Synopsis

Name of Sponsor/Company: BIAL - Portela & C[a], S.A.

Name of Study Intervention: Eslicarbazepine acetate (development code: BIA 2-093)

Trade Name: Zebinix®, Exalief®, Aptiom®

Study Title: Open-label, 2-dose level trial to evaluate pharmacokinetics, safety, and tolerability of eslicarbazepine acetate (ESL) as adjunctive therapy in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years

Study Number: BIA-2093-211

Study Phase: 2

PIP number: EMEA-000696-PIP02-10-M02

Number of Study Centres and Countries: This study was conducted in 17 centres across 8 countries in Europe (Croatia, Czech Republic, Italy, Portugal, Romania, Russia, Serbia, and Ukraine). Subjects were enrolled in 7 centres across 4 countries in Europe (Czech Republic, Russia, Serbia, and Ukraine).

Publications (if any): Not applicable

Study Period: The study was initiated on 19-Apr-2018 (first subject, first visit) and completed on 03-Apr-2020 (last subject, last visit).

Methodology:
This was a Phase 2, multinational, open-label study to evaluate up to 4 doses of ESL in infants (≥1 month to <2 years of age) with refractory partial-onset seizures. Subjects were stratified and assigned to different dose groups based on their age (Age cohort A: ≥1 to <6 months; Age cohort B: ≥6 to <24 months).

After a Screening Period of up to 3 weeks, Group 1 began treatment. For Age cohort A, there was no titration and subjects were treated with 5 mg/kg once daily (QD) for 5 days in a 6-day Evaluation Period. For Age cohort B, subjects had a 5-day Up-titration Period at 5 mg/kg QD before increasing to 10 mg/kg QD for the Evaluation Period and a 5-day Down-titration Period if subjects did not continue in the extension study or discontinued the study early.

An interim pharmacokinetic (PK) analysis was performed separately for each age cohort after at least 4 subjects of a cohort in Group 1 had completed their 24-hour PK profile. Because this interim analysis indicated that exposure was not optimal at that dose for each cohort, a second evaluation dose of ESL was determined (20 mg/kg QD) and evaluated for both age cohorts in Group 2.

Subjects in both age cohorts in Group 2 began a 5-day Up-titration Period at 5 mg/kg QD, followed by a second 5-day Up-titration Period at 12.5 mg/kg QD, before proceeding to the

evaluation dose at 20 mg/kg QD for 5 days in a 6-day Evaluation Period. If subjects did not continue in the subsequent extension study or discontinued the study early, down-titration was to occur as follows:

- Age cohort A: one 5-day down-titration step at 12.5 mg/kg QD.
- Age cohort B: two 5-day down-titration steps, starting at 12.5 mg/kg QD followed by 5 mg/kg QD.

After completion of the Evaluation Period, the parent(s) or guardian(s) could choose to allow their child to enter in the optional 1-year extension study; a final End-of-treatment (EOT) visit was then performed on Day 6 of the Evaluation Period. Subjects who did not continue into the extension study were to enter the Down-titration Period, followed by a 4-week Follow-up Period after the last dose of study drug and a final EOT visit at the end of the Follow-up Period.

In the 3 weeks prior to the start of treatment at Visit 1, background anti-epileptic drugs (AEDs) were not to be started or discontinued. Dosage regimens of background AEDs were to remain stable during the Evaluation Period.

The 24-hour PK profile of the ESL active metabolite eslicarbazepine was assessed by determining eslicarbazepine plasma concentrations at pre-specified time points beginning on Day 5 of treatment in the Evaluation Period. Overall safety was assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, neurological examinations, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. Efficacy was assessed by evaluation of seizures (date, time, type, and duration) at each visit.

Number of Subjects (planned and analysed):
Planned: up to 24 subjects

Enrolled set (defined as all subjects for whom signed informed consent was obtained): 24 subjects

Safety set (defined as all subjects who received at least 1 dose of investigational medicinal product): 23 subjects: in Group 1, 4 subjects in Age cohort A and 10 in Age cohort B, and in Group 2, 4 subjects in Age cohort A and 5 in Age cohort B.

PK set (defined as all subjects who received a dose of investigational medicinal product provided they had adequate eslicarbazepine plasma concentration data): 23 subjects: in Group 1, 4 subjects in Age cohort A and 10 in Age cohort B, and in Group 2, 4 subjects in Age cohort A and 5 in Age cohort B. Eslicarbazepine plasma concentration data were received for all 23 subjects; however, 1 subject was incorrectly dosed on all dosing days, and, therefore, PK results for this subject were listed only but were excluded from summary statistics.

Diagnosis and Main Criteria for Inclusion and Exclusion:
The study population consisted of male and female infants, ≥1 month to <2 years of age, with epilepsy refractory to treatment with 1 to 2 AEDs and with clinical or electroencephalogram evidence of partial-onset seizures for at least 1 month in infants ≥6 months of age, or for at least 2 weeks in infants <6 months of age. Subjects were excluded if they started or discontinued an AED in the 3 weeks before Visit 1.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):
The study drug was ESL, an oral suspension of 50 mg/mL (batch numbers: 160690 and 190412). Doses in each group were as follows:

		Age cohort A (≥1 to <6 months)	Age cohort B (≥6 to <24 months)
Group 1	Up-titration dose	NA	5 mg/kg QD
	Evaluation dose	5 mg/kg QD	10 mg/kg QD
	Down-titration dose	NA	5 mg/kg QD
Group 2	Up-titration dose, step 1	5 mg/kg QD	5 mg/kg QD
	Up-titration dose, step 2	12.5 mg/kg QD	12.5 mg/kg QD
	Evaluation dose	20 mg/kg QD	20 mg/kg QD
	Down-titration dose, step 1	12.5 mg/kg QD	12.5 mg/kg QD
	Down-titration dose, step 2	NA	5 mg/kg QD

NA = not applicable; QD = once daily.

Duration of Study Intervention:
Planned: ESL was planned to be given for 5 days in Group 1 Age cohort A, for up to 15 days in Group 1 Age cohort B and Group 2 Age cohort A, and for up to 25 days in Group 2 Age cohort B.

Actual: ESL was given for 5 days in Group 1 Age cohort A, for 10 days in Group 1 Age cohort B, and for 15 days in Group 2 Age cohorts A and B.

Objectives, Endpoints, and Statistical Methods
Listed below are the objectives and endpoints that are described in this report.

Objectives	Endpoints	Statistical Analyses
Primary objectives	Primary endpoints	
To evaluate the steady state PK profile of ESL	The following PK parameters were derived by non-compartmental analysis from the plasma concentration vs. time profiles, when appropriate: • C_{min} • C_{max} • Dose-normalised C_{max} • t_{max} • AUC_{τ} • Dose-normalised AUC_{τ} • $t_{1/2}$ • CL/F	Plasma concentrations of eslicarbazepine and corresponding PK parameters were summarised using descriptive statistics by age cohort and dose.
Secondary	Secondary endpoints	
To assess the safety and tolerability of ESL in the defined patient population at the doses used	• TEAEs • Clinical laboratory safety tests • Physical examination • Vital signs • Neurological examination • ECG	Continuous variables were summarised using descriptive statistics, and categorical variables were summarised by frequency counts and percentages based on the Safety set. Fisher exact test was used to compare clinically significant laboratory values between age cohorts within each treatment group, as well as among all age cohorts.

To perform exploratory analyses of efficacy	• Standardised seizure frequency (number of seizures per week) over the Baseline, Up-titration, Evaluation, Down-titration, and Follow-up Periods • Absolute change in seizure frequency from the Baseline Period to the corresponding period • Relative change in seizure frequency from the Baseline Period to the corresponding period • Relative change in seizure frequency from the Baseline Period to the corresponding period categorised as follows: - ≥25% (25% exacerbation or greater) - >-50% to <25% (no relevant change) - ≤-50% to ≥-75% (reduction between 50% and 75%) - <-75% (reduction greater than 75%) • Proportion of subjects who are seizure-free during the corresponding period • Standardised seizure frequency by seizure type during the corresponding period • Seizure duration	Descriptive statistics of seizure data (number of seizures, type of seizure and duration) based on the Safety set.

AUC_τ = area under the concentration-time curve during a dose interval; CL/F = apparent clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; ECG = electrocardiogram; ESL = eslicarbazepine acetate; TEAE = treatment-emergent adverse event; t_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal half-life.

Summary of Results and Conclusions:

Demography and Baseline Characteristics:
In total, 23 of 24 enrolled subjects started treatment: 4 in Group 1 Age cohort A, 10 in Group 1 Age cohort B, 4 in Group 2 Age cohort A, and 5 in Group 2 Age cohort B. No subjects discontinued from the study. All 23 subjects completed the study and continued in the 1-year extension study.

Baseline demographics within each age cohort were balanced across the 2 treatment groups. For Age cohort A, mean (standard deviation [SD]) age was 3.8 (0.50) months in Group 1 and 3.8 (1.50) months in Group 2. For Age cohort B, mean (SD) age was 14.7 (6.75) months in Group 1 and 16.2 (5.81) months in Group 2. There was an even distribution of male and female subjects across treatment groups. All subjects were white and not Hispanic or Latino. The treatment groups were also balanced in terms of epilepsy history and baseline disease characteristics, apart from a higher frequency of complex partial seizures prior to study entry in Group 2 Age cohort B. The median (range) number of complex partial seizures was 15.0 (0 to 121) in Group 1 Age cohort A, 0.0 (0 to 205) in Group 1 Age cohort B, 3.5 (0 to 41) in Group 2 Age cohort A, and 90 (0 to 900) in Group 2 Age cohort B.

Exposure:
The mean treatment duration during the Evaluation Period was consistent across treatment groups: 5.0 days in Group 1 Age cohort A, 5.0 days in Group 1 Age cohort B, 5.0 days in Group 2 Age cohort A, and 4.8 days in Group 2 Age cohort B. As expected by study design, the total mean treatment duration was 5.0 days in Group 1 Age cohort A, 10.0 days in Group 1 Age cohort B, 15.0 days in Group 2 Age cohort A, and 14.8 days in Group 2 Age cohort B. The mean daily doses received in the Evaluation Period were in accordance with the planned evaluation doses for each treatment group.

Pharmacokinetic Results:
Eslicarbazepine plasma concentrations were highly variable, as indicated by the coefficient of variation (CV%) values, which were >50% at most time points in each group. Mean pre-dose and 24-hour plasma concentrations of eslicarbazepine were roughly similar, indicating that steady state conditions were attained in this study. Median time to reach maximum concentration (t_{max}) varied from 1.50 to 2.25 hours, whereas the elimination phase, which appeared to be monophasic, was characterised by a geometric mean apparent terminal half-life ($t_{1/2}$) that varied between 6.36 and 7.37 hours. Values for t_{max} and $t_{1/2}$ were similar between age cohorts and were not affected by dose. Similar to plasma concentrations, eslicarbazepine PK parameters were highly variable, with geometric CV% values ranging from 8.39% to 117%. Exposure (maximum concentration [C_{max}] and area under the concentration-time curve during a dose interval [AUC_{τ}]) to eslicarbazepine increased with increasing dose. This increase appeared to be dose-proportional in Age cohort B, whereas in Age cohort A, the increase appeared to be less than dose-proportional. At a dose of 20 mg/kg, the geometric mean ratio (90% confidence interval [CI]) was 2.12 (1.33; 3.37) for C_{max} and 2.25 (1.30; 3.91) for AUC_{τ}, indicating higher exposure

in Age cohort B than in Age cohort A, whereas $t_{1/2}$ was similar in both age cohorts. No apparent effect of gender on the PK of eslicarbazepine was found in these age groups.

Summary of Pharmacokinetic Parameters by Age Cohort and Dose

Group, Dose	Statistic	t_{max} (h)	C_{max} (ng/mL)	C_{max}/dose ([ng/mL]/[mg/kg])	AUC_τ (h*ng/mL)	AUC_τ/dose ([h*ng/mL]/[mg/kg])	$t_{1/2}$ (h)	CL/F (mL/h/kg)
Group 1 Age cohort A, 5 mg/kg	n	4	4	4	4	4	4	4
	Median (Min–Max)	2.25 (0.500–3.00)	–	–	–	–	–	–
	Geometric mean (Geometric SD)	–	3960 (1.78)	792 (1.78)	42100 (1.81)	8430 (1.81)	6.36 (1.34)	119 (1.81)
	Geometric CV%	–	63.1	63.1	65.2	65.2	29.7	65.2
Group 1 Age cohort B, 10 mg/kg	n	10	10	10	9	9	7	9
	Median (Min–Max)	2.25 (0.500–4.50)	–	–	–	–	–	–
	Geometric mean (Geometric SD)	–	10400 (1.51)	1040 (1.51)	122000 (1.78)	12200 (1.78)	7.25 (1.28)	82.0 (1.78)
	Geometric CV%	–	43.0	43.0	62.8	62.8	24.7	62.8
Group 2 Age cohort A, 20 mg/kg	n	3	3	3	3	3	3	3
	Median (Min–Max)	1.50 (0.500–3.00)	–	–	–	–	–	–
	Geometric mean (Geometric SD)	–	10800 (2.19)	542 (2.19)	128000 (2.53)	6410 (2.53)	7.37 (1.34)	156 (2.53)
	Geometric CV%	–	92.1	92.1	117	117	29.7	117
Group 2 Age cohort B, 20 mg/kg	n	5	5	5	5	5	4	5
	Median (Min–Max)	2.00 (0.500–6.00)	–	–	–	–	–	–
	Geometric mean (Geometric SD)	–	19800 (1.09)	992 (1.09)	229000 (1.26)	11500 (1.26)	6.98 (1.22)	87.2 (1.26)
	Geometric CV%	–	8.39	8.39	23.1	23.1	20.4	23.1

AUC_τ = area under the concentration-time curve during a dose interval; AUC_τ/dose = dose-normalised AUC_τ; CL/F = apparent clearance; C_{max} = maximum concentration; C_{max}/dose = dose-normalised C_{max}; CV = coefficient of variation; Max = maximum; Min = minimum; n = number of subjects with evaluable pharmacokinetic data; SD = standard deviation; t_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal half-life.

Note: Age cohort A: ≥1 to <6 months, Age cohort B: ≥6 to <24 months.

Efficacy Results:

Efficacy data were analysed in an exploratory manner based on the Safety set. The relevance of any observed differences must be considered in the context of the small sample size as well as different ESL treatment durations between the groups and lack of placebo control.

A slight increase from baseline in the proportion of seizure-free subjects in the Evaluation Period was observed in Group 2 Age cohort A (from 0% to 25%) and in Group 1 Age cohort B (from 10% to 30%) while the proportion was maintained in Group 1 Age cohort A (from 25% to 25%)

and Group 2 Age cohort B (from 20% to 20%). No clinically relevant differences were observed between the 2 dose levels within each age cohort or between the age cohorts. In addition, no noteworthy differences were found between male and female subjects.

During the Evaluation Period, a reduction from baseline in standardised seizure frequency (defined as the number of seizures per week [7 days]) was observed in both age cohorts and treatment groups, and within each age cohort the reduction was higher at the 20 mg/kg dose than at the lower dose. The mean (SD) absolute change from baseline in standardised seizure frequency in the Evaluation Period was -5.13 (11.989) and -17.17 (12.419) in Groups 1 and 2 of Age cohort A and -3.78 (14.421) and -6.83 (16.017) in Groups 1 and 2 of Age cohort B, respectively. The mean relative change from baseline in standardised seizure frequency in the Evaluation Period was -37.35% and -75.74% in Groups 1 and 2 of Age cohort A and -8.67% and -30.38% in Groups 1 and 2 of Age cohort B, respectively.

In Age cohort A, the proportion of subjects with a relevant reduction from baseline in standardised seizure frequency (i.e. ≥50% reduction) during the Evaluation Period was higher at the 20 mg/kg dose (50% had a 50% to 75% reduction and 50% had a >75% reduction) than at the 5 mg/kg dose (25% had a >75% reduction). In Age cohort B, there was no indication of a dose response relationship with ESL in the proportion of subjects with a relevant reduction from baseline in standardised seizure frequency (Group 1: 10% had a 50% to 75% reduction and 40% had a >75% reduction, Group 2: 20% had a 50% to 75% reduction and 20% had a >75% reduction). At the 20 mg/kg dose, a relevant reduction from baseline in standardised seizure frequency appeared to occur more frequently in male than in female subjects. All male subjects in Group 2 (3 in Age cohort A and 2 in Age cohort B) had a ≥50% reduction from baseline compared with 1 of 4 female subjects in Group 2 (1 of 1 subject in Age cohort A and none of 3 subjects in Age cohort B).

The most common seizure type reported during the study was complex partial, followed by partial evolving to secondarily generalised, simple partial, and unclassifiable. No subjects experienced generalised or other seizure types. Noteworthy changes from baseline in standardised seizure frequency in the Evaluation Period were primarily observed for complex partial seizures and partial evolving to secondarily generalised seizures, which reflected an overall pattern of improvement (i.e. reduction in standardised seizure frequency). The mean relative change from baseline in standardised seizure frequency of complex partial seizures in both age cohorts showed a clear reduction at the 20 mg/kg dose compared with the lower dose (-8.96% and -82.25% in Groups 1 and 2 of Age cohort A and 42.66% and -35.69% in Groups 1 and 2 of Age cohort B, respectively). A reduction from baseline in standardised seizure frequency was also observed for partial seizures evolving to secondarily generalised, but there was no indication of a dose response relationship with ESL (mean relative change from baseline: -76.67% and -69.23% in Groups 1 and 2 of Age cohort A and -74.67% and -14.44% in Groups 1 and 2 of Age cohort B, respectively).

Safety Results:
The relevance of any observed differences in safety results must be considered in the context of the small sample size, different ESL treatment durations between the groups, and lack of placebo control.

Overall, 6 subjects (26.1%) experienced at least 1 TEAE during the study: 1 subject (25%) in Group 1 Age cohort A, 3 (30%) in Group 1 Age cohort B, 2 (50%) in Group 2 Age cohort A, and none in Group 2 Age cohort B. All TEAEs were assessed as mild except for 1 TEAE of moderate intensity reported in Group 1 Age cohort B. No subjects experienced a TEAE leading to death, a serious TEAE, a TEAE leading to discontinuation of study drug, or an adverse event of special interest. There were no clinically relevant differences between the treatment groups in the incidence of TEAEs by system organ class (SOC) and preferred term, and there was no relationship with age or increasing dose. The overall pattern of TEAEs reflected the known safety profile of ESL. Overall, the most common SOCs in which TEAEs were reported were nervous system disorders (13.0%), gastrointestinal disorders (8.7%), and investigations (8.7%). The most common TEAE was somnolence, reported by 2 subjects (20%) in Group 1 Age cohort B, 1 subject (25%) in Group 2 Age cohort A, and no subjects in both Group 1 Age cohort A and Group 2 Age cohort B. All other TEAEs were each reported in 1 subject overall. The most common treatment-related TEAE was somnolence, reported by 2 subjects (20%) in Group 1 Age cohort B and 1 subject (25%) in Group 2 Age cohort A.

There were no clinically meaningful changes over time or differences between treatment groups in haematology, biochemistry, or urinalysis parameters. Overall, 1 subject (Group 2 Age cohort A) had clinically significant low sodium values on Day 2 (Visit 3) and Day 6 of the Evaluation Period, which was reported as a mild TEAE of hyponatraemia that was assessed by the investigator as related to the study drug.

The mean absolute change from baseline in QT interval corrected for heart rate using Bazett's formula (QTcB) values ranged between -9.2 and 1.5 milliseconds (ms) in the 4 treatment groups, which were not clinically relevant. The mean absolute change from baseline in QT interval corrected for heart rate using Fridericia's formula (QTcF) values ranged between -6.2 and 0.3 ms in the different treatment groups, which were not clinically relevant. Categorical observations for QTcB and QTcF values were reviewed and quantified according to the Committee for Proprietary Medicinal Products (CPMP/ICH/2711/99) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E14 guidelines. No subjects had absolute or change from baseline values in the pre-specified categories for QTcB and QTcF. No clinically significant changes were observed in heart rate (HR), PR interval, or QRS duration in any dose group on by-time-point analysis. Categorical analysis revealed only few subjects with low HR, high PR interval, and high QRS duration values. Some of these subjects were reported with high baseline values as well. Only 1 subject was reported with a TEAE of PR prolongation (see below); this event was also listed as first-degree atrioventricular block. Only 2 types of treatment-emergent morphological abnormalities, sinus bradycardia and first-degree atrioventricular block, were reported during the study. No treatment-emergent U-wave

abnormalities were reported. No subjects had treatment-emergent arrhythmias that would suggest a potential pro-arrhythmic effect.

No clinically meaningful changes over time or differences between treatment groups were observed in ECG findings as evaluated by the investigator. One subject in Group 1 Age cohort B had a clinically relevant abnormal ECG (prolongation of the PR interval, 173 ms; normal range for gender and age: PR interval ≤147 ms) at EOT, which was reported as a mild TEAE of ECG PR prolongation that was assessed by the investigator as related to the study drug.

No clinically meaningful changes over time or differences between treatment groups were observed in vital sign parameters and physical and neurological examinations.

Conclusions:
Pharmacokinetics

- A high inter-individual variability was found in the PK of eslicarbazepine in both Age cohort A (≥1 to <6 months) and Age cohort B (≥6 to <24 months) at the dose levels tested.
- Values for t_{max} and $t_{1/2}$ were similar in both age cohorts. At a dose of 20 mg/kg, the geometric mean ratio (90% CI) was 2.12 (1.33; 3.37) for C_{max} and 2.25 (1.30; 3.91) for AUC_{τ}, indicating higher exposure to eslicarbazepine in Age cohort B than in Age cohort A.

Safety

- ESL was well tolerated in infants (1 month to <2 years of age) with refractory epilepsy with partial-onset seizures. There were no new safety signals observed, and the safety profile reflected the known safety profile for ESL.
- ESL at doses of 5, 10, and 20 mg/kg QD does not cause a clinically relevant prolongation of the QTc interval in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years.

Efficacy

Efficacy data were analysed in an exploratory manner based on the Safety set.

- A slight increase from baseline in the proportion of seizure-free subjects in the Evaluation Period was observed in Group 2 Age cohort A (0% to 25%) and in Group 1 Age cohort B (10% to 30%) while the proportion was maintained in Group 1 Age cohort A (25% to 25%) and Group 2 Age cohort B (20% to 20%).
- The mean relative change from baseline in standardised seizure frequency was higher at 20 mg/kg than at the lower dose: -37.35% and -75.74% in Groups 1 and 2 of Age cohort A and -8.67% and -30.38% in Groups 1 and 2 of Age cohort B.

- The proportion of subjects with a relevant reduction from baseline (≥50%) in standardised seizure frequency in Age cohort A was higher at 20 mg/kg (50% had a 50% to 75% reduction and 50% had a >75% reduction) than at 5 mg/kg (25% had a >75% reduction). There was no dose response relationship with ESL in relevant changes from baseline in standardised seizure frequency in Age cohort B.
- An overall pattern of improvement (i.e. reduction in standardised seizure frequency) was observed in the mean relative change from baseline for complex partial seizures (-8.96% and -82.25% in Groups 1 and 2 of Age cohort A and 42.66% and -35.69% in Groups 1 and 2 of Age cohort B, respectively) and partial evolving to secondarily generalised seizures (-76.67% and -69.23% in Groups 1 and 2 of Age cohort A and -74.67% and -14.44% in Groups 1 and 2 of Age cohort B, respectively).

Overall

- No definite conclusion can be drawn regarding the optimal ESL dose for further investigation in Phase 3 studies based on the totality of PK, safety, and efficacy data from this study, which is due to the small sample size, different ESL treatment durations between the groups, and lack of placebo control.

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