2. STUDY SYNOPSIS

Sponsor: BIAL – Portela & C[a], S.A. Product: BIA 2-093 Active ingredient: Eslicarbazepine acetate		*(For National Authority Use only)*
Title of study: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, randomised, active-controlled, parallel-group, multicentre clinical study		
Coordinating investigator: Prof. Dr. Eugen Trinka		
Study centres: 135 study centres in 31 countries (Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, India, Israel, Argentina, Brazil, Chile and Peru)		
Study period: Date first subject enrolled: 27-Jan-2011 Date last subject completed the study: 08-Sep-2016		Clinical Phase: 3
Objectives: The primary objective of the study was to demonstrate that monotherapy with eslicarbazepine acetate (ESL, 800 to 1600 mg once daily [QD]; BIA-2093) was not inferior to monotherapy with carbamazepine controlled-release (CBZ-CR, 200 to 600 mg twice daily [BID]) in adults (≥18 years) with newly diagnosed epilepsy experiencing partial-onset seizures. The secondary objective of the study was to further demonstrate the efficacy, safety and pharmacokinetics of ESL in this subject population at the doses used. The results from the final analysis of the study (all data until the end of controlled treatment) have been reported below. The results of the primary statistical analysis based on the cut-off date of 24-Sep-2015 have been previously reported in the clinical study report (CSR) dated 29-Mar-2016.		
Methodology: This was a Phase 3, multinational, double-blind, parallel-group, active-controlled study conducted in adults (≥18 years) with newly diagnosed epilepsy experiencing partial-onset seizures. After a Screening Period of up to 7 days, subjects were randomly assigned to enter a 1-week Titration Period during which they received either ESL 400 mg QD or CBZ-CR 200 mg QD before increasing to the first target dose, Dose level A (ESL 800 mg QD, CBZ-CR 200 mg BID). This was followed by a 1-week Stabilisation and a 26-week Evaluation Period. Subjects who experienced a seizure during the Evaluation Period at Dose level A had their assigned treatment dose increased to Dose level B (ESL 1200 mg QD or CBZ-CR 400 mg BID) within 7 days of the seizure. Dose level B was reached by a 1-week Titration Period during which subjects received either ESL 1200 mg QD or CBZ-CR 300 mg BID before increasing to 400 mg BID in the CBZ-CR group; the ESL group remained at 1200 mg QD. This was followed by a 1-week Stabilisation and a 26-week Evaluation Period, as before. If a subject had another seizure during the Evaluation Period at Dose level B, their assigned treatment was increased to Dose level C (ESL 1600 mg QD or CBZ-CR 600 mg BID) within 7 days of the seizure. Dose level C was reached by a 1-week Titration Period during which subjects received either ESL 1600 mg QD or CBZ-CR 500 mg BID before increasing to 600 mg BID in the CBZ-CR group; the ESL group remained at 1600 mg QD. This was followed by a 1-week Stabilisation and a 26-week Evaluation Period,		

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as before.

Subjects who remained seizure free for 26 weeks at any dose in the Evaluation Period continued to receive the allocated treatment under double-blind conditions during the 26-week Maintenance Period and a subsequent Extension Phase.

Subjects who had a seizure at Dose level C during the Evaluation Period or at any dose during the Maintenance Period or the Extension Phase were withdrawn from the study.

Number of subjects:	Planned:	900 subjects
	Randomised:	815 subjects (ESL: 401 subjects, CBZ-CR: 414 subjects)
	Treated:	813 subjects (ESL: 401 subjects, CBZ-CR: 412 subjects)
	Analysed for efficacy:	813 subjects (Full Analysis Set [FAS]); 785 subjects (Per Protocol [PP] Set, the primary analysis population) 786 subjects (PPcor Set, accounting for data corrections to the PP Set after the primary analysis)
	Analysed for safety:	813 subjects

Diagnosis and main criteria for inclusion:

Male or female subjects ≥18 years of age with newly diagnosed epilepsy with at least 2 well-documented, unprovoked, clinically evaluated and classified partial seizures; had at least 1 seizure during the previous 3 months. Former or current use of any anti-epileptic drug (AED) was prohibited, except for the use of a single AED for a maximum duration of 2 weeks before Visit 1 and with a drug-free period of at least 5 days before Visit A1. An acute treatment for a seizure during the study (e.g. in the emergency room) was allowed and was not considered a deviation. Benzodiazepines were allowed for an epileptic indication and as rescue medication during the ≥5-day drug-free period.

Test product, dose and mode of administration, batch number:

Encapsulated tablets of ESL were orally administered at the following doses: 400 mg QD; 800 mg QD; 1200 mg QD; 1600 mg QD. Batch numbers are available in the Appendix 16.1.6 of the report.

Duration of treatment:

Study duration up to the end of the Main Treatment Phase for individual subjects was expected to last a minimum of 55 weeks for subjects who did not experience a seizure (i.e. up to 7 days screening and 54 weeks treatment). Due to the escalation in dosage if a seizure occurred, this could have increased up to a maximum of 111 weeks per subject, excluding the Extension, Down-titration and Follow-up Phases of the study. All subjects were to continue treatment until the last subject finished their last visit. The maximum study duration for an individual, including the Main Treatment Phase, Extension, Down-titration and Follow-up Phases, was expected to be about 300 weeks.

Reference therapy and mode of administration:

Oral capsules of CBZ-CR were administered at the following doses: 200 mg QD; 200 mg BID; 300 mg BID; 400 mg BID; 500 mg BID; 600 mg BID. Batch numbers are available in the Appendix 16.1.6 of the report.

Criteria for evaluation:

Efficacy

The primary efficacy variable was the proportion of subjects in the PP Set who were seizure free for the entire 26-week Evaluation Period at the last received dose level. Subjects who dropped out during this 26-week period were considered as non-seizure free. Subjects who dropped out during the Escalation/Stabilisation Period were considered as non-seizure free at the last received dose level.

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The secondary efficacy variables were:

- Proportion of seizure-free subjects during 1 year of treatment at the last evaluated dose.
- Time to first seizure at the last evaluated dose (treatment failure time).
- Seizure type and duration of the last seizure that led to up-titration (i.e. the last seizure in the respective dose) or discontinuation in any study period up to the end of the Evaluation Period.
- Time to treatment failure at the first evaluated dose, defined as the time of the first occurrence of 1 of the following during the Evaluation or Maintenance Period of Dose level A: seizure; withdrawal of investigational medicinal product (IMP) due to adverse event (AEs); withdrawal of IMP due to lack of efficacy.
- Treatment retention time, defined as the time of the first occurrence of 1 of the following: withdrawal of IMP due to AEs; withdrawal of IMP due to lack of efficacy.
- Time to withdrawal for any reason at the last evaluated dose.
- Dose level at which subjects reached 26-week seizure freedom (dose-response relationship).
- Seizure rate during the individual study periods at Dose level A, at any dose level, at the last evaluated dose and at the last evaluated individual dose.
- Changes in quality of life assessed using the validated Quality of Life in Epilepsy Inventory-31 (QOLIE-31) survey.

Safety

- Treatment-emergent adverse events (TEAEs) including serious TEAEs. TEAEs were defined as all AEs with onset or worsening after first intake of randomised study treatment until 4 weeks after last intake of randomised study treatment.
- Clinical laboratory safety tests:
    - Biochemistry: sodium, potassium, chloride, calcium, phosphate, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase (GGT), lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, creatinine, glucose, C-reactive protein, albumin, total protein, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides and total bilirubin.
    - Haematology: haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count and differentials: neutrophils, eosinophils, lymphocytes, monocytes and basophils.
    - Coagulation: international normalised ratio and activated partial thromboplastin time.
    - Thyroid function: total triiodothyronine, free triiodothyronine, total thyroxine, free thyroxine and thyroid stimulating hormone.
    - Bone turnover markers: serum 25-hydroxyvitamin D, parathyroid hormone, osteocalcin, bone-specific alkaline phosphatase and N-telopeptides of type I collagen cross-links.
    - Serum pregnancy test: only in female subjects of childbearing potential.
- Urinalysis: pH, specific gravity, protein, blood, glucose, ketones, bilirubin and urobilinogen (local dipstick). Microscopy and other appropriate tests could be performed as needed if a significant abnormality was detected.
- Physical examinations, vital signs, neurological examinations and 12-lead electrocardiogram (ECG) readings.
- An assessment of suicidal tendencies as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).
- An assessment of mental and physical sedation as measured by Bond-Lader visual analogue scales (BL-VAS).

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Statistical methods:

One primary analysis, after the primary endpoint was available for all subjects and the database was locked, was planned for the study (cut-off date: 24-Sep-2015). The results for the primary analysis have been previously reported in the CSR dated 29-Mar-2016. The final analysis of the study was performed after all subjects completed the study and the final database lock was performed on 26-Jan-2017. The results for the final analysis of the study are presented below.

In general, continuous variables were summarised using descriptive statistics, i.e. number of subjects in the respective analysis sets, number of subjects with data, number of subjects with missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Categorical variables were summarised using frequency counts and percentages. In addition, the number of subjects with missing values was presented.

The significance level of the primary analyses to establish non-inferiority in the PP Set and the FAS and superiority in the FAS was 2.5% one-sided. The confidence level for calculation of confidence intervals (CIs) was chosen as 95% two-sided, which corresponded to the one-sided 2.5% significance level. A sequential testing procedure ensured that the familywise error rate of 2.5% (one-sided) was controlled. All other statistical tests were explorative without adjustment for multiple testing. The sensitivity and robustness analyses of the primary analyses were performed on the nominal significance level of 2.5% one-sided. As one-sided hypotheses were not formulated for all other statistical tests, these tests were performed on the two-sided 5% level.

The primary efficacy variable was the proportion of subjects who were seizure free (seizure freedom) for the entire 26-week Evaluation Period (Evaluation Study Day [ESD] 1 to ESD 182) at the last evaluated dose level.

The sample size of 360 subjects per treatment group was estimated to have a power of at least 90% to establish non-inferiority of ESL compared with CBZ-CR using a non-inferiority margin of -12%, with the assumption that the proportion of subjects who were seizure free for 26 weeks was 60% for both treatments. In order to achieve 360 evaluable subjects per treatment group in the PP Set (the primary analysis population) and assuming a rate of 20% of subjects would not qualify for the PP Set, 450 subjects were initially planned to be randomised per treatment group. However, during the continuous monitoring of protocol violations, it appeared that the actual rates of subjects not qualifying for the PP Set tended to be lower than estimated. The revised rate was estimated to be below 12%, and thus the minimal number of randomised subjects per treatment group was decreased to 407 subjects.

Summary – Results

Demographic and baseline characteristics:

Of 929 subjects enrolled in the study, 815 were randomised to the 2 treatment groups: 401 subjects to ESL and 414 to CBZ-CR. The majority of subjects (ESL: 67.6%, CBZ-CR: 76.9%) remained on treatment at Dose level A (ESL 800 mg QD or CBZ-CR 200 mg BID) and the number of subjects that needed up-titration to higher dose levels was relatively small: at Dose level B, 70/401 subjects (17.5%) were treated with ESL and 61/412 (14.8%) with CBZ-CR, and at Dose level C, 60/401 (15.0%) subjects were treated with ESL and 34/412 (8.3%) with CBZ-CR. Of the 401 ESL subjects and 412 CBZ-CR subjects who received treatment, the majority of subjects in both groups (ESL: 70.8%, CBZ-CR: 74.5%) completed the 26-week Evaluation Period. By the end of the study, 59.9% of subjects in the ESL group and 64.1% in the CBZ-CR group also completed the 26-week Maintenance Period, i.e. a total of 54 weeks of treatment. Roughly a quarter of subjects in both treatment groups did not complete the 26-week Evaluation Period, the most common reason for which was AEs (serious or not).

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There were no relevant differences in demographic characteristics between the treatment groups. The mean age was 37.6 years in the ESL group and 38.7 years in the CBZ-CR group, most subjects were <65 years (ESL: 93.3%, CBZ-CR: 91.5%), there were slightly more male than female subjects and at least 80% of subjects were Caucasian. The treatment groups were also balanced in terms of epilepsy history and characteristics.

Efficacy results:

The results of the final efficacy analysis of the BIA-2093-311 study were consistent with those reported at the time of the primary analysis (data cut-off: 24-Sep-2015). The primary objective of the study was met. ESL was non-inferior to CBZ-CR for subjects to be seizure free during the 26-week Evaluation Period (lower limit of 95% CI: -10.30%) with 71.1% of subjects classified as seizure free in the ESL group and 75.6% in the CBZ-CR group. Results from the sensitivity analyses were consistent with the primary analysis results. Data corrections made after the primary analysis had no impact on the primary efficacy results. The treatment effect observed during the 26-week Evaluation Period was maintained over 1 year of treatment and ESL continued to be non-inferior to CBZ-CR (lower limit of 95% CI: -11.88%). Non-inferiority was also shown in the explorative analyses of the relative risk difference to be seizure free in both the Evaluation Period and during the 1-year treatment period.

The majority of subjects (ESL: 67.6%, CBZ-CR: 76.9%) remained on treatment at Dose level A (ESL 800 mg QD or CBZ-CR 200 mg BID) and did not need to be up-titrated to a higher dose. In these subjects, the efficacy of ESL 800 mg QD was as good as CBZ-CR: a similar proportion of seizure-free subjects completed the study at Dose level A at the last evaluated individual dose (ESL: 85.4%, CBZ-CR: 83.2%). A higher percentage of seizure-free subjects (>10% difference) in the CBZ-CR group completed the last evaluated individual dose at Dose level B than the ESL group during the Evaluation Period (ESL: 43/58 subjects [74.1%], CBZ-CR: 47/53 subjects [88.7%]), but at the last evaluated individual Dose level C, the percentage was more comparable between the groups (ESL: 23/53 subjects [43.4%], CBZ-CR: 16/32 subjects [50.0%]).

There were no significant differences in seizure freedom rates between the ESL and CBZ-CR groups at each dose level. Based on the total number of subjects in the PP Set for the entire treatment group (i.e. ESL: 388 subjects, CBZ-CR: 397 subjects), the overall proportions of seizure-free subjects at each dose level (i.e. those completing the Evaluation Period at the last evaluated dose) were similar in the ESL QD groups (54.1% [210/388] for 800 mg, 11.1% [43/388] for 1200 mg and 5.9% [23/388] for 1600 mg) and in the CBZ-CR BID groups (59.7% [237/397] for 200 mg, 11.8% [47/397] for 400 mg and 4.0% [16/397] for 600 mg).

Based on the number of subjects in the PP Set by randomised treatment group at the individual dose level (i.e. for ESL, 388 subjects in the 800 mg group, 126 subjects in the 1200 mg group and 57 subjects in the 1600 mg group), the proportion of seizure-free subjects at each dose level in the ESL group was 54.1% [210/388] for 800 mg, 34.1% [43/126] for 1200 mg and 40.4% [23/57] for 1600 mg. For CBZ-CR, there were 397 subjects in the 200 mg group, 93 subjects in the 400 mg group and 33 subjects in the 600 mg group in the PP Set, and the proportion of seizure-free subjects by dose level was 59.7% [237/397] for 200 mg, 50.5% [47/93] for 400 mg and 48.5% [16/33] for 600 mg.

If the total of seizure-free subjects in the PP Set during the Evaluation Period (i.e. ESL: 276 subjects, CBZ-CR: 300 subjects) was broken down by dose level, the proportion of seizure-free subjects at each dose level in the ESL group was 76.1% [210/276] for 800 mg, 15.6% [43/276] for 1200 mg and 8.3% [23/276] for 1600 mg, and in the CBZ-CR group, 79.0% [237/300] for 200 mg, 15.7% [47/300] for 400 mg and 5.3% [16/300] for 600 mg.

No interaction was indicated between treatment and region for seizure freedom during the 26-week Evaluation Period. The majority of subjects in the study were <65 years old and there was also no

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interaction between treatment and age or age group during the 26-week Evaluation Period or during 1 year of treatment. While a similar proportion of subjects in the subgroup with ≤4 seizures before baseline were seizure free in each treatment group, in the subgroup with >4 seizures before baseline, the CBZ-CR group had a higher proportion of seizure-free subjects than the ESL group. However, there was no interaction between treatment and seizure frequency at baseline.

The majority of subjects were not previously treated with AEDs (85.1%) and the percentage of seizure-free subjects in this subgroup was similar between the treatment groups during the Evaluation Period and the 1-year treatment period. For subjects who previously received a single AED (maximum 2 weeks; 14.9%), the percentage of seizure-free subjects was lower in the ESL group than the CBZ-CR group; however, the numbers of subjects in this subgroup were low and these results need to be interpreted with caution.

The time to first seizure (treatment failure time) was earlier in the ESL group, with an increased risk of having a seizure during the first 60 days of treatment compared with the CBZ-CR group. Thereafter, the risk was the same in both treatment groups. This was true overall and for subjects on Dose level A.

The duration of seizures that led to up-titration or discontinuation during the Evaluation Period was less than 1 minute in a similar proportion of subjects in both treatment groups (for about a third of subjects at Dose level C, 40% of subjects at Dose level A and 50% of subjects at Dose level B). Except for Dose level C, the incidence of seizures lasting more than 5 minutes was slightly lower in the ESL group than in the CBZ-CR group (Dose level A, ESL: 10.3%, CBZ-CR: 17.0%; Dose level B, ESL: 9.9%, CBZ-CR: 10.5%; Dose level C, ESL: 11.5%, CBZ-CR: 0.0%). In both groups, the most common type of seizure that led to up-titration or discontinuation at all dose levels in both groups was complex partial seizures. Simple partial seizures were reported less in the ESL group, whereas partial evolving to secondarily generalised seizures were reported by more subjects in the ESL group.

Similar improvements in QOLIE-31 scores were seen in both treatment groups over time.

Safety results:

By last evaluated individual dose, a similar percentage of subjects experienced at least 1 TEAE in both groups (ESL: 76.3%, CBZ-CR: 79.6%) and the majority of events were mild (ESL: 70.6%, CBZ-CR: 73.1%). TEAEs categorised as severe were fewer in the ESL group (9.5%) compared with the CBZ-CR group (15.0%). Moreover, fewer subjects in the ESL group reported TEAEs considered at least possibly related to IMP, both overall (ESL: 42.1% versus CBZ-CR: 51.5%) and at Dose level A (ESL: 40.2% versus CBZ-CR: 50.5%). There was no indication of a dose relationship in the incidence of TEAEs. The most frequently reported TEAEs in both treatment groups were headache (ESL: 22.9%, CBZ-CR: 22.1%) and dizziness (ESL: 14.5%, CBZ-CR: 13.3%). The overall pattern of TEAEs reflected the known safety profile of the 2 treatments. Headache and dizziness were reported for similar proportions of subjects in both treatment groups at Dose level A and B; whereas at Dose level C, the proportions were lower in the ESL group than the CBZ-CR group for both events. No relevant differences between the groups were seen for other commonly reported TEAEs, but increased GGT was reported by a higher percentage of subjects (>5% difference) in the CBZ-CR group (15.3%) than in the ESL group (4.5%) overall and at all dose levels.

Four subjects, 2 in each treatment group, experienced TEAEs that led to death (glioblastoma multiforme and cardiac arrest in the ESL group, suicide and lung adenocarcinoma in the CBZ-CR group). None of the deaths in the ESL group were considered related to ESL. The suicide in the CBZ-CR group was considered to be possibly related to IMP (suicidal risk is a class effect of AEDs).

Serious TEAEs (ESL: 10.7%, CBZ-CR: 11.9%) and possibly related serious TEAEs (ESL: 2.0%, CBZ-CR: 2.7%) were reported in a similar proportion of subjects in the treatment groups overall. The serious TEAE reported by >2 subjects in the ESL group was status epilepticus (3 subjects [0.7%]),

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and in the CBZ-CR group were syncope (5 subjects [1.2%]) and convulsion (4 subjects [1.0%]). By preferred term, all possibly related serious TEAEs were reported by ≤1 subject in either treatment group. At Dose level A, fewer subjects in the ESL group reported serious TEAEs (ESL: 8.9% versus CBZ-CR: 13.9%) and serious TEAEs possibly related to IMP (ESL: 1.1% versus CBZ-CR: 3.2%). At Dose levels B and C, serious TEAEs were reported by more subjects in the ESL group, but only 3 and 2 subjects, respectively, experienced possibly related serious TEAEs.

Fewer subjects discontinued IMP due to a TEAE in the ESL group (14.0%) compared with the CBZ-CR group (18.4%), and the same pattern was seen at Dose level A (ESL: 12.5%, CBZ-CR: 18.6%). Of the most common events leading to IMP discontinuation, fatigue, somnolence and disturbance in attention led to more subjects discontinuing in the ESL group compared with the CBZ-CR group, whereas more subjects on CBZ-CR than ESL discontinued the IMP due to allergic dermatitis, headache, convulsion, increased GGT and hypersensitivity.

The proportions of subjects with TEAEs of special interest and possibly related TEAEs of special interest were generally comparable between the treatment groups. Hepatic disorder TEAEs were reported by a lower percentage of subjects in the ESL group (11.0%) compared with the CBZ-CR group (20.6%); this was mainly due to fewer "increased GGT" events in the ESL group.

No relevant changes over time or differences between the treatment groups were observed for the parameters of haematology, coagulation, thyroid function, urinalysis or bone turnover markers. Among biochemistry parameters, the mean increases in GGT over time were larger in the CBZ-CR group compared with the ESL group. Values still remained within the normal range in the ESL group at post-baseline visits, whereas more subjects in the CBZ-CR group (approximately 40%) had high values at post-baseline visits. More subjects in the CBZ-CR group (25.7%) had a change in GGT from normal at baseline to an abnormally high value at endpoint compared with the ESL group (10.2%). In addition, clinically significant post-baseline GGT values were also reported for more CBZ-CR subjects (18.7%) than ESL subjects (7.3%).

For almost all hepatic parameters, the percentage of subjects with clinically significant abnormalities or elevations was low in both treatment groups. The majority of subjects in both treatment groups had sodium values >130 mEq/L (ESL: 91.6%, CBZ-CR: 97.0%) throughout the study. Although there was a sodium decrease from baseline of >10 mEq/L in 11.6% of subjects in the ESL group compared with 4.7% in the CBZ-CR group, and sodium levels ≤125 mEq/L were found in 1.5% of subjects in the ESL group and in 0.7% of subjects in the CBZ-CR group, none of the low sodium levels resulted in a TEAE that led to discontinuation from study medication.

There were no clinically meaningful changes over time or differences between treatment groups in vital signs, neurological examinations or ECGs. For the assessment of skin, fewer ESL subjects (3.9%) than CBZ-CR subjects (7.8%) had a worsening from baseline at any post-baseline visit. The most common skin-related TEAEs were rash (3.2% in both groups) and allergic dermatitis (ESL: 0.5%, CBZ-CR: 2.4%). Few subjects (≤2%) in either treatment group reported suicidal ideation or behaviour recorded via the C-SSRS and improvement in suicidal ideation was similar between the groups at endpoint. No trends in the mean scores for alertness, calmness or contentedness based on the BL-VAS were observed over time in both treatment groups.

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Conclusions:
Monotherapy with ESL (800 to 1600 mg QD) was non-inferior to monotherapy with CBZ-CR (200 to 600 mg BID) in adults (≥18 years) with newly diagnosed epilepsy experiencing partial-onset seizures. Non-inferiority was demonstrated for the proportion of seizure-free subjects for the entire 26-week Evaluation Period as well as during 1 year of treatment. The majority of subjects remained on ESL doses of 800 mg QD (Dose level A), and the subjects that required up-titration achieved seizure rates at Dose level C (1600 mg ESL QD) that were similar to CBZ-CR.
Treatment with ESL at doses of 800 to 1600 mg QD in this population had a safety profile that was similar or more favourable than that of CBZ-CR and reflected the known safety profile for ESL.

Date of final report: 03-Apr-2017