2 STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], S. A. Product: Eslicarbazepine acetate (BIA 2-093) Active ingredient: Eslicarbazepine acetate (ESL)		*(For National Authority Use only)*
Title of study: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial.		
Coordinating investigator: Not applicable		
Study centres: 73 centres in 20 countries (Austria, Bosnia and Herzegovina, Croatia, Czech Republic, France, Germany, Hungary, Italy, Malaysia, Philippines, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Taiwan, Ukraine, and United Kingdom).		
Study period: Date first patient enrolled: 07 Dec 2007. Date last patient completed the double-blind treatment period (Part I): 20 Aug 2012. Date last patient completed the first open-label extension period (Part II): 22 Oct 2013.		Clinical Phase: III
Objectives: The primary objective of the study was to assess the efficacy of ESL as an adjunctive therapy in children and adolescents with refractory partial seizures. The primary analysis variables for the assessment of the efficacy were: 1. Responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised seizure frequency. 2. Relative reduction in the standardised seizure frequency. The secondary objectives of the study were to assess: • The safety and tolerability of ESL as an adjunctive therapy in children and adolescents with refractory partial seizures. • The proportion of seizure-free patients and of patients with more than 75% reduction in seizure frequency. • The frequency of patients with exacerbations. • The duration of seizures and severity of seizures (using the Hague seizure severity scale). • The potential for rebound effects and withdrawal phenomena. • The potential for interactions between ESL and concomitant antiepileptic drugs (AEDs). • The seizure frequency by seizure type. • The maintenance of the therapeutic effect of ESL during long-term treatment in Part II, Part III,		

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Part IV, and Part V of the study.

As this study report include only data from Parts I and II of the study, the last secondary objective is only covered with regard to Part II. Separate reports will be written for Parts III-V.

Methodology:

This was a multinational phase III study, which consisted of a randomised, double-blind, placebo-controlled, parallel-group part (Part I), and 4 subsequent long-term, open-label extension periods (Parts II-V). In the following, only the procedures and results related to Part I and Part II of the study are described. Part I consisted of the following treatment periods:

- An 8-week observational baseline period: Patients entered the baseline period after the screening visit (Visit 1). At the end of the baseline period (Visit 2), eligible patients were randomised in a 1:1 ratio (stratified by age: stratum I: 2-6 years; stratum II: 7-11 years; stratum III: 12-18 years) to receive ESL or placebo in addition to concomitant therapy with 1 or 2 AEDs.
- A 6-week double-blind titration period: The recommended dose ("target dose") of double-blind study treatment was 20 mg/kg/day (up to a maximum of 1200 mg/day).
- A 12-week double-blind maintenance period: After the titration period, patients entered the 12-week maintenance period (from Visit 4 to 7). Patients received a maximum dose of 30mg/kg/day (maximum of 1200 mg/day). Up-titration was not permitted during the maintenance period; down-titration was allowed only once.
- An up to 4-week double-blind tapering-off period: Study treatment was tapered off in 10 mg/kg/day steps or in the same doses given during the titration period (as applicable) every 2 weeks.
- A 4-week observational follow-up period.

On 04 Jun 2009, the distribution of oral suspension of study medication was stopped due to stability issues resulting in dark spots visible in the vials. On 19 Jun 2009 it was decided to recall all oral suspension study medication. The investigators were informed on 22 Jun 2009 that patients had to perform their early discontinuation and follow-up visits. Affected patients were excluded from primary efficacy analyses. Stratum I patients (2-6 years of age) were offered to switch to the tablet formulation if parents and investigators were of the opinion that the patient could swallow tablets.

Part II of the study consisted of the following:

- A 48-week open-label extension period. The starting ESL dose was 10 mg/kg/day (maximum 800 mg/day). The dose was titrated according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to a maximum of 1200 mg/day). Down-titration was allowed.
- After completion of Part II, patients had the option to further continue treatment in the next 1 year, open-label extension periods (Part III). If the patient did not continue receiving ESL after Part II or in case of early discontinuation of ESL during Part II, the respective patient entered a tapering-off/follow-up period, in which study treatment was down-titrated and standard anti-epileptic treatment introduced.

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Number of patients:

Planned: 252 patients (126 per treatment groups).

Treated: 304 (155 with ESL, 149 with placebo).

Analysed for efficacy:

Part I: 263 in intention-to-treat (ITT) set (134 ESL, 129 placebo) (excluding stratum I before investigational medicinal product [IMP] recall); 198 in per protocol set (97 ESL, 101 placebo); . 41 in stratum I before IMP recall (21 ESL, 20 placebo).

Part II: 225 ESL in the ITT set.

Analysed for safety:

Part I: 263 in the safety set (134 ESL, 129 placebo) (excluding stratum I before IMP recall); 41 in stratum I before IMP recall (21 ESL, 20 placebo).

Part II: 260 ESL in the combined safety set (i.e. all treated patients).

Diagnosis and main criteria for inclusion:

- Diagnosis of epilepsy for at least 6 months prior to enrolment; for patients from the Czech Republic: diagnosis of epilepsy for at least 24 months prior to enrolment (Amendment 1 Czech Republic, 05 Oct 2007).
- Children 2 to 16 years of age; as per Global Amendment 4 (16 Sep 2010): children 2 to 18 years of age; for patients from Romania: children 2 to 17 years of age (Amendment 1 Romania, 09 Nov 2010).
- At least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 1 or 2 AEDs; for patients from the Czech Republic: at least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 2 AEDs (Amendment 1 Czech Republic, 05 Oct 2007).
- At least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period.
- Stable dose regimen of AEDs during the 8-week baseline period.
- Current treatment with 1 or 2 AEDs (any AED except oxcarbazepine); if present, vagus nerve stimulation is considered an AED (this last addition was introduced per Global Amendment 1 [20 Dec 2007]).

Patients with primarily generalised seizures, known progressive neurological disorders, known second or third degree atrioventricular block (introduced per Global Amendment 4 [16 Sep 2010]), history of status epilepticus within the 3 months prior to enrolment, seizures of non-epileptic origin, Lennox-Gastaut syndrome or West syndrome were excluded from the study.

Test product, dose and mode of administration, batch number (Part I and Part II):

ESL was provided as an oral suspension (50 mg/mL) for use in the age group of 2–6 years (stratum I) or as white oblong tablets (200 mg) for use in the older children and adolescents (≥7 years of age; strata II and III).Batch numbers are available in the appendix of the report. The oral suspension formulation was recalled based on the Sponsor's decision on 19 Jun 2009 due to stability issues of the oral suspension of ESL.

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Duration of treatment:

Up to 26 weeks in Part I; 12 months in Part II.

Reference therapy and mode of administration (Part I only):

Placebo was provided as oral suspension identical in appearance to the 50 mg ESL suspension (for stratum I) or as tablets identical in appearance to the 200 mg ESL tablets (for strata II and III).

Criteria for evaluation:

Efficacy:

Two primary efficacy variables were defined:

1. Responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.
2. Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

Part I of the study

The secondary efficacy variables were:

- Standardised seizure frequency per period of the baseline, titration, maintenance, and tapering-off periods.
- Relative change in seizure frequency from the baseline period to the 12-week maintenance period (≥25%; >–50% to <25%; ≥–75% to ≤–50%; <–75%).
- Proportion of patients who are seizure-free during the maintenance period.
- Standardised seizure frequency by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other) during the maintenance period. Seizures with missing seizure type information were considered as unclassified for the analysis.
- Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, ≥5 min, unknown.
- Seizure severity assessed with the 13-item Hague seizure severity scale.
- Number of days with seizures (standardised to 4-week time period).
- Treatment retention time, defined as the time to first occurrence of one of the following during the titration or maintenance period: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
- Seizure exacerbations during tapering-off or follow-up period.

Part II of the study

- Standardised seizure frequency per 4-/12-week interval (weeks 1-4, 5-16, 17-28, 29-40, ≥41).
- Absolute and relative change from Part I baseline in seizure frequency per 4-/12-week interval.
- Responder rate per 4-/12-week interval: responders were defined as those patients with a relative seizure reduction of at least 50% in the respective time interval compared to Part I baseline.

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- Categorised relative change in seizure frequency per 4-/12-week interval: relative change in seizure frequency from the Part I baseline period to each 4-/12-week interval (≥25%; >–50% to <25%; ≥-75% to ≤–50%; <–75%).
- Exacerbations in seizure frequency (increase in relative change in seizure frequency of ≥25%) per 4-/12-week interval compared to the Part I baseline and maintenance periods.
- Seizure free patients per 4-/12-week interval.
- Standardised seizure frequency per 4-/12-week interval by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other): seizures with missing seizure type information were considered as unclassified for analysis.
- Standardised number of days with seizures per 4-/12-week interval.
- Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, and ≥5 min.
- Treatment retention time, defined as the time to first occurrence of withdrawal of study medication due to AEs or due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
- Seizure severity (Hague seizure severity scale).

Safety:

In both study parts, safety was assessed on the basis of the following observations and measurements:

- Reports of adverse events (AEs), including serious adverse events (SAEs).
- Safety laboratory (haematology, biochemistry, and urinalysis).
- Vital signs.
- 12-lead electrocardiogram (ECG) parameters.
- Physical and neurological examinations.
- Sexual maturation assessment.

Statistical methods:

Sample size calculation

The sample size calculation was based on the 2 primary efficacy variables. At least 100 patients treated with ESL were to be followed-up for at least 1 year and included in safety analyses. Considering a drop-out rate of approximately 15%, approximately 252 patients were to be randomised (126 per treatment group). Both primary variables were intended to be sufficiently powered with at least 80% power to show a significant difference following a hierarchical testing procedure at a 2-sided significance level of 0.05.

Efficacy analysis:

Primary (applicable to Part I only):

The responder rate was analysed by a Cochran-Mantel-Haenszel (CMH) test with stratum group (I: 2-6 years; II: 7-11 years; III: 12-16 [18] years) as the stratification factor.

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The relative reduction in standardised seizure frequency was compared between treatment groups using an analysis of covariance (ANCOVA) that modelled the relative change in standardised seizure frequency as a function of stratum group (I: 2-6 years; II: 7-11 years; III: 12-16 [18] years), baseline seizure frequency, and treatment.

The second primary null hypothesis (no treatment difference with regard to the relative reduction in standardised seizure frequency) was only tested if the first primary null hypothesis (no treatment difference with regard to response rates) had been rejected following the hierarchical testing strategy, which controlled for type I error inflation due to multiple testing. Tests were performed 2-sided at a significance level of 0.05.

Secondary and Part II efficacy variables:

Secondary efficacy variables and efficacy variables for Part II of the study were analysed descriptively. Additional statistical tests were conducted for Part I of the study, but were of exploratory nature only and included the following:

The responder rate was also analysed using a logistic regression models that assessed the effect of region, age/age category, and number of concomitant AEDs. The relative change in standardised seizure frequency was also compared between treatment groups using ANCOVAs that included additional factors for region, age, and number of concomitant AEDs. Results on the primary efficacy variables were also provided by study period and by seizure type.

The standardised number of days with seizures was analysed by a CMH test. The distribution of the treatment retention time was descriptively summarised using Kaplan-Meier estimates and pairwise logrank tests stratified by region were carried out to compare the treatment groups.

Safety analysis

All safety variables were analysed descriptively.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number and frequencies of patients with TEAEs are given by primary system organ class (SOC) and preferred term within each SOC and by treatment group for any TEAE category.

The number and frequency of patients with clinically significant values at each visit are presented for vital signs. All laboratory values were classified as normal or abnormal according to the laboratories normal ranges and as clinically significant or not clinically significant according to the investigator. Descriptive summaries, shift tables, and number and frequency of patients with clinically significant laboratory values are presented for all laboratory parameters.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Part I:

For both primary efficacy variables, the response rate and the relative change in the standardised seizure frequency during the maintenance period, no statistically significant difference between ESL and placebo was found. Forty-one patients (30.6%) in the ESL group compared to 40 patients (31.0%) in the placebo group were responders, resulting in a non-significant odds ratio of 0.97 (95% confidence interval [CI]: 0.57, 1.63; p=0.9017). The least square (LS) mean relative change in the standardised seizure frequency was higher in the ESL group (-18.1%) than in the placebo group (-8.6%), resulting in a LS mean difference of 9.5% (95% CI: -6.71, 25.77; p=0.2490). Results from pre-planned sensitivity analyses and additional post-hoc analysis methods were consistent with the primary analysis results. There were also no relevant between-treatment differences concerning seizure type or other study periods.

Secondary efficacy findings were as follows:

- Frequency of seizure-free patients: maintenance period: 3.9% ESL, 2.4% placebo; tapering-off period: 9.2% ESL, 12.6% placebo.
- Frequency of patients with seizure reduction of at least 75%: maintenance period: 15.6% ESL, 12.9% placebo; tapering-off period: 13.4% ESL, 20.3% placebo.
- Frequency of patients with exacerbation (increase of ≥25%): maintenance period: 13.3% ESL, 13.7% placebo; tapering-off period: 14.3% ESL, 15.3% placebo.
- Seizure duration: The majority (>80%) of seizures during the maintenance period lasted <1 minute in both treatment groups.
- Seizure severity: During the study, small mean increases in the total score of the Hague seizure severity scale were seen in both treatment groups, slightly larger in the ESL group (mean increases between 1.4 and 2.5) than in the placebo group (mean increases between 0.5 and 1.6).
- Number of days with seizures: In each study period, the mean standardised number of days with seizures was slightly lower in the ESL group than in the placebo group. In both treatment groups, the mean standardised number of days with seizures was highest during the baseline period (12.2 days ESL; 13.9 days placebo) and lowest during the maintenance period (9.3 days ESL; 11.9 days placebo).
- There was no interaction between the number of concomitant AEDs or concomitant carbamazepine and treatment in the ANCOVA of the relative change in standardised seizure frequency.
- No rebound effects were observed. The standardised seizure frequency during tapering-off and follow-up periods increased in relation to maintenance period, but not to a value greater than that observed at baseline. Furthermore, the increase in standardised seizure frequency during tapering-off and follow-up periods in relation to baseline was similar in both treatment groups.
- Efficacy results showed a trend in favour of ESL compared to placebo when the standardised seizure frequency is based on the titration + maintenance period instead of the maintenance period, and also when the ITT set is restricted to patients from strata II and III. However, between-treatment

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differences were not statistically significant.

- A statistically significant difference in favour of ESL compared to placebo was observed in an analysis of the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III (difference 16.2%; p=0.0359)

Part II:

Efficacy findings in Part II per variable in the total ITT set were as follows:

- The total responder rate during Part II was 46.7%. Responder rates steadily increased during Part II, from 44.9% during weeks 1-4 to 57.5% during weeks >40.
- The total median standardised seizure frequency during Part II was 6.1, resulting in a median relative change compared to the baseline period of -46.7%. The median relative change was larger in the previous placebo group (-51.4%) than in the previous ESL group (-40.4%). The total median standardised seizure frequency decreased from 7.0 during weeks 1-4 to 4.0 during weeks >40.
- Five patients (2.2%) were seizure-free during Part II. The proportion of seizure-free patients was 8.9% during weeks 1-4, 6.7% during weeks 5-16, 13.8% during weeks 17-28, and 14.2% during weeks 29-40.
- The proportion of patients with exacerbation (increase of ≥25%) compared to the baseline period was 14.2%. Respective proportions decreased during Part II, in particular during the first half (from 19.6% during weeks 1-4 to 8.2% during weeks 17-28). The total proportion of patients with a seizure reduction of at least 50% compared to the baseline period was 46.6%; it was 44.9% during the first interval, 48.0% during the second interval and at least 54.8% during each of the subsequent intervals.
- Seizure severity: small mean increases in the total score of the Hague seizure severity scale were seen during Part II.
- The median standardised number of days with seizures was 4.8 days overall; it continuously decreased over the course of Part II, from 5.0 days during the first to 2.9 days during the last time interval.

SAFETY RESULTS:

Part I:

The safety results did not reveal any new findings of concern, compared to prior studies. The main safety results were as follows:

- 112 patients (83.6%) in the ESL group compared to 94 (72.9%) in the placebo group experienced at least 1 TEAE. Most frequently reported TEAEs (>5% of patients in any treatment group) were headache (18 patients [13.4%] ESL, 8 patients [6.2%] placebo), nasopharyngitis (15 [11.2%] ESL, 15 [11.6%] placebo), somnolence (15 [11.2%] ESL, 6 [4.7%] placebo), convulsion (13 [9.7%] ESL, 14 [10.9%] placebo), pyrexia (10 [7.5%] ESL, 7 [5.4%] placebo), pharyngitis (9 [6.7%] ESL, 9 [7.0%] placebo), vomiting (8 [6.0%] ESL, 8 [6.2%] placebo), diplopia (8 [6.0%] ESL, 2 [1.6%] placebo), respiratory tract infection (7 [5.2%] ESL, 7 [5.4%] placebo), nausea (7 [5.2%] ESL, 1 [0.8%] placebo), bronchitis (5 [3.7%] ESL, 7 [5.4%] placebo), and rhinitis (4 [3.0%] ESL, 7 [5.4%]

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placebo). A higher number of patients treated with ESL compared to placebo (>2% absolute difference) reported headache, somnolence, pyrexia, diplopia, nausea, decreased appetite, vertigo, agitation, dizziness, increased weight, upper abdominal pain, influenza, and asthma.

- 56 ESL patients (41.8%) compared to 32 placebo patients (24.8%) had at least 1 possibly related TEAE. Most commonly reported possibly related TEAEs (≥5% of patients in the ESL group) were somnolence (12 patients [9.0%] ESL, 5 patients [3.9%] placebo), convulsion (7 [5.2%] ESL, 6 [4.7%] placebo), and diplopia (7 [5.2%] ESL, 2 [1.6%] placebo).
- 15 ESL patients (11.2%) compared to 9 placebo patients (7.0%) had at least 1 serious TEAE. The only serious TEAEs reported by more than 1 patient in any treatment group were status epilepticus (3 patients [2.2%] ESL, 0 placebo), convulsion (2 [1.5%] ESL, 2 [1.6%] placebo), bronchopneumonia (2 [1.5%] ESL, 0 placebo), device malfunction (2 [1.5%] ESL, 0 placebo), and pneumonia (1 [0.7%] ESL, 3 [2.3%] placebo). Of the 3 status epilepticus cases, 2 occurred during the tapering-off/follow-up period.
- 5 patients (3 [2.2%] ESL, 2 [1.6%] placebo) had at least 1 possibly related serious TEAE. These events were vertigo, drug withdrawal syndrome, status epilepticus, and vascular purpura in the ESL group, and irritability, convulsion, and hypotonia in the placebo group.
- Study treatment was discontinued due to a TEAE for 7 patients (5.2%) in the ESL group and 3 (2.3%) in the placebo group. The only TEAE leading to treatment discontinuation reported more than once overall was convulsion (1 patient [0.7%] ESL, 3 [2.3%] placebo).
- Two patients died due to an AE during Part I: a 6-year-old female patient treated with ESL, due to convulsion, brain oedema, bronchopneumonia, and brain herniation, and a 5-year-old female patient treated with placebo due to asphyxia. The events were considered unrelated or unlikely related to study medication.
- During the tapering-off or follow-up period, 16 patients (12.4%) in the ESL group and 10 patients (7.9%) in the placebo group had at least 1 neurological TEAE.
- Changes from a normal laboratory value at baseline to an abnormal value at endpoint occurred in fewer than 25% of patients per laboratory parameter and treatment group and with mostly similar frequency between treatment groups. For any laboratory parameter, no more than 2 patients per treatment group had a laboratory value considered clinically significant by the investigator, with the exception of gamma-glutamyltransferase (GGT) that was clinically significant for 3 patients (2.3%) in the ESL group compared to none in the placebo group. Of these patients, 1 patient in each treatment group also had alanine or aspartate aminotransferase above the upper limit of normal (ULN) (but <2×ULN). In addition, 4 patients (3.0%) in the ESL group and 1 patient (0.8%) in the placebo group had a decrease from baseline in sodium levels of ≥10 mmol/L. Twelve patients (9.0%) in the ESL group and 3 patients (2.3%) in the placebo group had post-baseline sodium values ≤135 mmol/L (8 patients [6.0%] in the ESL group compared with 3 patients [2.3%] in the placebo group had a sodium value of >130-135 mmol/L).
- No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index (BMI), head circumference, sexual maturation assessment, and ECG.

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- The safety profile in the subgroup of patients in strata II and III was similar to that seen in the overall safety set.

Part II:

Safety results during Part II did not reveal any findings of concern with regard to the long-term safety of ESL in the included population. Frequencies for AE categories were generally similar between groups by previous treatment with the exception of the period of the first 4 weeks of Part II where more patients previously treated with placebo had TEAEs considered at least possibly related. This is also not a finding of concern as the reported TEAEs were central nervous system related (somnolence, diplopia, and ataxia) and it is known that the overall incidence of TEAEs increase with the start of ESL or the increase of ESL doses.

The main safety results during Part II in all patients treated with ESL were as follows:

- 191 patients (73.5%) experienced at least 1 TEAE. Most frequently reported TEAEs were convulsion (39 patients [15.0%]), nasopharyngitis (33 [12.7]), somnolence (24 [9.2%]), vomiting (24 [9.2%]), headache (23 [8.8%]), and pyrexia (22 [8.5%]).
- 86 patients (33.1%) had at least 1 TEAE that was considered at least possibly related to ESL by the investigator. Most commonly reported such TEAEs (≥5% of patients) were somnolence (22 patients [8.5%]) and convulsion (15 [5.8%]).
- 27 patients (10.4%) had at least 1 serious TEAE; the only serious TEAEs reported by more than 2 patients were convulsion (6 patients [2.3%]) and pneumonia (4 [1.5%]).
- 14 patients (5.4%) had at least 1 TEAE leading to treatment discontinuation; the only such TEAEs reported more than once were convulsion (7 patients [2.7%]), abnormal behaviour (2 [0.8%]), and hypotonia (2 [0.8%]).
- No cases of death were reported during Part II.
- Changes from a normal laboratory value at baseline (OL) to an abnormal value at endpoint occurred in fewer than 30.1% of patients per laboratory parameter. For any laboratory parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of GGT that was clinically significant for 13 patients (5.8%), and free thyroxine (T4) that was clinically significant for 5 patients (2.2%). In addition, 1 patient (0.9%) in the previous ESL group and 5 patient (4.3%) in the previous placebo group had a decrease from baseline in sodium levels of ≥10 mmol/L. Seven patients (6.3%) in the previous ESL group and 10 patients (8.7%) in the previous placebo group had post-baseline sodium values ≤135 mmol/L (5 patients [4.5%] in the previous ESL group compared with 10 patients [8.7%] in the previous placebo group had a sodium value of >130-135 mmol/L).
- No clinically relevant findings were seen in the analysis of vital signs, height, weight, BMI, head circumference, sexual maturation assessment, and ECG during Part II.

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CONCLUSIONS:

In this confirmatory multinational phase III study in children and adolescents with refractory partial seizures, ESL as adjunctive therapy did not show superior efficacy over placebo. Subsequent 1 year open-label treatment with ESL following the initial double-blind part of the study led to steady improvements in efficacy endpoints over the course of this extension period. In both study parts, the known safety profile of ESL was confirmed without any findings of concern.

Date of final report:
20 March 2014