1 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: –		
Name of Active Ingredient: Eslicarbazepine Acetate (BIA 2-093)	**Volume:** **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, randomised, dose-titration, placebo-controlled, multicentre clinical trial

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Investigators: S. Kasper, H. Schubert, J. Bouček, V. Fait, Z. Vyhnánková, Z. Šolle, E. Herman, J. Pišvejc, P. Korcsog, P. Molcan, E. Pálová, L. Virčík, I. Dóci, J. Chválová, L. Figueira, M. Nica-Udangiu, M. Ladea, G. Marian, I. Plavitu, C. Iordache, P. Pena, G. Badescu, M. Lapadat

Study centres: 23 centres: 2 centres in Austria, 6 centres in Czech Republic, 6 centres in Slovakia, 1 centre in Portugal, and 8 centres in Romania.

Publication (reference): none

Study period:	**Phase of development:**
First patient enrolled: 02 December 2005 Last patient completed: 23 November 2006	Phase II / therapeutic exploratory

Objectives:
The *primary objective* was to evaluate the dose-dependent efficacy of 2 dose-titration regimens of Eslicarbazepine Acetate compared with placebo as therapy in patients with acute mania.
The *secondary objective* was to evaluate the safety and tolerability of 2 dose-titration regimens of Eslicarbazepine Acetate in comparison to placebo.

Methodology:
Multicentre, double-blind, randomised, parallel-group, placebo-controlled dose-titration study; depending on clinical efficacy, up-titration of dosage 3 and 6 days after start of treatment; maintenance of individual maximum dose for the rest of the total 3-week treatment period; subsequently, down-titration (according to the dose steps and the time intervals of up-titration) and administration of an established anti-manic therapy during the tapering-off period (in patients who discontinued treatment) or entry into a recurrence prevention study (Protocol PRA+SCO/BIA-2093-205; reported under separate cover) as an option for patients who responded to the study treatment

Number of patients (planned and analysed):
Planned: 160 patients; analysed: 160 in the intention-to-treat (ITT) population, 131 in the per-protocol (PP) population, 161 in the safety population

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Diagnosis and main criteria for inclusion:
Patients were to be/have: 18 years or more; 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) score ≥20; symptoms of current manic episode starting within 2 weeks prior to randomisation.

Test product, dose and mode of administration, batch number:
Eslicarbazepine Acetate (BIA 2-093), tablets containing 400 or 600 mg; initial doses of 600 or 800 mg; potential up-titration from 600 mg to 1800 mg (in 600 mg steps) or from 800 mg to 2400 mg (in 800 mg steps), 1 step being taken every 3 days; if deemed necessary after up-titration and if possible, down-titration by 1 step; oral administration once daily; batch nos: 050057-L (400 mg Placebo), 050058-L, (400 mg Eslicarbazepine Acetate), 050059-L (600 mg Eslicarbazepine Acetate)

Duration of treatment:
Up to 3 weeks (titration and maintenance) plus up to 6 days (tapering-off, i.e. down-titration conducted on an individual basis corresponding to up-titration); patients who responded to treatment had the option of entering a recurrence prevention study (Protocol PRA+SCO/BIA-2093-205, reported under separate cover) instead of completing the tapering-off period

Reference therapy, dose and mode of administration, batch number:
Placebo tablets; potential up-titration of initial number of tablets administered by up to 2 steps, 1 step being taken every 3 days; if deemed necessary after up-titration and if possible, down-titration by 1 step; oral administration once daily, batch nos: 050058-L, (400 mg Eslicarbazepine Acetate placebo), 050059-L (600 mg Eslicarbazepine Acetate placebo); treatment for up to 3 weeks (titration and maintenance) plus up to 6 days (tapering-off)

Criteria for evaluation:
Efficacy variables:
Primary endpoint: Change in the YMRS total score at the end of the 3-week treatment period, in relation to the baseline.
Secondary endpoints: Responder rate (proportion of patients with ≥50% improvement in the YMRS total score or with a total score <12 points); change in the YMRS total score at each visit over the 3-week treatment period; proportion of patients in full remission, defined as an YMRS total score <12; Clinical Global Impressions – Bipolar Version (CGI-BP); proportion of patients using benzodiazepines; treatment retention time (time to withdrawal due to lack of efficacy or adverse events); proportion of patients remaining on treatment for 3 weeks.

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Safety variables:
Adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), occurrence of symptoms of depression assessed by the Montgomery-Asberg Depression Rating Scale (MADRS), plasma levels of BIA 2-194 (main active metabolite of Eslicarbazepine Acetate).

Statistical methods:

Primary Efficacy Analysis: Change in YMRS total score from baseline until the end of the 3-week treatment period was compared between placebo and the final Eslicarbazepine Acetate dosage groups by an analysis of covariance (ANCOVA), using the baseline YMRS value as covariate.

Secondary Efficacy Analyses: The proportion of patients showing ≥ 50% improvement or achieving < 12 points in the YMRS at the end of the 3-week treatment period was compared between groups by using a Cochran-Mantel-Haenszel (CMH) test. Change in YMRS total score at each visit over the 3-week treatment period was analysed by ANCOVA with the baseline YMRS value as covariate. The proportion of patients in full remission, the proportion of patients remaining on treatment for the duration of the study and the proportion of patients using benzodiazepines was analysed by using a CMH test. The time to withdrawal because of lack of efficacy or adverse events was analysed by using survival analysis techniques and the respective proportion of patients was compared between treatment groups using a CMH test. Treatment group comparisons were performed by using the log-rank test. Kaplan-Meier survival curves were presented for each treatment group. The CGI-BP measurements were summarised by treatment group at the last assessment and treatment comparisons were made by an ANCOVA with baseline score as a covariate.

Safety Analysis: Adverse events were summarised by treatment group. All treatment-emergent adverse events (TEAEs) were summarised by calculating the number and proportion of patients with adverse events by treatment group, and preferred term and system organ class. Additionally, TEAEs were summarised by time to onset of adverse event, severity (intensity), seriousness and relationship to treatment. Brief written narratives were prepared describing each death, each serious adverse event, and for all patients who withdrew from the study because of adverse events. Clinical laboratory variables and vital signs variables were summarised for each treatment group by calculating summary statistics on the actual values and on the change from baseline at key time points. Shift tables were provided to summarise values that fall outside clinically significant limits. The number and proportion of patients with values outside the limits of clinical significance was summarised. Physical examination data were summarised by treatment group by calculating the frequency and percent of changes (e.g. normal to abnormal) in each examination category from baseline to the end of study. ECG parameters were calculated and analysed centrally. ECG was summarised for each

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treatment group by calculating summary statistics on the actual values and on the change from baseline. The MADRS measurements were summarised by treatment group and were compared between treatment groups by an ANCOVA model with the baseline MADRS score as covariate. Plasma levels of BIA 2-194 were tabulated by visit and treatment group.

Summary – Conclusions:

Efficacy results

In the primary analysis (ITT population), ESL 800 mg produced a greater reduction in YMRS total score than placebo (–14.2 vs –10.3), and this finding was of borderline statistical significance (P = 0.0523). The reduction in YMRS total score in the ESL 600 mg group was also in favour of the active treatment, but the effect was smaller (–12.5) than that for the ESL 800 mg group. The PP population showed similar results to those observed in the ITT population, with the largest difference again observed between the ESL 800 mg and placebo groups (P = 0.0562).

For nearly all efficacy variables, there tended to be a increase in efficacy across the randomised dosage regimens from placebo to the ESL 800 mg group. A significantly higher percentage of patients in the ESL 800 mg group than the placebo group were in full remission at visit 7, but no statistically significant differences were observed between the ESL treatment groups and placebo with regard to responder rate at visit 7.

On the basis of the exposure data, dosage step D-2 appeared to be the most effective dosage step in both ESL treatment groups. The 1600 mg dose may have provided slightly better efficacy than the 1200 mg dose.

Safety results

TEAEs occurred more frequently in the ESL treatment groups than in the placebo group (800 mg: 50.9%, 600 mg: 53.1%, placebo: 35.0%). However, the overall frequency of TEAEs in the 2 ESL treatment groups was very similar, and no relationship to dosage could be observed.

In all 3 treatment groups, the most frequent types of TEAE were nervous system disorders and, gastrointestinal disorders. The most common individual TEAEs observed after treatment with Eslicarbazepine Acetate (≥5% of patients) were headache, dizziness, nausea, vomiting and diarrhoea. Of these events, only headache and diarrhoea were more frequent in both ESL treatment groups than in the placebo group; neither headache nor diarrhoea were reported in the placebo group.

In all 3 treatment groups, most TEAEs were mild or moderate in intensity and resolved by the end of the study.

The number of patients with serious TEAEs was small and comparable in all 3 treatment groups (800 mg: 3.5%, 600 mg: 3.1%, placebo: 2.5%). One placebo patient died following

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an ischaemic stroke in the tapering-off period after visit 7. TEAEs led to withdrawal in more patients in the ESL treatment groups than in the placebo group (800 mg: 7.0%, 600 mg: 6.3%, placebo: 2.5%). No pattern was observed in the types of TEAE leading to withdrawal from Eslicarbazepine Acetate.

No differences were detectable between the treatment groups with respect to the frequency and types of bipolar disorder TEAE reported.

No relevant changes were seen in the mean or median data for laboratory safety parameters over time. There was a tendency to a higher overall frequency of clinically significant laboratory values under Eslicarbazepine Acetate treatment, in particular in the ESL 600 mg group; however, no relationship to treatment group was observed for individual laboratory parameters.

No relevant differences were detected between the treatment groups with respect to vital signs, ECG, physical examination or MADRS total score.

Pharmacokinetic results

Pharmacokinetic analyses showed an approximately linear relationship between dosage of Eslicarbazepine Acetate and plasma levels of the main active metabolite BIA 2-194.

Conclusion

The ESL 800 mg dose-titration regimen was more effective than the ESL 600 mg and placebo regimens, although the primary treatment comparison did not quite reach statistical significance.

The 2 ESL treatments exhibited a comparable safety profile, but were generally not as well tolerated as the placebo treatment.

Date of the report: 30 March 2007