2. SYNOPSIS

Sponsor: BIAL-Portela & C[a] SA	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: Zebinix®		
Name of Active Ingredient: Eslicarbazepine acetate (ESL, also known as BIA 2-093)		

Title of study: Effects of Eslicarbazepine Acetate (BIA 2-093) on Cognitive Function in Children With Partial Onset Seizures: An Add-On, Double Blind, Randomized, Placebo Controlled, Parallel Group, Multicenter Clinical Trial

Principal investigators: Investigators are listed in the appendix of the full clinical study report.

Study centers: The study was conducted at 33 investigational sites in 4 countries: Italy, Poland, Russia, and Ukraine.

Publications (reference): None

Studied period (years): **Double-Blind Period:** First patient first visit: 10 August 2010 Last patient last visit: 21 March 2012 **Open-Label Period:** First patient first visit: 02 December 2010 Last patient last visit: 27 May 2013	**Phase of development:** 2

Objectives:

Primary: The primary study objective was to evaluate the effects of ESL on cognition in comparison with placebo as adjunctive therapy in children aged 6 to 16 years old with refractory partial-onset seizures over a 12-week double-blind (DB) period.

Secondary:

- To evaluate the safety and tolerability of ESL in comparison with placebo, over an 8-week maintenance period preceded by a 4-week titration period and followed by a tapering-off period.
- To evaluate the efficacy of ESL compared with placebo as adjunctive therapy in children with refractory partial epilepsy over an 8-week maintenance period.
- To evaluate the effect of ESL on global cognitive skills, social competence and quality of life (QOL) in comparison with placebo over a 12-week DB period.
- To evaluate the effects of long-term treatment with ESL as adjunctive therapy on global cognitive skills, social competence and QOL over a one-year open-label (OL) period.
- To evaluate the safety, tolerability, and sustainability of the therapeutic effect of ESL during a one-year OL-period.

Methodology: The study consisted of three parts; the results from Part I and Part II are addressed in this CSR. The results of Part III will be provided in a future CSR. Part I was a multicenter, DB, randomized, placebo-controlled, parallel-group clinical study conducted in patients aged 6 to 16 years with a diagnosis of

partial-onset seizures that were refractory to treatment with 1 to 2 AEDs. Part I of the study comprised three periods: an observational baseline period of 4 weeks; a DB period of 12 weeks, with a 4-week up-titration period and an 8-week maintenance period; a tapering-off period conducted in 2-week steps of down- titration. At the end of the observational baseline period, patients who met the selection criteria were randomly assigned in a 1:2 ratio to receive either placebo QD or ESL 30 mg/kg/day QD (maximum 1200 mg). Cognitive, efficacy, and safety assessments were conducted at baseline and at specified time points throughout the study.

Part II consisted of one-year, OL, uncontrolled period which started after completion of the last 2-week, 10 mg/kg/day down-titration step in Part I. All patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). Patients entering the one-year OL extension attended the study clinic for 6 scheduled visits during Part II for ongoing safety monitoring and performance of study assessments. At the end of Part II, patients either entered a tapering-off/follow-up period or an additional two-year OL extension in which all patients will receive ESL (Part III).

Number of patients (randomized): This international multicenter study was conducted in 123 patients with partial-onset seizures that were refractory to treatment with 1 to 2 AEDs. A total of 133 patients were screened for eligibility to participate in the study, of these 123 patients were randomized to study drug and were analyzed in the intention-to-treat (ITT) analysis population.

Diagnosis and main criteria for inclusion: Patients aged 6 to 16 years with documented diagnosis of epilepsy since at least 12 months prior to screening who were currently receiving treatment with 1 or 2 AEDs in a stable dose regimen at least 4 weeks prior to screening, with at least 2 partial-onset seizures during the 4 weeks prior to screening. Current treatment with 1 to 2 AEDs (any except oxcarbazepine). Has an intelligence quotient (IQ) of at least 70 as assessed within the one year prior to screening and a parent or legal representative able to understand and willing to complete the CBCL and CHQ throughout the study.

Test product, dose and mode of administration, batch number: ESL was provided as white oblong tablets of 200 mg that were scored so that they could be broken in half when necessary. Matching placebo tablets, identical in appearance were supplied for Part I. The medication was taken orally. The full drug batch by-patient listing during each part is in the appendix of the full clinical study report.

Duration of treatment: For patients who continued on to Part II, the maximum duration of Part I was 20 weeks, while patients who opted not to enter Part II had an additional 4-week observational follow up period with a ninth visit at the end, for a total maximum duration of 24 weeks. Duration of Part II was one year.

The total study duration will be about 3.5 years for those patients who complete all three parts of the study.

Analysis populations:

Part I:

- **Safety population** – all randomized patients who received at least one dose of study treatment after randomization.
- **Modified Cognitive Intent-to-Treat (ITT) population** – all randomized patients who received at least one dose of study treatment after randomization and had at least one post baseline assessment of cognition.
- **Modified Efficacy ITT population** – all randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment.
- **Cognitive Per-protocol (PP) population** – all patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not IPDs with respect to the primary cognitive endpoint.
- **Efficacy PP population** – all patients in the Modified Efficacy ITT population who completed the 8-week maintenance period and were not IPDs with respect to the secondary efficacy endpoints.

During Part I, safety data were summarized for the Safety population. Patients were included in the safety summaries according to the treatment that they actually received.

Part II:

- **Safety population** – all patients who entered Part II and who received at least one dose of study treatment.
- **Modified Cognitive Intent-to-Treat (ITT) population** – all patients who entered Part II, who received at least one dose of study treatment and had at least one post baseline assessment of cognition.
- **Modified Efficacy Intent-to-Treat (ITT) population** – all patients who entered Part II, who received at least one dose of study treatment and had at least one post-baseline seizure frequency assessment during Part II.

Safety data were summarized for the Safety population, efficacy data were summarized for the Modified Efficacy ITT population, and cognitive endpoints were summarized for the Modified Cognitive ITT population.

Criteria for evaluation:

Primary endpoint: The primary endpoint was change from baseline to the end of the Part I DB period in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed. There was no primary analysis for Part II of the study.

Secondary endpoints:

Safety Endpoints (Part I and Part II)

- Treatment-emergent adverse events (TEAEs)
- Change from baseline in clinical laboratory tests (hematology, biochemistry, thyroid function and urinalysis)
- Vital signs
- Body weight, height and head circumference
- 12-lead ECG readings

Efficacy Endpoints

Part I:

- Relative reduction from baseline in seizure frequency over the evaluation period as compared with placebo
- Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period to the 8-week maintenance period (responders)
- Proportion of seizure-free patients (100% seizure reduction) over the 8 week maintenance period
- Proportion of patients with a 25% or greater exacerbation in seizure frequency versus baseline

Part II:

- Relative reduction from baseline in seizure frequency over the OL period
- Proportion of patients with a 50% or greater reduction in seizure frequency from the baseline period (responders)
- Proportion of seizure free patients (100% seizure reduction)
- Proportion of patients with a 25% or greater exacerbation in seizure frequency versus baseline

Cognitive Endpoints

Part I:

The following measures were used to assess global cognitive skills, social competence, and QOL:

- From the CDR neurocognitive test battery, change from baseline to the end of the DB period in the score of:
  - Continuity of attention
  - Quality of working memory
  - Quality of episodic secondary memory (children aged ≥ 9 years only)

- Word recognition (children aged ≥ 9 years only)
- Picture recognition (children aged < 9 years only)
- Speed of memory.

- In addition, change from baseline to the end of the DB period in the following:
  - Number of correct answers on the Raven's Standard Progressive Matrices (SPM) test
  - Competence summary score from the Child Behavior Checklist (CBCL)
  - Physical and psychosocial functioning summary score from the Child Health Questionnaire (CHQ)

Part II:

The following measures were used to assess global cognitive skills, social competence, and quality of life:

- From the CDR neurocognitive test battery, change from baseline to the end of the Part II (one-year OL-period) in the score of:
  - Power of Attention
  - Continuity of attention
  - Quality of working memory
  - Quality of episodic secondary memory (children aged ≥ 9 years only)
  - Picture recognition (children aged < 9 years only)
  - Speed of memory
- In addition, change from baseline to the end of the OL period in the following:
  - Number of correct answers on the Raven's SPM test
  - Competence summary score from the CBCL
  - Physical and psychosocial functioning summary score from the CHQ

Statistical methods: All statistical analyses of the cognitive, efficacy and safety data were performed after the study was completed and the database was released for unblinding. Analyses of the neurocognitive data (both primary and secondary variables) were performed by Bracket. Analyses of the CHQ physical and psychosocial health summary scores, CBCL overall competence score, and Raven's SPM total number of correct responses were performed by UBC. Specific details of all derivations and analyses are included in the statistical analysis plan (SAP).

Primary Analysis:

The change from baseline to the end of the DB period in the primary endpoint, Power of Attention score, was compared between the treatment groups using analysis of covariance (ANCOVA). This analysis was performed for all patients and for each age group separately. In the analysis in all patients, the ANCOVA model included treatment and country as fixed effects and baseline Power of Attention score, age and sex as covariates. In the analyses in each age group, the model included treatment and country as fixed effects and baseline Power of Attention score and sex as covariates.

The least squares means (LSM) for the change from baseline in each treatment group obtained from the main ANCOVA model were presented together with their SEs and 95% confidence intervals (CIs). The differences between the LSM for the ESL versus placebo comparison were also presented together with the associated 95% CI and *P* value. Non-inferiority of ESL versus placebo was assessed by comparing the 95% CI's upper bound of the difference of LSMs between treatment groups (ESL-placebo) with 121 milliseconds (ms). If the upper bound was greater than 121 ms, then the null hypothesis that the change from baseline in the Power of Attention score in ESL group is at least 121 ms inferior than the placebo group was rejected. The analyses of the primary endpoint were performed for both the Modified Cognitive ITT and Cognitive PP populations.

Secondary Global Cognitive Skills/Social Competence/Quality of Life Analyses:

Changes from baseline in each of the secondary global cognitive skills/social competence/QOL endpoints were compared between the treatments using ANCOVA models as described for the primary analysis. UBC neurocognitive test variables used to derive the primary and secondary cognitive endpoints together with individual concepts from the CHQ were summarized descriptively.

Secondary Efficacy Analyses:

Change from baseline in seizure frequency were compared between the treatment groups using an ANCOVA model including treatment, baseline seizure frequency, age and gender as covariates. The proportion of patients in each of the various categories of seizure frequency reduction (≥ 50% reduction [responders], 100% reduction (seizure-free patients) and ≥ 25% exacerbation compared with baseline) were compared between treatment groups using the Cochran-Mantel-Haenszel statistic for ordinal data.

Safety:

All patients who are randomized and receive investigational product were evaluated for safety. AEs were summarized by treatment received during the DB assessment period. All TEAEs were summarized by calculating the number and percentage of patients with TEAEs by treatment group, system organ class (SOC), and preferred term (PT). Additionally, TEAEs were summarized by severity (intensity). Brief written patient narratives were prepared describing each death, each serious adverse event (SAE), and for all patients who withdrew from the study because of AEs.

Clinical laboratory variables and vital signs variables were summarized 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 summarize values that fell outside clinically significant limits. The number and percentage of patients with values outside the limits of clinical significance were summarized.

SUMMARY – CONCLUSIONS

NEUROCOGNITIVE RESULTS:

- For the primary endpoint of Power of Attention, non-inferiority analysis failed to reject the null hypothesis that the change from baseline in the Power of Attention score in the ESL group was at least 121 ms inferior to the placebo group for all age groups.
- In the superiority testing for the Power of Attention, there was no significant difference between ESL and placebo for the overall age group or among the 2 age groups, in a study adequately powered study to detect such an effect. In fact there was a non-significant benefit of ESL over placebo with an effect size of 0.28. Further, in the OL extension, maturational development on this domain of cognition at least matched, if not exceeded, the expected rate of development seen in an age-matched cohort from the CDR System database.
- Of the four secondary cognitive domains assessed in this study, ESL was found not to negatively influence sustained attention, working memory or memory retrieval speed.
- ESL did have a statistically reliable negative effect on the Episodic Memory Index, a measure of delayed recognition of previously presented information. However, the two groups had notably different pre-study scores on this measure, the ESL group being initially superior to placebo, and the effect may instead have represented 'regression to the mean'. Importantly, during the one-year follow-up, the group previously treated with ESL caught up with the group who initially received placebo; indicating that there was no long-term consequence for the possible effects seen in the DB period.
- In conclusion, the findings of this study are that in epilepsy patients aged 6 to 16 years, ESL does not thus appear to have negative consequences for attention, information processing and working memory in, or in the longer term for episodic memory.

COGNITIVE SKILLS, SOCIAL COMPETENCE AND QUALITY OF LIFE RESULTS:

- Child Health Questionnaire (CHQ-PF50)
    - Mean baseline scores were similar between the treatment groups for some of the components, but suggested small differences favoring ESL for others, most notably for the Parental Impact – Time. Post-baseline scores reveal similar patterns of change with treatment and place, with mean scores revealing no change or comparable small improvement at Visit 7 (Week 12) or at the EDB period. There was evidence of greater improvement with ESL in Bodily Pain scores in children aged 6 to 11 years, with a mean increase of 4.2 points compared with a decline of 1.8 points in the mean scores for the placebo group. This is in contrast with results in the adolescent age group (12 to 16 years), where the placebo group showed a 2-fold greater improvement in scores compared with ESL (11.4 versus 5.3 point change at EDB). Analyses of the PP population revealed consistent patterns with those observed in the Cognitive ITT analyses, with slightly larger magnitudes of

improvement.

- No statistically significant differences in the change from baseline at the EDB period for mean physical health summary scores were observed (Cognitive ITT population and PP population); interaction tests between treatment and age group, sex and country did not reach statistical significance.
- The mean psychosocial health summary scores at baseline were similar and remained almost unchanged at the EDB period.
- The mean CBCL scores at baseline were similar between the treatment groups and changed very little at the EDB period (Cognitive ITT population and PP population). The difference in LS means between treatment groups were not statistically significant within the 2 age groups, however; ESL was associated with slightly larger decline in children aged 6 to 11 years and small incremental improvement in adolescents aged 12 to 16 years.
- There similar improvements in both groups in the Raven's SPM during the DB part of the study.
- For all the variables (CHQ-PF50, CBCL and Raven's SPM) there were non-significant changes during the OL part, similar in patients initially randomized to placebo or ESL in the DB part.

EFFICACY RESULTS:

Part I:

- Standardized seizure frequency was lower in the ESL treatment group compared with placebo. The ESL group was statistically significantly different compared with placebo with respect to the relative change from baseline in standardized seizure frequency during the maintenance period ($P < 0.001$) in both the Modified Efficacy ITT and Efficacy PP populations.
- There was no rebound effect observed in the subset of patients who completed the tapering-off period.
- The results from the analyses of the other efficacy endpoints in the Modified Efficacy ITT population, for example, the proportion of responders during the maintenance period, are consistent with the conclusions noted above on the relative change from baseline in standardized seizure frequency during the maintenance period; that is, the proportion of responders was higher in the ESL group and the difference compared with placebo was statistically significant.
- There were no statistically significant treatment-by-age group, treatment-by-sex, or treatment by country interactions in the analysis of standardized seizure frequency during the maintenance period, thus indicating that the treatment effect was consistent in each age group, sex, and country.

Part II:

- Standardized seizure frequency was lower in the previous DB ESL treatment group compared with the previous DB placebo group.
- The previous DB placebo group experienced a decrease in standardized seizure frequency during the OL period, gradually becoming numerically similar to the previous DB ESL group.
- The results from the analyses of the other efficacy endpoints in the Modified Efficacy ITT population, for example the proportion of responders during the one-year OL period, are consistent with the conclusions noted above on the relative change from baseline in standardized seizure frequency during the one-year OL-period; that is, the proportion of responders was higher in the previous DB ESL group.

SAFETY RESULTS:

Part I:

- There were no deaths during the study.
- The prevalence of SAEs was low overall. A total of 5 patients reported at least one treatment-emergent SAE, with 2 patients in the placebo group and 3 patients in the ESL group.
  - One of these patients experienced severe status epilepticus, which was deemed probably related to study drug (ESL). The patient discontinued study drug due to the event and the patient recovered.
  - No serious potentially related treatment-emergent events of special interest (cutaneous,

cardiovascular, and cerebrovascular) were reported during the study.

- Five patients had TEAEs that led to discontinuation of study drug, all of which occurred in the ESL group.
    - Two patients who discontinued study drug experienced cutaneous events, which were considered potentially related to study drug (moderate rash, definitely related and mild allergic dermatitis, probably related). Both patients recovered following discontinuation of study drug and neither event was considered serious.
- The proportion of patients who experienced at least one TEAE was similar between the placebo (47.5%) and ESL (41.0%) groups.
    - Treatment-emergent AEs that were more frequent in the ESL group than the placebo group were respiratory tract infection, including viral, vomiting, diplopia, and allergic dermatitis but these were few overall. Headache was more frequent in patients receiving placebo compared with those receiving ESL. The incidences for dizziness and somnolence were similar between the placebo and ESL groups.
    - Overall, rash occurred in few patients; 1 patient in the placebo group and 6 patients in the ESL group reported any type of cutaneous rash (including rash, rash pruritic, and allergic dermatitis). Other cutaneous events that occurred in 1 patient in each treatment group were ecchymosis (placebo) and alopecia (ESL).
- The majority of TEAEs were of mild or moderate intensity for both treatment groups. Treatment-emergent AEs that were reported as severe occurred in no more than 1 patient in either treatment group.
- Comparable results were seen for the incidences of TEAEs that were reported as potentially related to study drug (15.0% placebo; 24.1% ESL). Headache and somnolence accounted for the majority of the events and incidences were similar between the placebo and ESL groups. All reported events of potentially related vomiting (5 patients) and allergic dermatitis (1 patient) occurred in the ESL group.
- Overall hematology and biochemistry laboratory parameters did not show any substantial changes in either treatment groups and no TEAEs of hyponatremia were reported.
- A slight reduction in total and free T3 levels was observed in the ESL group but these changes were mostly within normal range. In the ESL group, there were some reductions in T4 (total and free) levels, with a number of these values falling outside of the normal range. One event of hypothyroidism was reported in the placebo group.
- Two patients had shifts from normal to abnormal in ECG parameters at Visit 4; 1 patient in the placebo group had low height of T-waves and 1 patient in the ESL group had irregular sinus rhythm with arrhythmia that was deemed NCS. One patient in the ESL group had an abnormal ventricular extrasystole during the tapering-off period. No other patients had changes from normal to abnormal during the study.
- Any negative shifts in physical and neurological examinations were minimal for the placebo and ESL treatment groups.
- Overall, the mean and mean changes from baseline for vital sign parameters, body weight, height, and head circumference were not substantially different across visits for the placebo and ESL treatment groups.

Part II:

- There were no deaths during the study.
- The prevalence of SAEs was low overall. A total of 8 patients reported at least one treatment-emergent SAE: 4 patients each who received previous DB treatment with placebo and ESL.
    - None of these patients experienced SAEs that were considered to be potentially related to study drug.
    - No serious potentially related treatment-emergent events of special interest (cutaneous, cardiovascular, and cerebrovascular) were reported during the study.
- One patient who received previous DB placebo treatment had a TEAE of convulsion that led to premature

discontinuation of study drug.

- The proportion of patients who experienced at least one TEAE was slightly higher in patients who received previous DB treatment with placebo (45.9%) compared with those who received ESL (37.3%).
    - Headache was more frequent in patients who received previous DB placebo (8.1%) compared with those who received previous DB ESL (4.0%).
    - Overall, skin and subcutaneous tissue disorders occurred in 4 patients in the previous DB placebo group: 1 patient each had dermatitis allergic and ecchymosis, and 2 patients had urticaria. None of the patients who received previous DB ESL treatment reported any type of skin or cutaneous tissue disorder.
- The majority of TEAEs were of mild or moderate intensity; only 1 severe TEAE of pyrexia occurred in 1 patient who previously received DB ESL treatment.
- Overall, the incidence of TEAEs that were reported as potentially related to study drug was low with only 4.5% of patients.
- Overall hematology and biochemistry laboratory parameters did not show any substantial changes in either treatment groups and no TEAEs of hyponatremia were reported.
- A slight reduction in total and free T3 levels was observed in the previous DB ESL group but these changes were mostly within the normal range. In the previous DB ESL group, there were some reductions in T4 (total and free) levels, with a number of these values falling outside of the normal range. One event of autoimmune thyroiditis was reported in the previous DB ESL group.
- One patient in the previous DB ESL group had an abnormal ventricular extrasystole that started during the tapering-off period. No other patients had ECG changes from normal to abnormal during the study.
- Any negative shifts in physical and neurological examinations were minimal for the previous DB placebo and ESL treatment groups. Overall, the mean and mean changes from baseline for vital sign parameters, body weight, height, and head circumference were not substantially different across visits for the previous DB placebo and ESL treatment groups.

CONCLUSIONS:

- In conclusion, the findings of this study are that in epilepsy patients aged 6 to 16 years, ESL does not appear to have negative consequences for attention, information processing, and working memory in, or in the longer term for episodic memory.
- The ESL group was statistically significantly different from placebo with respect to the primary efficacy endpoint, improvement in standardized seizure frequency.
- ESL was safe and well tolerated.

Date of the Report: 31 March 2014