# 2. SYNOPSIS

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| **Sponsors:**<br>Sunovion Pharmaceuticals Inc.<br>BIAL-Portela & C[a] SA | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | **(For National Authority Use Only)** |
| **Name of Finished Product:**<br>Zebinix™ and Exalief™ | | |
| **Name of Active Ingredient:**<br>Eslicarbazepine acetate (ESL, also known as BIA 2-093 or SEP-0002093) | | |

**Title of study:** Efficacy and Safety of Eslicarbazepine Acetate (BIA 2-093) as Adjunctive Therapy for Refractory Partial Seizures in a Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial (Part I Results)

**Principal investigators:** A total of 173 investigational sites in 19 countries (North America, 89 sites; Rest-of-World [ROW], 84 sites) screened and enrolled subjects. Of these, 160 sites randomized subjects into the study.

**Study centers:** The study was conducted at 173 investigational sites in 19 countries: Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and the United States.

**Publications (reference):** None

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| **Studied period (years):**<br>First subject first visit: 02 December 2008<br>Last subject last visit: 12 January 2012 (Part I) | **Phase of development:** 3 |

**Objectives:**

**Primary:** The primary objective of this study was to evaluate the efficacy of ESL administered once daily (QD) at doses of 800 mg and 1200 mg compared with placebo as adjunctive therapy in subjects with refractory partial epilepsy over a 12-week maintenance period.

**Secondary (Part I objectives only):**

- To evaluate the safety and tolerability of ESL at 800 mg and 1200 mg daily doses in comparison with placebo, over a 12-week maintenance period preceded by a 2-week titration period.
- To assess the maintenance of therapeutic effects of ESL over a 12-week maintenance period preceded by a 2-week titration period.
- To assess the drug-drug pharmacokinetic (PK) interactions between ESL and concomitant anti-epileptic drugs (AEDs) over the double-blind maintenance period.
- To assess the health-related quality-of-life and depressive symptoms over the double-blind maintenance period.

**Methodology:** The study was designed to include 3 parts; only the first part is described in this report. Part I of the study was an international, randomized, placebo-controlled, double-blind, parallel-group, multicenter clinical study conducted in 19 countries at 173 sites in 653 subjects with refractory simple partial or complex partial seizures, with or without secondary generalization. After screening procedures and confirming eligibility, subjects entered Part I of the study, which consisted of 3 periods.

The first period was an 8-week observation baseline period (Week -8 to Week -1) during which subjects were instructed on how to complete the seizure diary. At the end of the 8-week observational baseline period, eligible subjects were randomized in a 1:1:1 allocation ratio to 1 of 3 treatment groups (with a blinded treatment

assignment):

- Placebo
- ESL 800 mg QD
- ESL 1200 mg QD

Subjects then entered the second period of Part 1, the 2-week, double-blind, up-titration period (Week 1 to Week 2). During this period, subjects in the ESL 800 mg group received ESL 400 mg QD, subjects in the ESL 1200 mg group received ESL 800 mg QD, and subjects in the placebo group received placebo QD.

Subjects then entered the third period of Part I, the 12-week, double-blind, maintenance period (Week 3 to Week 14) where subjects in the ESL 800 mg group received ESL 800 mg QD, subjects in the ESL 1200 mg group received ESL 1200 mg QD, and subjects in the placebo group received placebo QD.

At the completion of the maintenance period, subjects who did not enter Part II were to be tapered off study drug while maintaining the blind according to the following down-titration procedure: subjects on 800 mg were down-titrated to 400 mg for a duration of 2 weeks, and subjects on 1200 mg were down-titrated to 800 mg for 1 week and then down-titrated to 400 mg for 1 week and subjects in the placebo group received placebo QD for 2 weeks. During Part I, 1 to 2 concomitant AEDs were allowed in this study and were to be kept stable during the course of the study.

**Number of subjects (planned and analyzed):** This international multicenter study was planned to be conducted in approximately 615 subjects with refractory simple partial or complex partial seizures, with or without secondary generalization. A total of 653 subjects were randomized and are analyzed in the intention-to-treat (ITT) analysis population.

**Diagnosis and main criteria for inclusion:** Subjects aged ≥ 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 (any except oxcarbazepine ) in a stable dose regimen at least 1 month prior to screening, with at least 4 partial-onset seizures (simple partial, complex partial, and partial seizures evolving to secondarily generalized) on the 4 weeks prior to screening, and at least 8 partial-onset seizures during baseline with at least 3 partial-onset seizures in each 4-week section of the 8-week observational baseline period, with no seizure-free interval exceeding 28 consecutive days.

**Test product, dose and mode of administration, batch number:** The study drug was a conventional immediate-release tablet of eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide] and provided as either 400 mg or 800 mg dosage strengths (the 800 mg tablets were not used in North America). The composition was directly proportional between the strengths. The excipients used were standard pharmaceutical excipients of compendial grade, widely used in the pharmaceutical industry. The medication was taken orally.

Batch numbers:

| **Test Products** | **ROW** | **North America** |
|---|---|---|
| ESL 400 mg tablets | 080084, 100701, 110175 | C9J2011, CVXN, DVWS |
| ESL 800 mg tablets | 080066, 110167, 100850 | Not applicable |

**Reference therapy, dose and mode of administration, batch number:** Matching placebo tablets QD orally during Part 1, the 2-week, double-blind, up-titration period (Week 1 to Week 2), and the 12-week double-blind maintenance period (Week 3 to Week 14).

Batch numbers:

| **Reference Products** | **ROW** | **North America** |
|---|---|---|
| Placebo for ESL 400 mg tablets | 080075, 100700,110174 | C9J2010, CVXS, DVWP |
| Placebo for ESL 800 mg tablets | 080299, 100921 | Not applicable |

**Duration of treatment:** The duration of Part I of the study was 22 weeks.

**Analysis populations:**

**Efficacy analysis:**

- Intent-to-treat (ITT) population included all randomized subjects who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment. This population included both subjects who used the Event Entry (EE) diary and those who used the Daily Entry (DE) diary.
- DE Diary ITT population included all subjects in the ITT population who used the DE diary.
- EE Diary ITT population included all subjects in the ITT population who used the EE diary.
- Per-protocol (PP) population – all subjects in the ITT population who did not have any major important protocol deviations. This population includes subjects who used the EE diary and subjects who used the DE diary.

The ITT population was the primary population for the analysis of efficacy. All seizure frequency-related efficacy variables were also analyzed for the DE Diary ITT, EE Diary ITT and the PP population.

**Safety analysis, demographic and baseline clinical characteristics:** Safety population–all randomized subjects who received at least one dose of study treatment after randomization. All safety data will be summarized for the safety population. Subjects were included in the safety summaries according to the treatment that they actually received.

**Criteria for evaluation:**

**Efficacy:** Standardized seizure frequency, Clinical Global Impressions (CGI), Quality of Life In Epilepsy questionnaire-31 (QOLIE-31), Seizure Severity Questionnaire (SSQ), and Montgomery-Asberg Depression Rating Scale (MADRS).

**Pharmacokinetic:** Population PK evaluation for drug-drug interactions and pooled analysis with other study results.

**Safety:** Adverse events (AEs), clinical laboratory test results (hematology, biochemistry, coagulation, thyroid function, bone turnover markers, and urinalysis), physical and neurological examinations, vital sign measurements, body weight, 12-lead electrocardiogram (ECG) readings, Columbia Suicide Severity Rating Scale (C-SSRS), blood levels of eslicarbazepine and concomitant AEDs and Medical Outcomes Study Sleep Scale (MOS-SS).

**Statistical methods:** All efficacy analyses were performed for the 4 efficacy populations unless otherwise specified. Specific details of all derivations and analyses are included in the statistical analysis plan (SAP).

**Primary efficacy analysis:** The primary efficacy variable in this study was the standardized seizure frequency over the 12-week maintenance period. All seizures, regardless of their type (complex partial, partial evolving to secondary generalized, unclassifiable and other) were included in the calculation of the primary efficacy variable. Seizure frequency during the baseline, titration and maintenance periods was standardized on a "seizure frequency per four weeks" basis.

For the purpose of the primary efficacy analysis, standardized seizure frequency was natural logarithmically transformed (ln). The ln standardized seizure frequency during the maintenance period was analyzed using an analysis of covariance (ANCOVA) model. The model included treatment as a fixed effect, ln standardized seizure frequency at baseline, and diary version as covariates. Summary statistics for non-transformed values of standardized seizure frequency at baseline and during the maintenance period were presented together with the results from the ANCOVA analysis. Least square (LS) means and associated 95% confidence intervals (CIs) were back-transformed using the exponential function for presentation in the tables and figures. The differences between the mean standardized seizure frequencies for each of the ESL group comparisons with placebo were also presented together with associated 95% CIs and *P* values. The primary efficacy analysis was performed for ITT population and the *P* values and 95% CIs for the differences in LS means were adjusted using the Bonferroni method as the first stage of the two stage gate keeping type I error control procedure. In the analysis of the DE Diary ITT population, the adjustments were made using Dunnett's method in the second stage. Treatment-by-baseline and treatment-by-diary version interactions were tested in the overall analyses.

**Secondary efficacy analysis**: Additional sensitivity analyses of the primary efficacy variable (excluding subjects enrolled in Site 952, subjects with extreme values and including seizure data available post-database lock) were performed. Also, subjects who had missing seizure frequency data during the maintenance period due to early discontinuation during the titration period were included in a secondary analysis of the primary efficacy variable

using their standardized seizure frequency during the titration period. The same analysis described above for the primary efficacy variable was performed for all of these additional analyses without the adjustments for multiplicity in the ITT and DE Diary ITT populations. Summary statistics were also presented for the titration period and the combined titration+maintenance periods. The relative (percentage) change from baseline in standardized seizure frequency during the maintenance period was summarized and analyzed as described for the primary efficacy variable, except for the logarithmic transformation and adjustments for multiplicity. For the ITT population, an additional non-parametric ANCOVA analysis was performed. The proportion of responders (≥ 50% reduction in standardized seizure frequency), seizure-free subjects (100% reduction), exacerbations (≥ 25% increase) and the distribution of seizure reduction during the maintenance period was summarized and analyzed by region and overall. Exact 95% CIs were presented for the percentage of responders, subjects who were seizure-free and subjects who had an exacerbation during the maintenance period. Each ESL group was compared with placebo using a stratified CMH or chi-squared test (depending on the analysis population) and *P* values were presented on the tables. The standardized seizure frequency was summarized by study period, and an ANCOVA analysis was performed for the titration and maintenance periods combined for the ITT population, EE and DE Diary ITT populations, and PP population. Seizure frequency was summarized by week for the ITT population, EE and DE Diary ITT populations, and PP population. The standardized seizure frequency and relative change from baseline in standardized seizure frequency was summarized by seizure type for the ITT population, EE and DE Diary ITT populations, and PP population. Seizure diary card/data compliance was summarized by study period and overall for the EE and DE Diary ITT populations. In addition, the number of days of missing diary data was summarized by study period and overall for the DE Diary ITT population. The number and percentage of subjects who remained on treatment during Part I of the study were presented together with the exact 95% CIs for the proportion for the ITT population, EE and DE Diary ITT populations, and PP population. Treatment groups were compared using stratified CMH tests. The CGI and SSQ variables were summarized and analyzed for the ITT population, and QOLIE-31 and MADRS variables for the ITT and PP populations. Changes from baseline were analyzed using ANCOVA. Additional exploratory analyses of the primary efficacy variable, including subgroup analyses and time to onset of seizure control, were also performed.

**Pharmacokinetic analysis**: Eslicarbazepine plasma concentrations during the maintenance period were summarized descriptively by ESL treatment group.

**Safety analysis**: Summaries of TEAEs, potentially related TEAEs, treatment-emergent SAEs, treatment emergent potentially related SAEs, TEAEs leading to discontinuation of study treatment and TEAEs leading to death were presented by treatment group. Physical and neurological examination, vital signs, body weight, ECG, clinical laboratory data, MOS-SS and C-SSRS results were also summarized.

**SUMMARY – CONCLUSIONS**

A total of 936 subjects were screened for eligibility to participate in Part I of the study; 283 subjects failed screening and did not participate in the study. A total of 653 subjects were randomized to study treatment of which, 650 received at least 1 dose of study treatment. The analysis sets were as follows:

| Data Analysis Sets | Placebo n (%) | ESL 800 mg n (%) | ESL 1200 mg n (%) | Total n (%) |
|---|---|---|---|---|
| Safety Population | 224 (99.1%) | 216 (100.0%) | 210 (99.5%) | 650 (99.5%) |
| ITT Population | 220 (97.3%) | 215 (99.5%) | 205 (97.2%) | 640 (98.0%) |
| EE Diary ITT Population | 62 (27.4%) | 67 (31.0%) | 56 (26.5%) | 185 (28.3%) |
| DE Diary ITT Population | 158 (69.9%) | 148 (68.5%) | 149 (70.6%) | 455 (69.7%) |
| PP Population | 188 (83.2%) | 184 (85.2%) | 175 (82.9%) | 547 (83.8%) |

**EFFICACY RESULTS:**

**Primary Efficacy Analysis:**

*Primary Analysis of the Primary Efficacy Endpoint:* The primary analysis was performed on both the ITT population (Stage 1 of the Type I error control strategy) and just the DE Diary ITT population (Stage 2 of the Type I error control strategy). For the entire ITT population, the LS means were 7.88 for the placebo group, 6.54 for the ESL 800 mg group, and 6.00 for the ESL 1200 mg group. The difference from placebo was statistically significant for the ESL 1200 mg group (log difference = -0.26; adjusted *P* value = 0.004) but not for the ESL 800 mg group (log difference = -0.18; adjusted *P* value = 0.058). There were no statistically significant interactions between treatment and diary version or between treatment and seizure frequency during the baseline

period. Thus, the treatment effect was demonstrated to be consistent at all levels of the covariates; and, importantly, consistent treatment effects were shown in both diary card versions. For the DE Diary ITT population, the trend was consistent with that observed in the ITT population.

*Secondary Analyses of the Primary Endpoint:*

Sensitivity Analyses:

- The results of a sensitivity analysis in which subjects who dropped out during the titration period had their data imputed for the maintenance period were consistent with the ITT analysis that included only subjects who contributed data during the maintenance period: the highest occurrence of seizures was seen in the placebo group, and the lowest occurrence in the ESL 1200 mg group. The unadjusted *P* values for the difference from placebo were *P* value = 0.003 for the ESL 800 mg group and *P* value < 0.001 for the ESL 1200 mg group. For the analysis of the DE Diary ITT population, the unadjusted *P* values for the difference from placebo were *P* value > 0.05 for both active treatment groups.
- Three sensitivity analyses were done to evaluate the impact of early discontinuations: one that included only those subjects who completed the maintenance period, one in which missing scores for discontinuations were imputed using the standardized seizure frequency from the baseline period, and one in which missing scores for discontinuations were imputed using the standardized seizure frequency from the 2 weeks prior to discontinuation. The results of all 3 of these analyses were similar. In each case, lower LS means were observed in each ESL group than in the placebo group. For the ESL 800 mg group, the unadjusted *P* values for pairwise comparison with placebo were *P* < 0.05 in each case; and for the ESL 1200 mg group, they were *P* value < 0.001, *P* value = 0.016, and *P* value < 0.001, respectively.
- The results of analyses conducted on the overall ITT population and the DE Diary ITT population that excluded subjects enrolled at Site 952 (due to compliance issues identified) were similar to those observed in the analyses that included this site.
- The results of analyses performed in the overall ITT population that 1) excluded subjects with extreme seizure rates and 2) included seizure data that was identified post-lock were similar to those seen with the primary analysis of the ITT population.

EE Diary ITT Population: The trend across treatment groups was comparable to that observed in the ITT and DE Diary ITT populations.

By Region Analyses: For North America, the LS means of the seizure frequency were 7.90 for the placebo group, 7.63 for the ESL 800 mg group (unadjusted *P* value = 0.794), and 6.57 for the ESL 1200 mg group (unadjusted *P* value = 0.181); and for ROW, they were 7.80, 5.87 (unadjusted *P* value = 0.010), and 5.59 (unadjusted *P* value = 0.003), respectively. Regional results for the DE Diary ITT population were consistent with the results observed in the ITT analysis.

**Secondary Efficacy Analyses:** The results of the secondary efficacy and exploratory efficacy analyses included in this synopsis are for the ITT population unless otherwise specified; results for additional populations are presented with the clinical study report.

Proportion of Responders: Subjects who had at least a 50% reduction from baseline in standardized seizure frequency during the maintenance period were classified as responders. The overall percentage of responders was 23.1% in the placebo group, 30.5% in the ESL 800 mg group, and 42.6% in the ESL 1200 mg group. The unadjusted *P* values for the difference from placebo were *P* value = 0.068 for the ESL 800 mg group and *P* value < 0.001 for the ESL 1200 mg group.

Percent Changes From Baseline in Standardized Seizure Frequency: All subjects were categorized according to their percentage change from baseline in standardized seizure frequency, in 6 categories ranging from seizure-free (100% reduction) to exacerbation (≥ 25% increase). Achievement of 100% reduction was 1.4% in the placebo group, 3.5% in the ESL 800 mg group, and 3.3% in the ESL 1200 mg group. A > 75% to < 100% reduction was seen in 7.1%, 12.0%, and 13.7%, respectively; ≥ 50% to ≤ 75% reduction in 14.6%, 15.0%, and 25.7%, respectively; 0% to < 50% reduction in 50.5%, 41.5%, and 33.9%, respectively; and increase of ≥ 25% from baseline in 14.6%, 13.0%, and 13.1%, respectively.

Relative Change from Baseline in Standardized Seizure Frequency by Study Period: The median percentage

change from baseline in standardized seizure frequency in the maintenance period was -21.78%, -29.70%, and -35.56% in the placebo, ESL 800 mg, and ESL 1200 mg groups, respectively. The unadjusted *P* value from the non-parametric analysis, based on ranked data, was ≤ 0.05 for ESL 1200 mg versus placebo, but > 0.05 for ESL 800 mg versus placebo. Similarly, in the parametric analysis, the unadjusted *P* value was ≤ 0.05 for ESL 1200 mg versus placebo and > 0.05 for ESL 800 mg versus placebo.

Standardized Seizure Frequency by Study Period: For the titration period and each of 4-weekly periods during the maintenance period (Weeks 1 to 4, Weeks 5 to 8, and Weeks 9 to 12), the frequency of seizures was lowest in the ESL 1200 mg group as compared to the ESL 800 mg and placebo groups. For the titration and maintenance periods combined, the standardized seizure frequency was lowest in the ESL 1200 mg group, followed by the ESL 800 mg group, and placebo. The unadjusted *P* values were ≤ 0.001 for ESL 800 mg versus placebo and ESL 1200 mg versus placebo for this time period.

Seizure Frequency by Week: Mean post-baseline seizure frequencies tended to be the lowest in the ESL 1200 mg group and generally decreased over time.

Standardized Seizure Frequency by Seizure Type: LS mean standardized seizure frequencies of complex partial seizures during the maintenance period were 5.18, 4.74, and 4.22 for the placebo, ESL 800 mg, and ESL 1200 mg groups, respectively. The standardized seizure frequencies of simple partial seizures and partial seizures evolving to secondary generalized seizures were less in the ESL 800 mg and ESL 1200 mg groups when each was compared to the placebo group.

Relative Change from Baseline in Standardized Seizure Frequency by Seizure Type: Decreases were observed in median relative change from baseline in standardized seizure frequencies of each type of seizure in all three groups, with the larger decreases observed in the ESL dose groups.

Diary Card/Data Compliance: The results from both summaries of EE diary card compliance and DE diary data compliance indicate that a high level of compliance was observed across the three treatment groups. In the EE Diary ITT population, mean overall percentage compliance for the baseline, titration, and maintenance periods combined was 100% in each group. Mean overall percentage compliance with the DE diary cards for the baseline, titration, and maintenance periods combined was 98.25% for the placebo group, 98.57% for the ESL 800 mg group, and 97.86% for the ESL 1200 mg group.

Proportion of Subjects Remaining on Treatment: The placebo group had the largest proportion of subjects remaining on treatment for at least 81 days in the maintenance period (82.5%), as compared to the ESL 800 mg group (80.0%) and the ESL 1200 mg group (67.2%).

Clinical Global Impression: LS mean changes from baseline indicated that the most improvement in the severity of illness portion of the CGI scale was observed in the ESL 800 mg group (-0.5), followed by the ESL 1200 mg group (-0.4) and the placebo group (-0.3) (overall results). The unadjusted *P* values were 0.054 for ESL 800 mg versus placebo and 0.125 for ESL 1200 mg versus placebo. At the last assessment, the combined frequencies for the 3 categories representing minimal disease severity (not ill at all, borderline ill, and mildly ill) were 39.4% for placebo, 53.9% for ESL 800 mg, and 46.0% for ESL 1200 mg. Overall, in the global improvement scores of the CGI, the ESL 1200 mg group had the largest proportion of subjects who were either "very much improved" or "much improved" at the last assessment (36.2%), followed by the ESL 800 mg group (34.4%), and placebo group (20.7%).

Seizure Severity Questionnaire: At the last assessment, the mean overall severity scores of the SSQ were 34.9, 32.1, and 33.1 for the placebo, ESL 800 mg, and ESL 1200 mg groups, respectively. However, only a portion of subjects in each group provided this data in each group.

Quality of Life in Epilepsy – 31 Inventory: Although each ESL group demonstrated a greater improvement in the QOLIE-31 overall score than the placebo group, there were no unadjusted *P* values ≤ 0.05 in the comparisons of each ESL treatment versus placebo. The scores for cognitive functioning in the health concepts portion of the QOLIE-31 indicated that cognitive functioning did not worsen over the course of treatment; the scores increased slightly from baseline in each treatment group.

Montgomery-Asberg Depression Rating Scale: No treatment-related changes were seen.

**Exploratory Efficacy Analyses:**

Subgroup Analyses: The following covariates were found to be statistically significant in the ANCOVA analyses,

thus indicating that there were differences between the levels of these covariates with respect to standardized seizure frequency: sex, carbamazepine use during the baseline period, lamotrigine use during the baseline period, and valproic acid use during the baseline period (*P* value ≤ 0.05). Male subjects tended to have lower standardized seizure frequencies than females. Unadjusted *P* values for between treatment comparisons were ≤ 0.05 for each ESL treatment versus placebo in males, but only for ESL 1200 mg versus placebo in females. In a subgroup of subjects with carbamazepine use during the baseline period, there was no dose-dependent trend observed in standardized seizure frequencies during the maintenance period; however, in subjects without carbamazepine during the baseline period, LS mean standardized seizure frequencies were notably lower in the ESL groups compared to placebo (with unadjusted *P* values ≤ 0.05 for each between treatment comparison). Standardized seizure frequencies in subjects who were taking lamotrigine during the baseline period were notably higher than in subjects who were not taking the AED during the baseline period. Unadjusted *P* values were ≤ 0.05 for each ESL treatment versus placebo in the subgroup without lamotrigine use during the baseline period; in subjects with lamotrigine use during the baseline period, the unadjusted *P* value was ≤ 0.05 for ESL 1200 mg versus placebo only. Standardized seizure frequencies were notably lower in subjects taking valproic acid during the baseline period compared with subjects who were not taking this AED during the baseline period; in each of these subgroups, the unadjusted *P* values ≤ 0.05 for ESL 1200 mg versus placebo, but not for ESL 800 mg versus placebo.

The subregion covariate and treatment-by-subregion interactions were not statistically significant in this exploratory covariate analysis, and therefore it can be concluded that the treatment effect was the same across the different subregions.

Time to Onset of Seizure Control: The median time to seizure control, from the start of treatment in the titration period, was 30.5 days for the placebo group and 24.5 days for each ESL group. There were no unadjusted *P* values ≤ 0.05 between either ESL group and placebo based upon the log-rank test. The median time to seizure control, from the start of treatment in the maintenance period, was 14.0 days for the placebo group and 10.5 days for each ESL group. Based upon the log-rank test, the unadjusted *P* value for ESL 1200 mg versus placebo was ≤ 0.05.

**PHARMACOKINETIC RESULTS:**

Plasma concentrations of eslicarbazepine increased with increasing dose in the overall analysis as well as the by-region analyses for North America and ROW.

**SAFETY RESULTS:**

- There were 2 deaths during Part I of the study, 1 event occurred in the placebo group and was considered not related to study drug and 1 event occurred in the ESL 800 mg group during the titration phase and was considered possibly related to study drug.
- Overall a small proportion of subjects experienced at least one SAE (3.7%). More subjects reported SAEs in the placebo (3.1%) and ESL 800 mg (6.5%) groups compared to the ESL 1200 mg (1.4%) group; there were no real discernible differences in the types of serious TEAEs among the 3 treatment groups and no dose-dependent trends emerged.
  - One subject reported a suicide attempt during the study. The subject had a history of suicidal tendencies; however, due to the positive response to study drug by the subject she was allowed to continue with study drug. The subject continued on ESL 800 mg and no other psychiatric events were reported. The event was considered by the investigator to be serious and of moderate intensity.
  - There was 1 serious cutaneous event reported during the study (leukocyctoclastic vasculitis). The subject had received a dose of ESL 800 mg. Study treatment was discontinued due to the event. The investigator considered the leukocyctoclastic vasculitis to be of severe intensity and definitely related to study drug.
- Discontinuation of study drug due to TEAEs were more frequent in the active treatment groups than in the placebo group, and the frequency of these discontinuations increased with increasing ESL dose (8.0% placebo, 12.0% ESL 800 mg, and 25.7% ESL 1200 mg).
- The majority (≥ 55.8%) of subjects in each treatment group experienced at least 1 TEAE (55.8% placebo versus 67.1% ESL 800 mg and 77.6% ESL 1200 mg). The incidence of TEAEs was higher in the active treatment groups than in the placebo group and increased in a dose-dependent manner.
- The incidences of dizziness, somnolence, nausea, and headache were lower for placebo than for the 2 active

treatments. Within the ESL dose groups, these incidences increased with increasing ESL dose, although this trend was less evident for headache. Similar dose proportionality trends were seen for the incidences of diplopia, vertigo, and fatigue.

- Rash was seen in 1.8% in the placebo group, 1.4% in the ESL 800 mg group, and 2.4% in the ESL 1200 mg group (including rash, rash macular, rash papular, and rash vesicular).
- The prevalence of decreased sodium levels and reported events of hyponatremia was low overall; and occurred only in the active treatment groups. Decreased sodium occurred in 0.5% of subjects in the ESL 800 mg group and 1.9% of subjects in the ESL 1200 mg group; hyponatremia in 1.9% and 3.3%, respectively.
- The majority of TEAEs were of mild or moderate intensity across the 3 treatment groups. The incidence of severe TEAEs was higher in the active treatment groups and tended to increase with increasing dose (6.7% placebo, 11.1% ESL 800 mg, 14.8% ESL 1200 mg). Treatment-emergent AEs reported as severe with an incidence of ≥ 1% of subjects in any treatment group by PT were dizziness, vertigo, diplopia, vomiting, ataxia, and somnolence.
- Subjects in the placebo group (37.1%) had fewer TEAEs that were reported as potentially related to study drug compared to subjects in the active treatment groups (51.4% ESL 800 mg and 66.7% ESL 1200 mg). Dizziness, somnolence vertigo, diplopia, nausea, vomiting, and fatigue were higher in the active treatment groups compared to the placebo group and a treatment- and dose-dependence was observed.
- Few subjects in each treatment group (11 to 13 subjects in each group) met the pre-specified criteria for PR prolongation, without any apparent difference in incidence between placebo and active treatment for PR prolongation within 220 msec. A PR longer than 250 msec was reported for 1 subject in the ESL 800 mg group and 2 subjects in the ESL 1200 mg group. Pre-specified changes from baseline in QTc-F, QTc-B and QRS duration and ventricular HR were found in approximately the same proportion of subjects in each treatment group and the results were not significant.
- The incidence of potentially clinically significant sodium levels, defined as a sodium level ≤ 125 mEq/L at any post baseline measurement, was low. Similar results were seen in the incidence of subjects who exhibited post baseline chloride levels ≤ 90 mEq/L.
- Premature discontinuation of study treatment due to TEAEs of blood sodium decreased or hyponatremia were reported in 4 subjects (1.9%), all in the ESL 1200 mg group.
- There were small shifts from normal to abnormal in all physical and neurological examinations during the study; no dose-dependent trends were evident. Any negative shifts for mental status, motor systems, co-ordination, and gait were minimal for the placebo and active treatment groups.
- Overall, the means and mean changes from baseline for vital signs and body weight were not substantially different across visits for the placebo and active treatment groups.
- No treatment-effect was observed in the number of hours subjects spent sleeping each night; median was 8.0 hours for each treatment group. For all other sleep scale questions, minor changes from baseline in subject responses were observed and these were similar within each treatment group but any differences between the 3 treatment groups were negligible.
- No statistically significant changes between subjects in the placebo group and subjects in the active treatment groups were observed for any of the C-SSRS parameters. More importantly, treatment with ESL 800 mg or ESL 1200 mg did not appear to have any effect on suicidality.

**CONCLUSIONS:**

- The ESL1200 mg dose group was statistically significantly different from placebo with respect to the primary efficacy endpoint. The ESL 800 mg dose group was not statistically significantly different from placebo but the results suggest a trend towards an improvement in standardized seizure frequency with this dose.
- ESL was safe and well tolerated at both dosages.

**Date of the Report: 29 June 2012**