2 SYNOPSIS

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	**INDIVIDUAL STUDY SYNOPSIS**	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093) **NAME OF ACTIVE INGREDIENT(S):** Eslicarbazepine acetate	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(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 a Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicentre Clinical Trial (BIA-2093-304)		
Investigators: A list of the Investigators and their affiliations is provided in Appendix 16.1.4.		
Study Sites: This study was conducted at 173 sites in 19 countries (North America, 89 sites; ROW, 84 sites).		
Publication (Reference): None.		
Studied Period: 03 August 2009 (FPFV Part II) to 12 April 2013 (LPLV Part II) 02 February 2011 (FPFV Part III) to 16 May 2018 (LPLV Part III)	Phase of Development: 3	

Objectives:

Primary: To evaluate the efficacy of Eslicarbazepine acetate (ESL) administered once daily (QD) at doses of 800 mg and 1200 mg compared with placebo as adjunctive therapy in patients with refractory partial epilepsy over a 12-week maintenance period.

The primary objective was evaluated in Part I of the study and is reported in the Part I Clinical Study Report (CSR).

Secondary:

The secondary objectives evaluated in Part II and Part III were:

- To evaluate the safety and tolerability of ESL at doses titrated to an efficacy or safety endpoint over a 1-year open-label period (Part II).
- To assess the maintenance of therapeutic effects of ESL over a 1-year open-label period (Part II).
- To assess the drug-drug pharmacokinetic (PK) interactions between ESL and concomitant anti-epileptic drugs (AEDs) in Part II of the study.
- To assess the health-related quality-of-life and depressive symptoms in Part II of the study.
- To study the effects of long-term use of ESL in Part III of the study.

Methodology: This was a 3-part multicenter study in patients with refractory simple partial or complex partial seizures, with or without secondary generalization.

Part I followed a parallel-group, randomized, placebo-controlled design and consisted of an 8-week baseline period followed by a double-blind 2-week titration period and a 12-week maintenance period. The total Part I duration was 22 weeks. The results of the Part I study are reported in the Part I CSR dated 29 June 2012.

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

Part II was a 1-year open-label study with ESL starting dosage of 800 mg QD for a month and titrated later upwards or downwards as clinically appropriate. Part III could be up to 2 years (the duration of Part III was longer than 2 years in some countries - Brazil: additional 1 year, USA and Canada: additional 2 years, Argentina and South Korea: additional 4 years) open-label extension of the ongoing treatment until the drug was made available on the market or until clinical development was discontinued.

Number of Patients: Sample size estimation for the primary efficacy endpoint based on Part I data is described in the CSR for Part I.

Part II was an extension to Part I including patients who had completed treatment in Part I, and Part III was an extension to Part II including patients who had completed treatment in Part II. Therefore no sample size calculation was applicable for these parts. The number of patients included was dependent on the number of patients who completed treatment in Part I and Part II and were willing to participate in the extension parts, ie, Part II and Part III, respectively.

A total of 504 patients completed the double-blind period (Part I) of the study. A total of 496/504 patients who completed Part I of the study entered the 1-year open-label period of the study (Part II): 186 patients from the Part I placebo group, 170 patients from the Part I ESL 800 mg group, and 140 patients from the Part I ESL 1200 mg group. Of these 496 patients, 479 patients (96.6%) received at least 1 dose of study treatment in the open-label extension period. There were 346 patients (69.8%) who completed Part II, and 150 patients (30.2%) prematurely discontinued from Part II.

A total of 240/346 patients who completed Part II of the study entered the open-label extension period of the study (Part III): 78 patients from the Part I placebo group; 87 patients from the Part I ESL 800 mg group; and 75 patients from the Part I ESL 1200 mg group. Of these 240 patients, 222 patients (92.5%) received at least 1 dose of study treatment in the open-label extension period. There were 54 patients (22.5%) who completed Part III, and 186 patients (77.5%) prematurely discontinued Part III.

Inclusion Criteria:

All patients who completed Part I were eligible to enter Part II. Patients who did not enter Part II were tapered off study drug while maintaining the blind.

At the end of Part II, all patients were eligible to enter Part III, which could be up to 2 years (the duration of Part III was longer than 2 years in some countries - Brazil: additional 1 year, USA and Canada: additional 2 years, Argentina and South Korea: additional 4 years) in duration or until the drug was made available on the market or until clinical development was discontinued.

For the inclusion/exclusion criteria for Part I, please refer to the Study Protocol (Appendix 16.1.1).

Test Product, Dose, Mode of Administration, and Batch Numbers:

All patients received ESL in Part II and Part III.

The tablets were taken QD by mouth, swallowed at approximately the same time each day, Patients were instructed not to chew or crush the study medication.

NAME OF COMPANY: BIAL - Portela & Cª, S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

Batch numbers used during Part II of the study

Penn/PCI Lot	Drug Lot	Number Range
C2683/B0229/B0230/B0231	11PCT02	300181-300480
C2683/B0244/B0243/B0242	11PCT02	600181-600390
C2683/B0284/B0282/B0283	11PCT02	600391-600510
C2683/B0303/B0304/B0305/B0310	11PCT02	600511-600870
C2683/B0323	110168	900001-901500
C2683/B0328	110167	901501-901650
C2683/B0387	110167	902252-902751
C2683/B0386	110169	902752-903751
C2683/B0343	110175	901651-901950
C2683/B0382	110175	901951-902251
C2683/B0577	110175	903752-904002
C2683/E0264	110439	906003-906402
C2683/F0069	140053	907913-908032
C2683/F0199	140054	908033-908152
C2683/F0251	140307	908153-908280
C2683/G0196	140308	908968-909100
C2683/J0046	150333	909102-909221

Batch numbers used during Part III of the study

Penn/PCI Lot	Drug Lot	Number Range
C2683/B0478	110170	X00001-X01000
C2683/D0374	110170	904003-905002
C2683/E0265	110170	905003-905692
C2683/F0019	120024	907147-907539
C2683/F0020	120024	907540-907912
C2683/F0301	140309	908281-908502
C2683/G0085	140851	908503-908723
C2683/G0084	140852	908724-908967

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

Duration of Treatment: The individual study duration was 1 year in Part II (for those patients who entered the 1-year open-label extension), and up to 2 years in Part III (the duration of Part III was longer than 2 years in some countries - Brazil: an additional 1 year, USA and Canada: an additional 2 years, Argentina and South Korea: an additional 4 years) or until the drug was made available on the market or until clinical development was discontinued.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

Not applicable as Part II and Part III was an open-label study.

Criteria for Evaluation:

Efficacy:

Efficacy variables of Part II (Clinical Global Impressions [CGI], seizure frequency, Seizure Severity Questionnaire [SSQ], Quality Of Life In Epilepsy Inventory - 31 [QOLIE-31], and Montgomery-Asberg Depression Rating Scale [MADRS]) were summarized and analyzed for the Safety population. For Part III only CGI variable was used.

For the derivation of all efficacy variables, the data collected during Part II and Part III of the study were used. For patients who discontinued before the completion of Part II or Part III, all data up to the point of discontinuation was used.

Safety:

All summaries of safety data were presented for the Safety population. Summaries of treatment-emergent adverse events (TEAEs) and serious TEAEs, laboratory results for available visits (Part II), vital signs, and 12-Lead electrocardiogram (ECG) were summarized by region and overall.

Data collected at the early discontinuation visit (EDV) were allocated to the "Last Assessment" time point (ie, EDV data were combined with the V10 or V28 or the post-study visit depending on the data being summarized and in which part [Part II or Part III] this visit occurred).

The treatment groups were presented as in Part I.

Study Endpoints:

Primary: The primary endpoint of standardized seizure frequency over the 12-week maintenance period was analyzed in Part I and the results are reported in the Part I CSR dated 29 June 2012.

Secondary Efficacy Endpoints:

- CGI scale
- Seizure frequency
- Standardized seizure frequency
- SSQ
- QOLIE-31 assessments
- Symptoms of depression assessed by the MADRS

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093) **NAME OF ACTIVE INGREDIENT(S):** Eslicarbazepine acetate	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(FOR NATIONAL AUTHORITY USE ONLY)

Secondary Safety Endpoints:

- Adverse events (AEs)
- Clinical laboratory test results (hematology, biochemistry, coagulation, thyroid function, bone turnover markers, and urinalysis)
- Vital sign measurements and body weight
- Physical and neurological examination
- 12-lead ECG readings
- Blood levels of ESL and concomitant AEDs
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

Sample size:

Part II was an extension to Part I including patients who completed treatment in Part I, and Part III was an extension to Part II including patients who completed treatment in Part II. Therefore no sample size calculation was applicable for these parts. The number of patients included would depend on the number of patients who completed treatment in Part I and Part II and were willing to participate in the extension parts, ie, Part II and Part III, respectively.

Analysis Population:

For summaries presented for Part II, patients who continued in Part II and received at least 1 dose of study treatment in Part II were considered in the Safety population.

For summaries presented only for Part III, patients who continued in Part III and received at least 1 dose of study treatment in Part III were considered in Safety population.

General Methods

All statistical methods were based on the International Conference on Harmonization (ICH) E9 document "Statistical Principles for Clinical Trials" and the Committee for Proprietary Medicinal Products "Note for guidance on clinical investigation of medicinal products in the treatment of epileptic disorders."

All efficacy and safety data were summarized for the Safety population. Patients were included in the efficacy and safety summaries according to the treatment that they actually received in Part I of the study and overall (Placebo, ESL 800 mg, ESL 1200 mg, and overall). Some tables were presented using modal daily dose, which was calculated by selecting the most frequent dose when the patient's daily dose was arranged in ascending order.

Continuous variables were summarized using descriptive statistics: number of patients with an observation [n], mean, standard deviation [SD], median and range (minimum [min], and maximum [max]). Unless otherwise specified, the mean and median for a continuous variable were presented to 1 more decimal place than the original (raw) values and the SD was presented to 2 more decimal places than the original values. The min and max were presented to the same number of decimal

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

places as the original values.

Categorical variables were summarized using frequencies (counts) and percentages. Unless otherwise stated, percentage calculations were based on the number of patients with non-missing data in each of the treatment groups. Percentages were presented to 1 decimal place. In cases where the percentage calculated was >0% and <0.1%, "<0.1%" was presented against the count. A percentage was not presented against 0 counts in the tables. A "Missing" category was only presented on the categorical summaries if 1 or more patients had missing data for a categorical variable.

For the CGI, SSQ, QOLIE-31, and MADRS, change from baseline was defined based on the data recorded at V2 (Week 0) in Part I. For safety data (laboratory data, vital signs, 12-lead ECG, physical and neurological examination), baseline was defined as V2 (Week 0) from Part I. If data were missing at V2, then the last non-missing value prior to the first dose administration (eg, at V1 [Week -8]) was used, where applicable.

All data collected in Part II and Part III were presented in individual patient data listings for all patients continuing in Part II or Part III. These were sorted by treatment received in Part I in the following order: Placebo, ESL 800 mg, and ESL 1200 mg, and sorted by patient number.

All statistical analyses were performed using SAS® Version 9.3 or higher.

Secondary Efficacy Analyses:

Efficacy variables of Part II (CGI, seizure frequency, SSQ, QOLIE-31, and MADRS) were summarized and analyzed for the Safety population. For Part III, only CGI was used.

In Part II, CGI was summarized only at V10 (V5 + 12 months) for patients who continued in Part III. In Part III, CGI was summarized at all visits including early discontinuation. Change from baseline in CGI severity scale was also summarized at all visits in Part II and Part III. The data at V2 (Week 0) in Part I was used to calculate the change from baseline unless it was missing, in which case the data from V1 (Screening) in Part I were used. Frequencies and percentages for CGI severity of illness were also presented by treatment group (as received in Part I) and overall.

Data on the type and frequency of seizures experienced during the Part II period were summarized by treatment group for the Safety population. These summaries were also presented by region and overall.

Percentage change from baseline in standardized seizure frequency during the maintenance period was calculated as percentages and was categorized as follows for the purpose of the summary and analysis:

- 100% reduction (seizure-free)
- >75% to <100% reduction
- ≥50% to ≤75% reduction
- 0% to <50% reduction
- >0% to <25% increase
- ≥25% increase (exacerbation)

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

Patients were also classified according to whether they were a responder (≥50% reduction in seizure frequency).
For SSQ, scores which were assessed at all visits in Part II (including early discontinuation for patients who withdrew early from Part II) were summarized using frequency counts and percentages.
For QOLIE-31 and MADRS, the scores were assessed by treatment group (as received in Part I) at V8 (V5 + 6 months), V10 (V5+12 months), or at early discontinuation (for patients who withdrew early from the study).

Secondary Safety Analyses:
All summaries of safety data were presented for the Safety population. Summaries of TEAEs and serious TEAEs, laboratory test results (hematology, blood chemistry, coagulation, and thyroid function) for available visits, vital signs (height, body weight, systolic and diastolic blood pressure, and pulse rate), 12-Lead ECG, physical and neurological examination, and C-SSRS were summarized by region and overall.

AEs were coded using the latest Medical Dictionary for Regulatory Activities, Version 13.1. Coding included system organ class and preferred term.

SUMMARY OF RESULTS

Efficacy Results:

- There was an improvement from baseline in the CGI severity of illness over both long-term open-label study periods, Part II and Part III. The mean (SD) change from baseline in CGI severity of illness score for the total patients in Part II was -1.0 (1.37), and in Part III was -0.7 (1.51). In Part II and Part III, there were 20.2% and 14.1% of patients, respectively, who had a CGI severity of illness score of "normal, not ill at all," compared to 8.4% patients at baseline. There were 6.0% and 33.3% of patients in Part II and 8.5% and 25.7% of patients in Part III, who had a CGI severity of illness score of "borderline ill" and "mildly ill," respectively, compared to 5.6% and 15.2% of patients at baseline. The results demonstrated an increment in overall patients reporting CGI severity of illness as "normal-not ill at all," "borderline ill," and "mildly ill" in Part II and Part III of the study, compared to baseline (before ESL treatment). The percentage of overall patients who reported a CGI severity of illness as "markedly ill" or "severely ill" together decreased in Part II (10/168 patients, 6.0%) and Part III (36/319 patients, 11.3%), compared to baseline (124/479 patients, 25.9%). Improvements in CGI severity of illness score in Part II and Part III from baseline were higher for patients in the Part I ESL 800 mg dosage group, which was also the most frequent modal daily dose during Part II and Part III.
- At V10 , 278/336 (82.7%) patients experienced seizure frequency reduction compared to baseline, while less than 10% of patients reported an increase up to 25% in seizure frequency (31/336, 9.2%) and an exacerbation of seizure frequency compared to baseline(≥25% increase) (23/336, 6.8%).
  At V10, 146/336 (43.5%) patients were responders, while 33/336 (9.8%) overall patients

achieved a 100% reduction in seizure frequency from baseline.

At the last assessment in Part II (V10 or early discontinuation), the majority of patients (355/450, 78.9%) experienced seizure frequency reduction from baseline, while 10.2% (46/450) and 9.6% (43/450) of patients reported an increase up to 25% in seizure frequency and an exacerbation of seizure frequency (≥25% increase) from baseline, respectively. The percentage of responders at the last assessment in Part II (V10 or early discontinuation) was 40.0% (180/450 patients), while 43/450 (9.6%) overall patients achieved a 100% reduction in seizure frequency from baseline.

These results show the same seizure frequency effects were observed even for those patients who discontinued the study prior to V10.

- At V10, 57/87 (65.5%) of patients with a modal daily dose of ESL 1600 mg had a seizure reduction up to 75%, while 10/22 (45.5%), 69/132 (52.3%), and 55/95 (57.9%) of patients with a modal daily dose of ESL 400 mg, 800 mg, and 1200 mg had up to 75% seizure reduction, respectively. Regarding an increase in seizure frequency (including ">0% to <25% increase" and "≥25% increase"), 5/22 (22.7%) patients with modal daily dose of ESL 400 mg had increased seizure frequency, compared to 16/132 (12.1%) of patients with ESL 800 mg, 17/95 (17.9%) with 1200 mg, and 16/87 (18.4%) with 1600 mg modal daily doses. Patients at 800 mg of modal daily dose had the highest percentage of responder rate, 62/132 (47.0%).

  At last assessment in Part II (V10 or early discontinuation), from 46/450 (10.2%) overall patients with an increase of seizure frequency up to 25%, 12/129 patients (9.3%) were at modal daily ESL dose 1200 mg and 6/104 patients (5.8%) were at modal daily ESL dose 1600 mg. Among 43/450 (9.6%) patients with an increase of ≥25% in seizure frequency, 13/129 patients (10.1%) were at modal daily ESL dose 1200 mg and 12/104 patients (11.5%) were at modal daily ESL dose 1600 mg. The higher percentage of responders (81/187, 43.3%) were taking 800 mg of modal daily dose. These results show that almost 75% of the patients (71/89, 79.8%) that reported seizure aggravation did not exploit the highest ESL dosage as adjunctive therapy.
- Per the SSQ scores, 54.5% and 49.1% of patients had a warning before seizures at baseline and at the last assessment in Part II, respectively. A smaller percentage of patients had movements or actions during seizures at the last assessment in Part II compared to baseline (75.3% versus 81.7%). A smaller percentage of patients took a while to recover after a seizure at the last assessment in Part II compared to baseline (60.3% versus 64.1%), had emotional effects (42.5% at V10/early discontinuation versus 46.7% at baseline), and had physical effects (72.6% at V10/early discontinuation versus 76.8% at baseline), while a slightly higher percentage of patients had cognitive effects at the last assessment in Part II compared to baseline (77.3% versus 75.2%). There was an improvement in the mean overall severity score at all visits during Part II, when compared to the baseline.
- In the total patients, the QOLIE-31 overall score increased (improved) from baseline to the last assessment (V10/early discontinuation) in Part II. The mean (SD) QOLIE-31 overall score at baseline was 119.8 (32.17), at V8 (open-label Month 4 to 6) was 125.7 (34.91), and at the last

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093) NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

assessment (V10/early discontinuation) was 122.1 (34.46), indicating an improvement in quality of life over the 1-year open-label treatment period. A greater improvement in the QOLIE-31 overall score from baseline to V8 (open-label Month 4 to 6) and from baseline to the last assessment (V10/early discontinuation) was observed in the treatment groups that had been assigned to ESL 800 mg and ESL 1200 mg in Part I compared to the treatment group that had been assigned to placebo in Part I. These results demonstrate the improvement in patient's quality of life over a long-term exposure to ESL treatment (12 weeks in Part I and 1 year in Part II) compared to 1 year exposure in Part II.

- In the total patients, the MADRS total score decreased (improved) from baseline to the last assessment in Part II. The mean (SD) MADRS total score at baseline was 7.7 (7.17), at V8 (open-label Month 4 to 6) was 6.5 (6.76), and at the last assessment (V10/early discontinuation) was 6.9 (7.28), indicating a reduction in depressive symptoms over the 1-year open-label treatment period.

Safety Results:

- During Part II of the study, 38 patients (7.9%) experienced at least 1 serious TEAE, of which 20 patients (4.2%) experienced at least 1 serious TEAE that was considered to be potentially related to the study drug. The most common serious TEAEs related to study drug were partial seizures (reported in 0.8% of patients overall) and suicide attempt, therapeutic agent toxicity, and hyponatremia (each reported in 0.4% of patients overall).
- During Part III of the study, 36 patients (16.2%) experienced at least 1 serious TEAE, of which 13 patients (5.9%) experienced at least 1 serious TEAE that was considered to be potentially related to the study drug. The most common serious TEAEs related to study drug were partial seizures and hyponatremia (each reported in 2 patients [0.9%] overall).
- During Part II and Part III of the study, 31 patients (6.5%) and 7 patients (3.2%) experienced at least 1 TEAE leading to discontinuation of study drug, respectively. The most common TEAE leading to discontinuation of study drug during Part II was dizziness (reported in 1.3% of patients overall).
- A total of 361 patients (75.4%) and 148 patients (66.7%) experienced at least 1 TEAE during Part II and Part III of the study, respectively. The most common TEAEs during Part II were dizziness (18.4% of patients overall), headache (12.1% of patients overall), and somnolence (8.8% of patients overall), while during Part III were headache (13.1% of patients overall), dizziness (9.5% of patients overall), and partial seizures and tremor (reported in 5.4% of patients overall in each preferred term).
- A total of 281 patients (58.7%) and 75 patients (33.8%) experienced at least 1 TEAE which was assessed to be potentially related to study drug during Part II and Part III of the study, respectively. The most common TEAEs related to study drug during Part II were dizziness (16.7% of patients overall), somnolence (7.7% of patients overall), and diplopia (7.5% of patients overall), while during Part III were dizziness (5.9% of patients overall) and headache (5.0% of patients overall).

NAME OF COMPANY: BIAL - Portela & C[a], S.A. Sunovion Pharmaceuticals Inc.	INDIVIDUAL STUDY SYNOPSIS	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

- During Part II and III the incidence of any TEAEs, any potentially related TEAEs, and any serious potentially related TEAEs was the lowest in patients receiving ESL modal daily dose of 800 mg, which was the most frequent modal daily dose during Part II and Part III.
- The majority of TEAEs reported during Part II and Part III of the study were of mild or moderate intensity. TEAEs of severe intensity were reported in 11.5% and 12.6% of patients overall in Part II and III, respectively. In Part II, TEAEs that were reported as severe occurring in ≥1% of patients in any treatment group (as assigned in Part I) included: constipation, dyspepsia, therapeutic agent toxicity, dizziness, headache, partial seizures, somnolence, and nephrolithiasis. In Part III, TEAEs that were reported as severe occurring in ≥2% of patients in any treatment group (as assigned in Part I) included vertigo, dizziness, status epilepticus, and pneumonia aspiration.
- Four deaths occurred during the study. One patient died due to sudden unexplained death in epilepsy during Part II; the Principal Investigator (PI) considered this event as not related to the study drug. A second patient died due to a stab wound during Part II; the PI considered this event as not related to the study drug. A third patient died due to sudden unexplained death in epilepsy during Part III; the PI considered this event as not related to the study drug. A fourth patient died due to sudden unexplained death in epilepsy during Part III; the PI considered this event as possibly related to the study drug.
- Minimal changes from baseline were observed in hematology, biochemistry, coagulation, and thyroid function laboratory parameters over the study, and only small proportions of patients had laboratory findings that were outside of the normal range and considered to be clinically significant or PCS.
- Overall 35 patients (7.3%) showed a change from baseline of < -10 mEq/L in blood sodium levels at any post-baseline visit.
- There were minor clinically relevant shifts from normal to abnormal in 12-lead ECG recordings during the study.
- There were minor shifts from normal to abnormal in physical and neurological examinations during the study. Any negative shifts for mental status, cranial nerves, motor systems, sensory systems, coordination, and gait were minimal.
- Minimal changes from baseline were observed in vital signs and body weight over the study and only a small proportion of patients had changes that were considered to be PCS.
- Results for C-SSRS suicidality at baseline versus at the last assessment in Part II included: 22 patients (6.1%) had any suicidality at baseline (defined as any suicidal ideation or any suicidal behavior) versus 8 patients (2.0%) with any suicidality at the last assessment (defined as the emergence of any suicidal ideation, worsening of pre-existing suicidal ideation, or any suicidal behavior); no patients at baseline versus 3 patients (0.7%) at last assessment had any suicidal behavior; and 22 patients (6.1%) at baseline versus 12 patients (3.0%) at last assessment had suicidal ideation. Therefore, in general C-SSRS slightly improved from baseline to last assessment in Part II.

NAME OF COMPANY: BIAL - Portela & Cª, S.A. Sunovion Pharmaceuticals Inc.	**INDIVIDUAL STUDY SYNOPSIS**	
NAME OF FINISHED PRODUCT: Eslicarbazepine acetate (BIA 2-093; SEP-0002093)	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT(S): Eslicarbazepine acetate	**Volume:** **Page:**	

Conclusions:

- The therapeutic effects of ESL were maintained over the open-label extension period (Part II and Part III).
- Long-term use of ESL during the open-label extension period was found to be safe and well tolerated.

Date of Report: 29 July 2019