London, 28 June 2018
EMA/476835/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Zebinix

International non-proprietary name: eslicarbazepine acetate

Procedure no.: EMA/H/C/988/P46 025

Marketing authorisation holder (MAH): Bial-Portela & C[a]., S.A.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 23rd February 2018, the MAH submitted the final clinical study report (CSR) for the Parts III to V of Study BIA-2093-305 - a phase III, double-blind, randomised, placebo controlled, parallel group, multi-centre trial - to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in children aged 2 years to less than 18 years, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview and a line listing for the studies of the development program have also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the CSR for Parts I and II of BIA-2093-305 was submitted to the EMA on 9th April 2014, in accordance with the Article 46 of Regulation (EC) No 1901/2006, as amended. The double-blind (Part I) and 1 year open label extension (Part II) are part of the PIP for eslicarbazepine acetate (P/0015/2015 issued on 30th January 2015).

The three subsequent open-label extension periods of the study (Parts III to V) are not part of the PIP. BIAL, as sponsor of the study, decided to report these extensions, even though there were still 12 patients ongoing for the Asian region. For that purpose, a cut-off date for the Asian patients was set on 16th June 2014. The CSR, dated 16th December 2014, was submitted to the EMA on 25th February 2015 (under procedure no. EMEA/H/C/000988/P46/023.1).

All patients have now completed the trial (the last ongoing patient completed part V of the study on the 24th August 2017). With the present application, BIAL intends to submit the CSR (submitted in the scope of procedure P46/023.1) now updated to include the data from parts III to V for the remaining patients from the Asian region. The study has now been totally completed with the last ongoing patient completing part V of the study on the 24th August 2017. The CSR for parts III, IV and V dated 16th December 2014 has been updated and incorporates the data from parts IV and V related to patients from the Asian region. The CSR for parts III, IV and V including data for all patients is dated 19th February 2018.

Finally the MAH states that Study BIA-2093-305 is part of a clinical development program. The MAH states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for Zebinix and therefore do not require taking further regulatory action on the marketing authorisation for Zebinix.

2.2. Information on the pharmaceutical formulation used in the study

All patients received open-label ESL during the two 1-year open-label extension periods (Parts III and IV) and the subsequent 2-year open-label extension period (Part V). Study treatments were provided as an oral suspension (50 mg/mL) for use in the age group of 2–6 years (stratum I) or as white oblong tablets (200 mg) for use in the older children and adolescents (≥7 years of age; strata II and III).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the procedures and results related to Part III, IV and V of Study BIA-2093-305. Of the 183 patients who completed Parts I and II of the study, 152 patients were enrolled into Part III, 94 entered in Part IV and 67 in Part V.

Study BIA-2093-305 was a multinational, phase III, double-blind, randomised, placebo-controlled, parallel-group in 304 paediatric patients (treated) with a diagnosis of partial onset seizures that were refractory to treatment with 1 to 2 AEDs.

2.3.2. Clinical study

Clinical study number and title

Parts III, IV and V of Study BIA-2093-305

Description

Title of the study: Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial – Part III-V.

Study BIA-2093-305 was a multinational, phase III, double-blind, randomised, placebo-controlled, parallel-group in 304 paediatric patients (treated) with a diagnosis of partial onset seizures that were refractory to treatment with 1 to 2 AEDs.

Methods

Objective(s)

The objective pertaining to the open-label extensions of the study (Part II-V) was to assess the maintenance of the therapeutic effect of eslicarbazepine acetate (ESL) during long-term treatment in Part II, Part III, Part IV, and Part V of the study, while ensuring the provision of ESL to the patients who participated in the original investigational plan comprising Parts I and II. This was one of the secondary objectives of the entire study, which was primarily designed to assess the efficacy of ESL as an adjunctive therapy in children and adolescents with refractory partial seizures.

The primary study objective was to evaluate the efficacy of ESL (responder rate and relative reduction of standardised 4 week seizure frequency) in comparison with placebo as adjunctive therapy in children and adolescents with refractory partial onset seizures over a 18-week DB (Double Blind, Part I) period. Efficacy and tolerability of ESL in comparison with placebo, over a 12-week maintenance period preceded by a 6-week titration period was also evaluated. The long-term effect of ESL on global cognitive skills, tolerability, and sustainability of the therapeutic effect of ESL during a one-year open-label (OL, Part II) period was also evaluated.

After completion of Part II, patients had the option to continue treatment in up to 3 subsequent open-label extension periods: Part III (1 year), Part IV (1 year), and Part V (2 years). The study designs of the 1-year extension Parts III and IV were identical and consisted of a 48-week open-label extension period. Part V was a 2-year open-label extension period and the last planned period of the study.

In the following, only the procedures and results related to Part III, IV and V of the study BIA-2093-305 are described. Of the 183 patients who completed Parts I and II of the study, 152 patients were enrolled into Part III, 94 entered in Part IV and 67 in Part V.

Study design

This was a multinational phase III study, which consisted of a randomised, double-blind, placebo-controlled, parallel-group part (Part I), and 4 subsequent long-term, open-label extension periods (Part II-V). Part I consisted of an 8-week observational baseline period followed by a 6-week double-blind titration period, a 12-week double-blind maintenance period, an up to 4-week double-blind tapering-off period, and a 4-week observational follow-up period (unless the patient continued with open-label treatment in Part II). The 1:1 randomisation was stratified by age group (2-6 years [stratum I], 7-11 years [stratum II], or 12-18 years [stratum III]). After completion of Part I, patients had the option to enter a long-term, open-label extension period to receive ESL for 1 year (Part II). After completion of Part II, patients had the option to continue treatment in up to 3 subsequent open-label extension periods:

Part III (1 year), Part IV (1 year), and Part V (2 years).

The study designs of the 1-year extension Parts III and IV were identical and consisted of a 48-week open-label extension period. Part V was a 2-year open-label extension period and the last planned period of the study.

In each of Parts III, IV, and V, the starting ESL dose was the same dose that the patient was receiving at the end of the previous extension period (i.e. Parts II, III, and IV, respectively), unless the investigator decided to titrate this dose to achieve further reduction in seizure frequency or due to the occurrence of any intolerable adverse events (AEs). The daily dose could be titrated in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to maximum 1200 mg/day for patients with high body weight).

At the end of Parts III and IV, patients had the option to continue receiving ESL by entering the subsequent extension period (Part IV or Part V) until marketing authorisation was granted (or clinical development was discontinued) if both parent(s)/guardian(s)/patient and his/her physician agreed that this was in the patient's best interest. If the patient did not continue receiving ESL after an open-label extension period or in case of early discontinuation of ESL during an open-label extension period, the respective patient entered a tapering-off/follow-up period, in which study treatment was down-titrated and standard antiepileptic treatment introduced.

Study population /Sample size

Number of patients

Planned to be randomised in Part I: 252 patients (126 per treatment group)

Treated in Part I: 304 patients (155 with ESL, 149 with placebo)

Treated in Part II: 260 patients (128 with ESL in Part I, 132 with placebo in Part I)

Treated in Part III: 152 patients (65 with ESL in Part I, 87 with placebo in Part I)

Treated in Part IV: 94 patients (44 with ESL in Part I, 50 with placebo in Part I)

Treated in Part V: 67 patients (33 with ESL in Part I, 34 with placebo in Part I)

Analysed for efficacy in Part III-V: 148 patients (intention-to-treat [ITT])

Analysed for safety in Part III-V: 152 patients (i.e. all treated patients)

Treatments

During Part III-V, all patients received ESL. ESL was provided as an oral suspension (50 mg/mL) for use in the age group of 2–6 years (stratum I) or as white oblong tablets (200 mg) for use in the older children and adolescents (≥7 years of age; strata II and III). Batch numbers are available in the appendix of the clinical study report. Duration of treatment was up to 26 weeks in Part I; 12 months in Parts II, III, and IV, and 24 months in Part V. Thus, the treatment duration in Part III-V was 48 months.

Outcomes/endpoints

Efficacy during Part III-V:

- Standardised seizure frequency per period of Baseline Part I, Baseline Part III-V, each sub-period (by 12-week intervals), and overall.
- Absolute changes in seizure frequency per 12-week interval, defined as the difference between standardised seizure frequencies during each time interval and Baseline Part I and Baseline Part III-V.
- Relative changes in seizure frequency per 12-week interval calculated as absolute changes divided by the standardised seizure frequency at Baseline Part I and Baseline Part III–V.
- Responders per 12-week interval: responders were defined as those patients with a relative seizure reduction of at least 50% in the respective time interval compared to Baseline Part I and Baseline Part III–V.
- Categorised relative change from Baseline Part I and from Baseline Part III–V in seizure frequency per 12-week interval (≥25%; >-50% to <25%; ≥-75% to ≤-50%; <-75%).
- Exacerbations in seizure frequency (increase in relative change in seizure frequency of ≥25%) per time interval compared to Baseline Part I and Baseline Part III–V.
- Proportion of patients who are seizure-free per 12-week interval.
- Standardised seizure frequency per 12-week interval by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other); seizures with missing seizure type information were considered as unclassified for the analysis.
- Number of days with seizures (standardised to 4-week time period).
- Seizure duration (as classified in the diary): <30sec, ≥30 sec to <1 min, ≥1 min to <5 min, ≥5 min, unknown.

- Treatment retention time, defined as the time to first occurrence of 1 of the following during treatment: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period of Part I).
- Seizure severity assessed with the 13-item Hague seizure severity scale.

Safety during Part III-V:

Safety was assessed on the basis of the following observations and measurements:

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

Statistical Methods

The methods presented here refer to the analysis of data collected during Parts III, IV, and V of the study. All 3 parts were analysed jointly, i.e. as 1 period. All evaluations were of descriptive nature. No confirmatory analysis was carried out.

Efficacy analysis for Part III-V:

The efficacy analyses were performed for the ITT set, which included all patients treated with at least 1 dose of ESL during Part III-V and who had at least 1 seizure frequency assessment during Part III-V. Descriptive statistics, including absolute and relative change, are presented for each efficacy variable for Baseline Part I, Baseline Part III-V, each 12-week interval, each sub-period, and overall. Changes from Baseline (safety) and Baseline (OL) are also presented for the summary score of the Hague seizure severity scale. Selected analyses were also performed for subgroups by seizure type, age stratum, the subset of patients who switched to monotherapy during Part III-V, and for completers. Additionally, the Kaplan-Meier estimate for the median treatment retention time and its corresponding 95% confidence interval are presented. This analysis was performed for the safety set.

Safety analysis for Part III-V:

All safety variables were analysed descriptively. Selected analyses were also performed by age stratum. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number and frequencies of patients with treatment-emergent adverse events (TEAEs) are given by primary system organ class (SOC) and preferred term within each SOC and by treatment group for any TEAE category. The number and frequency of patients with clinically significant values at each visit are presented for

vital signs. All laboratory values were classified as normal or abnormal according to the laboratories normal ranges and as clinically significant or not clinically significant according to the investigator.

Recruitment / Number analysed

Planned to be randomised in Part I: 252 patients (126 per treatment group)

Treated in Part I: 304 patients (155 with ESL, 149 with placebo)

Treated in Part II: 260 patients (128 with ESL in Part I, 132 with placebo in Part I)

Treated in Part III: 152 patients (65 with ESL in Part I, 87 with placebo in Part I)

Treated in Part IV: 94 patients (44 with ESL in Part I, 50 with placebo in Part I)

Treated in Part V: 67 patients (33 with ESL in Part I, 34 with placebo in Part I)

Analysed for efficacy in Part III-V: 148 patients (intention-to-treat [ITT])

Analysed for safety in Part III-V: 152 patients (i.e. all treated patients)

Baseline data

Baseline definitions:

- Baseline (OL): Data from the visit when study medication for the open-label extension (Part II) was dispensed.
- Baseline (safety): Baseline (OL) for patients treated with placebo during Part I; baseline visit as defined for the analysis of the double-blind part for patients treated with ESL during Part I.
- The following baseline periods were defined as reference periods in efficacy analyses:
- Baseline Part I: from Visit V1 (screening visit) to the day before V2 of Part I.
- Baseline Part III–V: the last 4 weeks (in Part II) prior to first intake (Day 1) in Part III–V.

Efficacy results

The assessment of the long-term efficacy of ESL in Part III–V showed that the improvements in efficacy observed at the end of Part I–II were at least maintained throughout Part III-V. This maintenance could be demonstrated for all time intervals in Part III–V in terms of negative median relative changes of standardised seizure frequency as compared to Baseline Part III-V. In addition, the proportion of patients with seizure exacerbations did not exceed the total responder rate (i.e. the proportion of patients with seizure reduction of at least 50%) in most of the 12-week intervals.

Efficacy findings in Part III-V per variable in the total ITT set were as follows:

- The total responder rate during Part III–V was 26.6% compared to Baseline Part III–V and 70.3 % compared to Baseline Part I. Responder rates per 12-week intervals ranged between 21.9% (week 13-24) and 52.9% (week 145-156) with at least slightly higher responder rates

in Part V (week 97-108 onwards). However, due to high fluctuations between intervals no clear trend could be confirmed. Efficacy findings beyond week 205 should be interpreted with caution due to the small number of patients remaining on study treatment.

- The total median standardised seizure frequency during Part III–V was 2.4, resulting in a median relative change from Baseline Part III–V of -22.9%. The median relative change from Baseline Part III–V reached a decrease of up to -50.0% in the total population during week 145-156. The overall median relative decrease was greater in patients treated with ESL in Part I (-25.8%) than in patients treated with placebo in Part I (-16.4%).
- 12 patients (8.1%) were seizure-free during Part III–V. The proportion of seizure-free patients ranged from 16.7% to 28.8% of patients during each of the 12-week intervals with fluctuations in both previous treatment groups.
- In the total population, the proportion of patients with a seizure reduction between 50% and 75% compared to Baseline Part III–V was 14.7% (12.5% in patients treated with ESL in Part I and 16.4% in those treated with placebo in Part I), the proportion of patients with a seizure reduction greater than 75% was 11.9% (16.7% in patients treated with ESL in Part I and 8.2% in those treated with placebo in Part I. The overall proportion of patients with exacerbation (increase of ≥25%) compared to Baseline Part III–V was 25.7% and remained below the responder rate for most of the 12-week intervals. No consistent trend over time was observed for the proportion of patients in any category.
- No clinically relevant changes in the total score of the Hague seizure severity scale were seen during Part III–V.
- The median standardised number of days with seizures was 2.3 days overall, fluctuating close to 2 days for most time intervals during the course of the study until the week 133-144 interval and slightly increased to median values close to 3.5 days in most 12-week intervals after the week 145-156 interval.

The improvement over time in a study with such a large duration should be interpreted with caution, keeping in mind the selection bias over time which in general most likely favours the patients having better outcomes. However, in this study the number of patients terminating prematurely due to lack of efficacy was low (9 patients overall: 8 patients in Part III and 1 patient in Part V) and withdrawals most frequently were due to the specific request of the sponsor to switch to a compassionate use/donation program, i.e. treatment in these patients was continued. In addition, for all efficacy parameters comparison to Baseline Part III-V revealed overall and for most of the individual 12-week intervals that efficacy results after at least one year of ESL treatment, assessed during the last 4 weeks of Part II could be at least maintained. Thus, ongoing therapeutic benefits during longterm treatment can be assumed.

Safety results

Safety results during Part III–V did not reveal any findings of concern with regard to the long-term safety of ESL in the included population. Frequencies for AE categories were generally similar between groups by treatment received in Part I. During Part III–V, 63.8% of patients had at least 1 TEAE and in no more than 14.5% of the patients any TEAE was considered at least possibly related to study drug. Most frequently reported TEAEs were convulsion, nasopharyngitis, pyrexia, bronchitis and upper respiratory tract infection, and the most frequently reported related TEAE was increased GGT.

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

- 97 patients (63.8%) experienced at least 1 TEAE. Most frequently reported TEAEs were convulsion (20 patients [13.2%]), nasopharyngitis and pyrexia (16 10.5%] each), as well as bronchitis and upper respiratory tract infection (13 [8.6%]).
- 22 patients (14.5%) had at least 1 TEAE that was considered at least possibly related to ESL by the investigator. The most commonly reported such TEAE was increased gammaglutamyltransferase (GGT) (4 patients [2.6%]).
- 19 patients (12.5%) had at least 1 serious TEAE; the only serious TEAEs reported by more than 1 patient were pneumonia (4 patients [2.6%]) as well as asthma, bronchopneumonia, convulsion, dengue fever, and status epilepticus (2 patients [1.3%] each).
- No serious TEAEs were considered to be related to the study medication by the investigator, and no TEAEs (excluding death) led to treatment discontinuation.
- 2 patients died during Part III–V. One patient died due to a severe case of bronchopneumonia and one patient died due to infection and disseminated intravascular coagulation. For both patients, SAEs leading to death were assessed by the investigator as unrelated to the study drug.
- Changes from a normal laboratory value at Baseline (OL) to an abnormal value at endpoint occurred in no more than 23.1% of patients per laboratory parameter. Changes to abnormally low value were most frequently reported for bicarbonate, free T4 and total T4 while changes to abnormally high values were most frequently observed for GGT. For any laboratory parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of GGT (clinically significant for 15 patients [9.9%], leukocytes (clinically significant for 6 patients [3.9%]) and creatine kinase, activated by Nacetyl cysteine (clinically significant for 5 patients [3.3%]).
- The majority of the 148 patients who had post-baseline measurements of sodium levels, had normal sodium levels: 18 patients (11.8%) had low sodium levels and no patients had high sodium levels. Most of the patients (14/18) with low sodium levels had values >130 to 135 mmol/L, and 2 patients each had values >125 to 130 mmol/L and ≤125 mmol/L, respectively. Only one of these sodium levels was considered clinically significant.
- No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index, head circumference or sexual maturation assessment. For 7 patients, ECG abnormalities were reported as TEAEs during Part III–V. Out of these, 2 TEAS (electrocardiogram PR shortened and bundle branch block right) were assessed to be possibly related to IMP.

Compared to the safety results in Parts I and II (summarised in the final CSR Parts I and II, dated 20 March 2014), and despite the longer treatment duration in Part III-V, lower frequencies were observed in Part III–V for patients with at least 1 TEAE, patients with possibly-related TEAEs, and TEAEs leading to treatment discontinuation (2 cases of death in Part III–V). Frequencies of serious TEAEs were slightly higher, but death rates were comparable.

2.3.3. Discussion on clinical aspects

In the final 3 open-label treatment periods of this confirmatory, multinational, phase III study in children and adolescents with refractory partial seizures, the improved efficacy after the first 2 parts of the study was maintained or further improved with continued ESL treatment as adjunctive therapy. Safety results were consistent with the known safety profile of ESL without any findings of concern.

No new age or dose specific safety concern was identified from the overall evaluated data, but the incidence of TEAEs and possibly related TEAEs in the age group above 6 years seems to be more favourable in the higher dose groups.

Post-marketing experience on off-label use in the paediatric population is in agreement with the safety profile known to date. The dose range used from post-marketing clinical experience seems to be in agreement with the proposed dosage for children above 6 years. The analysis of the safety information received does not provide reasons to assume a different safety profile for ESL compared to adults.

3. Rapporteur's overall conclusion and recommendation

Results have been submitted from the open label extensions of study BIA-2093-305, including two 1-year open-label extension periods (Parts III and IV) and a subsequent 2-year open-label extension period (Part V). Study 305 (including part III-V) does allow for conclusion of efficacy of ESL as adjunctive treatment in paediatric patients above 6 years with refractory partial onset seizures with or without secondary generalisation. The current information given in the PI of Zebinix, that efficacy of eslicarbazepine acetate in children aged 2 to 6 years has not yet been established is considered further valid. No new unique safety concerns occurred within the final periods of this study. The AE profile was consistent with previous data on ESL.

The SmPC currently includes short term efficacy/safety paediatric data. It is noted that also paediatric data from the part II (1 year open label extension to BIA-2093-305) are also missing from the SmPC. Long term efficacy and safety paediatric data are relevant to prescribers, so it is proposed that they are added in relevant sections of the SmPC.

The MAH is requested to summarise the long term paediatric efficacy data (parts II, III, IV and V of study BIA-2093-305) and to propose SmPC update for section 5.1. A brief sentence should be included stating that given the limitations of open label uncontrolled data, the efficacy results were overall maintained for the specified long-term period, including the number of patients followed-up.

The MAH is asked to suggest SmPC updates for section 4.8 clarifying whether the long-term safety profile in children was similar to the one observed in the short term. The occurrence of "hyponatraemia in children" in the long term studies and its frequency should also be added in this section, as currently the SmPC states: "Hyponatraemia was only reported in adult population."

☒ Fulfilled:

No regulatory action required. The SmPC should be updated as outlined above.

Annex. Line listing of all the studies included in the development program, listed by chronological date of completion:

Non clinical studies

Product Name: Zebinix **Active substance: eslicarbazepine acetate**

Study title	Study number	Date of completion	Date of submission of final study report
Toxicity and toxicokinetic study of 28 days repeat doses of ESL in juvenile dogs	WIL-682001	September 2009	The report was included in the submission of paediatric indication (June 2015)
10-month oral (gavage) toxicity study of ESL in juvenile dogs with a 2-month recovery period	WIL-682002	April 2010	The report was included in the submission of paediatric indication (June 2015)

Clinical studies

Product Name: Zebinix **Active substance: eslicarbazepine acetate**

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, multiple dose study to evaluate pharmacokinetics, safety and tolerability of eslicarbazepine acetate (ESL) for partial onset epilepsy in paediatric patients from 2 years to less than 18 years	BIA-2093-202	April 2006	The CSR was included in the initial MAA of Zebinix for adjunct therapy in adult population, in 2008
Double-blind study in paediatric epileptic subjects aged from 5 to less than 8 years to compare the subject preference for ESL suspension formulation with alternative flavours	BIA-2093-212	December 2012	June 2013
Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures including effect on cognitive function of eslicarbazepine acetate (ESL) as adjunctive therapy in children aged 6 years to less than 16 years with a one year open label extension phase	BIA-2093-208	May 2013 (Part II) (Part III)	December 2013 (The final study report includes Part I and Part II) October 2015

Study title	Study number	Date of completion	Date of submission of final study report
Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in children aged 2 years to less than 18 years with a one year open label extension phase	BIA-2093-305	October 2013 (Part II) June 2014 (cut-off date for Asia) August 2017 (Parts IV and V in Asia)	April 2014 (The final study report includes Part I and Part II) February 2015 (The study report includes Part III, IV and V from Europe and part III from Asia). February 2018 (The study report includes Parts III to V from Asia)