensitivity to related compounds (carbamazepine, oxcarbazepine or licarbazepine); use of depot-neuroleptics in the current manic episode; abuse of stimulating drugs or use of systemic sympathicomimetic drugs within the previous 2 weeks; electroconvulsive therapy within the previous 3 months; history of dependence from or chronic abuse of alcohol, drugs or medications within the last year; clinically judged to be at risk of harm to self or others; second or third-degree atrioventricular blockade not corrected with a pacemaker; relevant electrocardiogram (ECG) or laboratory abnormalities; calculated creatinine clearance < 30 ml/min; pregnancy or nursing; participation in other drug clinical trial within the last 2 months before randomisation visit; not ensured capability to perform the trial or to comply with the study protocol (e.g., mental retardation or severe inability to communicate); any other uncontrolled clinically relevant disorder; or previous treatment with eslicarbazepine acetate.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER: Eslicarbazepine acetate (batch number: 050059-L), to be taken orally, was available as 600 mg tablets.

DURATION OF TREATMENT: The maximum individual treatment duration was 3 weeks. An additional tapering-off period of up to 6 days and a 4-week follow-up period were planned for patients who did not participate in the recurrence prevention study.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER: Matching placebo tablets were supplied.

CRITERIA FOR EVALUATION:
Efficacy: Primary Endpoint: Change in the YMRS total score from baseline until the end of the 3-week treatment period. Secondary endpoints: YMRS responder rate (≥ 50% improvement or < 12 points in total); proportion of patients in full remission (YMRS < 12); change of the YMRS score over the 3-week treatment period; clinical global impressions-bipolar disorder (CGI-BP); proportion of patients requiring rescue medication; benzodiazepine use; treatment retention time (time to withdrawal due to lack of efficacy or adverse events [AEs]); proportion of patients remaining on treatment for the duration of the study.

Safety: AEs, clinical laboratory tests (haematology, biochemistry, coagulation, and sex hormones), vital signs, ECG, occurrence of symptoms of depression assessed by the Montgomery-Asberg Depression Rating Scale and eslicarbazepine acetate plasma levels.

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STATISTICAL METHODS: Because the study was terminated early, no inferential analyses were performed. Descriptive statistics, including the number of patients, mean, standard deviation, median, and range (minimum and maximum) are presented. The population for all summaries was the ITT population, which consisted of all patients who were randomised and received at least 1 dose of study medication. For patients who did not complete the 3-week treatment period, the last observation was carried forward.

SUMMARY OF RESULTS AND CONCLUSIONS:

Efficacy:

Primary Comparison: In the ITT population, the change in the YMRS total score from baseline to the end of the 3-week treatment period, which was the primary efficacy variable, was comparable among all treatment groups, including placebo, on given visit days. The mean YMRS scores for all treatment groups decreased from baseline over time.

Secondary Comparison: Most patients in all groups were responders at the end of the 3-week treatment period, the YMRS total score decreased for all treatment groups over the 3-week treatment period, most patients in all groups except eslicarbazepine acetate 1800 mg were in full remission at the end of the 3-week treatment period, CGI-BP scores generally decreased for all groups and conditions over the course of the study, and only 1 patient required rescue medication at Day 10.

Safety:
No patients died while in the study. Two of 38 patients (5.3%) experienced treatment-emergent serious adverse events (SAEs). One patient who experienced a treatment-emergent SAE was in the eslicarbazepine acetate 1800 group and 1was in the placebo group. Both treatment-emergent SAEs were assessed as not related to treatment. Overall, 5/38 patients (13.1%), including the 2 with treatment-emergent SAEs, were prematurely withdrawn from the study due to AEs, with 2 each from the eslicarbazepine acetate 1200 mg and eslicarbazepine acetate 1800 mg groups, and 1 from the placebo group. Of the 3 prematurely-withdrawn patients who experienced non-serious treatment-emergent AEs (TEAEs), 1 was in the eslicarbazepine acetate 1800 mg group and 2 were in the eslicarbazepine acetate 1200 mg group. Of the 2 patients in the eslicarbazepine acetate 1200 mg group, one experienced 2, and one experienced 3, TEAEs that led to study treatment discontinuation. Those 6 TEAEs were assessed as possibly related to treatment. One patient was withdrawn from the study for non-compliance. Incidences of specific TEAEs were generally similar between treatment groups and most were of mild or moderate intensity.

CONCLUSIONS:
Due to the early termination of the study, the analysis specified in the protocol was reduced and no formal analysis was performed. In the ITT population, no apparent differences were observed in YMRS total scores between eslicarbazepine acetate-treated patients and placebo-treated patients. No patients died while in the study, 2/38 patients (5.3%)experienced treatment-emergent SAEs that were assessed as unrelated to study treatment, and 3/38 patients (7.9%) experienced TEAEs that were assessed as possibly related to study treatment. Ten patients were withdrawn from the study prematurely.

DATE OF REPORT:
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