25 June 2015
EMA/475393/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zebinix

International non-proprietary name: eslicarbazepine acetate

Procedure No. EMEA/H/C/988 P46 023.1

Note

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

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Introduction

On 25th February 2015, the MAH submitted a completed paediatric study for eslicarbazepine acetate, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Parts III to V (three subsequent open-label extension periods) of Study BIA-2093-305, for which the clinical study report is now submitted, are not part of the PIP for eslicarbazepine acetate (P/0015/2015 issued on 30 January 2015). Parts I (double-blind) and II (1 year open extension) of study BIA-2093-305 are part of the respective PIP and have already been submitted to and assessed by the EMA in 2014.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that study titled "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" No BIA-2093-305 is part of a clinical development program and that the variation application consisting of the full relevant data package (i.e. containing several studies) covering the development of eslicarbazepine acetate as adjunctive therapy for refractory partial seizures in children aged 2 to below 18 years old is expected to be submitted by July 2015. In addition, an extension application to register a new pharmaceutical form (oral suspension 50 mg/ml) is expected to be submitted simultaneously. A line listing of all the concerned studies is annexed.

Information on the pharmaceutical formulation used in the study(ies)

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).

On 19 Jun 2009 it was decided to recall all oral suspension study medication from the study due to quality issues; however, after closure of the part I database and unblinding, it was found that this quality issue only affected the placebo formulation of the oral suspension.

Clinical aspects

1. Introduction

The MAH submitted a final report for parts III to V of study BIA-2093-305, the three last of four open-label extension parts of a phase III study investigating eslicarbazepine acetate as adjunctive treatment in paediatric patients with partial onset seizures that were refractory to treatment with 1 to 2 AEDs.

2. Clinical study

Study BIA-2093-305, title "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"

Description

This was a phase III, double-blind, randomised, placebo controlled, multicentre, parallel group (part I) trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in children aged 2 to less than 18 years with a diagnosis of partial onset seizures that were refractory to treatment with 1 to 2 anti-epileptic drugs (AEDs) with 4 subsequent open-label extension phases (part II-V).

Parts I and II of the study have already been submitted to and assessed by the EMA. In part I of study 305 no superior efficacy of ESL over placebo could be shown as adjunctive treatment in children ≥ 2 years of age with refractory partial onset seizures.

A separate report for parts III-V has now been submitted.

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 last planned part of the study).

The study was performed in 43 centres in 14 counties in Europe and Asia.

Methods

- Objective(s)

The objective pertaining to the open-label extensions of the study (Parts 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.

- Study design/Treatments

A phase III randomised, double blind, placebo-controlled, multinational parallel-group (part I) study with 4 subsequent long-term, open-label extension periods (parts II-V).

Parts III, IV and V:

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 AEs.

The daily dose was titrated by the investigator according to clinical response 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).

- Study population

Main criteria for inclusion (in study part I):

• Diagnosis of epilepsy for at least 6 months prior to enrolment; for patients from the Czech Republic: diagnosis of epilepsy for at least 24 months prior to enrolment (Amendment 1 Czech Republic, 05 Oct 2007).

• Children 2 to 16 years of age; as per Global Amendment 4 (16 Sep 2010): children 2 to 18 years of age; for patients from Romania: children 2 to 17 years of age (Amendment 1 Romania, 09 Nov 2010).

• At least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 1 or 2 AEDs; for patients from the Czech Republic: at least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 2 AEDs (Amendment 1 Czech Republic, 05 Oct 2007).

• At least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period.

• Stable dose regimen of AEDs during the 8-week baseline period.

• Current treatment with 1 or 2 AEDs (any AED except oxcarbazepine); if present, vagus nerve stimulation is considered an AED (this last addition was introduced per Global Amendment 1 [20 Dec 2007]).

Patients with primarily generalised seizures, known progressive neurological disorders, known second or third degree atrioventricular block (introduced per Global Amendment 4 [16 Sep 2010]), history of status epilepticus within the 3 months prior to enrolment, seizures of non-epileptic origin, Lennox-Gastaut syndrome or West syndrome were excluded from the study.

• Sample size

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: 81 patients (37 with ESL in Part I, 44 with placebo in Part I),
Treated in part V: 56 patients (27 with ESL in Part I, 29 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).

Table 1 - Completion rates and reasons for study discontinuation during part III-V (all patients

enrolled)

	Number (%) of patients		
	Part III (N=152)	Part IV (N=81)	Part V (N=56)
Completed part	107 (70.4)	62 (40.8)	4 (2.6)
Discontinued after completing part	26 (17.1)	6 (3.9)	0
Withdrew during part	45 (29.6)	19 (12.5)	52 (34.2)
Reason for withdrawal			
At the specific request of the sponsor [a]	30 (19.7)	9 (5.9)	43 (28.3)
At their own request or at the request of their legally authorised representative	5 (3.3)	4 (2.6)	3 (2.0)
Lack of efficacy	8 (5.3)	0	1 (0.7)
Other reason	1 (0.7)	5 (3.3)	4 (2.6)
Adverse event	1 (0.7)	0	0
Non-response with increase of seizure frequency by 100% or more during the treatment periods compared to the baseline period	0	1 (0.7)	0
If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being	0	0	1 (0.7)

ESL = eslicarbazepine acetate; N = number of patients.

Note: All percentages are calculated based on the number of patients enrolled and treated in Part III-V (N=152).

[a] Mainly due to the switch to continued treatment with ESL as part of a compassionate use/donation program.

Source: Section 15, Table P3-5.A.3.1

The MAH decided to report these extension periods of study BIA-2093-305 after the last patient in Europe had completed part V of the study in November 2013, although there are still 12 patients ongoing for Asia region. A cut-off date for Asian patients of 16th June 2014 was established. The CSR is dated 16th December 2014.

Rapporteur's comment:

The most frequent reason for study discontinuation during parts III-V was due to switch to continued treatment with ESL as part of a compassionate use program.

During study parts III, IV or V, respectively 0%-5.3% of study subjects discontinued due to lack of efficacy and 0% -0.7% discontinued due to "adverse event".

- Outcomes/endpoints

Efficacy during part III-V:

● Standardised seizure frequency per period of Baseline Part I, Baseline Part III-V, each subperiod (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:
● 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

Part III-V:
In general, results are displayed for the total population and by the treatment patients received during Part I (ESL or placebo). All evaluations were of descriptive nature. No confirmatory analysis was carried out.

The following baseline periods were defined as reference periods in efficacy analyses:
• **Baseline Part I**: from Visit V1 (screening visit) to the day before Visit 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.

- Baseline data

The median standardised number of seizures during the baseline period (part I) was lower in the ESL group (11.5; range: 3.7, 605.8) than in the placebo group (17.0; range: 3.9, 1972.5).

Table 2 - Standardised seizure frequency during the baseline period (safety set)

Parameter	Placebo in Part I (N=87)			ESL in Part I (N=65)		
	n (%)	Mean (SD)	Median (range)	n (%)	Mean (SD)	Median (range)
Any seizure	87 (100)	49.1 (83.54)	15.5 (3.9, 446.5)	65 (100)	38.8 (91.40)	9.0 (3.7, 605.8)
Simple partial	43 (49.4)	22.4 (68.05)	0.0 (0.0, 418.5)	27 (41.5)	17.9 (80.05)	0.0 (0.0, 605.8)
Complex partial	49 (56.3)	14.9 (30.12)	1.4 (0.0, 150.6)	42 (64.6)	13.8 (40.19)	3.0 (0.0, 233.0)
Partial evolving to secondarily generalised	42 (48.3)	8.7 (23.82)	0.0 (0.0, 150.0)	34 (52.3)	5.2 (17.21)	0.5 (0.0, 132.0)
Unclassified	8 (9.2)	0.5 (2.24)	0.0 (0.0, 13.8)	7 (10.8)	1.8 (12.36)	0.0 (0.0, 99.4)
Other	5 (5.7)	2.6 (17.20)	0.0 (0.0, 141.5)	3 (4.6)	0.2 (1.22)	0.0 (0.0, 7.4)

Table 3 - Concomitant antiepileptic drugs during Part III-V (safety set)

AED	Number (%) of patients		
	Placebo in Part I (N=87)	ESL in Part I (N=65)	Total (N=152)
Total number of AEDs given concomitant at start of Part III–V			
0	2 (2.3)	1 (1.5)	3 (2.0)
1	15 (17.2)	21 (32.3)	36 (23.7)
2	61 (70.1)	40 (61.5)	101 (66.4)
3	8 (9.2)	3 (4.6)	11 (7.2)
4	1 (1.1)	0	1 (0.7)

- **Efficacy results**

Part III-V

Responder Rates:
The total responder rate during Part III–V was 25.7% when compared to Baseline Part III–V. Total responder rates steadily increased up to 50.0% during weeks 181-192, and then decreased to 25.0% during weeks >192.
Responder rates beyond week 181 should be interpreted with caution due to the small number of patients.

Table 4 - Table: Responder Rates of study parts III-V (compared to baseline part III-V, ITT set)

Analysis interval	Number (%) of patients		
Characteristic	Placebo in Part I	ESL in Part I	Total
Overall			
Total number of patients [a]	61 (100)	48 (100)	109 (100)
Number of responders	15 (24.6)	13 (27.1)	28 (25.7)
Weeks 37-48 (end of Part III)			
Total number of patients [a]	47 (100)	41 (100)	88 (100)
Number of responders	10 (21.3)	17 (41.5)	27 (30.7)
Weeks 85-96 (end of Part IV)			
Total number of patients [a]	27 (100)	23 (100)	50 (100)
Number of responders	7 (25.9)	10 (43.5)	17 (34.0)
Weeks 133-144 (end of first year in Part V)			
Total number of patients [a]	15 (100)	18 (100)	33 (100)
Number of responders	8 (53.3)	5 (27.8)	13 (39.4)
Weeks 181-192 (end of Part V)			
Total number of patients [a]	8 (100)	8 (100)	16 (100)
Number of responders	4 (50.0)	4 (50.0)	8 (50.0)
Weeks >192 (beyond Part V)			
Total number of patients [a]	5 (100)	7 (100)	12 (100)
Number of responders	2 (40.0)	1 (14.3)	3 (25.0)

Table 5 - Responder Rates of study parts III-V (compared to baseline part I, ITT set)

Analysis interval	Number (%) of patients		
Characteristic	Placebo in Part I	ESL in Part I	Total
Overall			
Total number of patients	83 (100)	65 (100)	148 (100)
Number of responders	60 (72.3)	44 (67.7)	104 (70.3)
Weeks 37-48 (end of Part III)			
Total number of patients	65 (100)	51 (100)	116 (100)
Number of responders	46 (70.8)	39 (76.5)	85 (73.3)
Weeks 85-96 (end of Part IV)			
Total number of patients	36 (100)	30 (100)	66 (100)
Number of responders	25 (69.4)	22 (73.3)	47 (71.2)
Weeks 133-144 (end of first year in Part V)			
Total number of patients	20 (100)	21 (100)	41 (100)
Number of responders	16 (80.0)	17 (81.0)	33 (80.5)
Weeks 181-192 (end of Part V)			
Total number of patients	12 (100)	8 (100)	20 (100)
Number of responders	11 (91.7)	5 (62.5)	16 (80.0)
Weeks >192 (beyond Part V)			
Total number of patients	8 (100)	7 (100)	15 (100)
Number of responders	7 (87.5)	5 (71.4)	12 (80.0)

Standardised seizure frequency and relative reduction:

The total median standardised seizure frequency during Part III-V was 2.6, resulting in a median relative change from baseline part III-V of -21.4% (and from baseline part I of -75.5%). The median relative change from baseline part III-V increased up to weeks 181-192 (to -40.5%).

13 patients (8.8%) were seizure-free during part III-V. The proportion of seizure-free patients ranged from 20.3% to 32.0% of patients during each of the 12-week intervals.

Whereas the overall median relative change from baseline part III-V was higher in patients treated ESL in part I (-28.4%) than in patients treated with placebo in part I (-14.7%), the proportion of seizure free patients were generally higher in patients treated with placebo in part I than in patients treated with ESL in part I.

2 patients (3.1%) treated with ESL in part I and 1 patient (1.1%) treated with placebo in part I were switched to monotherapy during part III–V.

Rapporteur's comment:

Taking into consideration the open-label character and high drop-out rate during part III-V of the study (i.e. 29.6% during part III, 12.5% during part IV and 34.2% during part V of the study and with only very few patients being treated beyond week 182) as well as further discontinuation after completion of parts III and IV, respectively, together with the results of part I of study 305 (in which no superior efficacy of ESL over placebo could be shown), no robust conclusions of efficacy of ELS in the evaluated population can be drawn from the this study part of study 305. In view of the presumed high selection bias it is nevertheless reassuring, that overall efficacy results of study parts III-V compared favorably

not only to baseline of study part I but also to baseline of study part III-V, i.e. the last 4 weeks of treatment during open-label extension part II of this study.

- **Safety results**

Table 6 - Summary of treatment-emergent adverse events (safety set)

TEAE categories	Number (%) of patients		
	Placebo in Part I (N=87)	ESL in Part I (N=65)	Total (N=152)
Any TEAE	51 (58.6)	45 (69.2)	96 (63.2)
At least possibly related TEAEs	11 (12.6)	9 (13.8)	20 (13.2)
Serious TEAEs	9 (10.3)	7 (10.8)	16 (10.5)
At least possibly related serious TEAEs	0	0	0
TEAEs leading to treatment discontinuation	0	0	0
Deaths	1 (1.1)	0	1 (0.7)

ESL = eslicarbazepine acetate; N = number of patients in the combined safety set; TEAE = treatment-emergent adverse event.
Source: Section 15. Table P3-5.S.0

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

● 96 patients (63.2%) experienced at least 1 TEAE. Most frequently reported TEAEs were convulsion (18 patients [11.8%]), nasopharyngitis (15 [9.9%]), and pyrexia (14 [9.2%]).

● 20 patients (13.2%) 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 gamma-glutamyltransferase (GGT) (6 patients [3.9%]).

● 16 patients (10.5%) had at least 1 serious TEAE; the only serious TEAEs reported by more than 1 patient were asthma, bronchopneumonia, convulsion, pneumonia, 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 led to treatment discontinuation.

● One patient died during Part III–V due to a severe case of bronchopneumonia, which was assessed by the investigator as unrelated to the study drug:
The patient was 4 years old, female and treated with placebo in part I.
Bronchopneumonia began 9 days prior to the patient's death, led to hospitalization and was treated with cefuroxime and paracetamol. No dose change was made in the study medication. During the period that she had serious respiratory infection with recurrent fever, she also suffered from a seizure while eating. She then became tachypneic and cyanotic for a period, and subsequently she developed bradypnea and went in respiratory arrest. The seizure most likely precipitated aspiration of food into the respiratory tract, which led to outcome of respiratory failure.

●Changes from a normal laboratory value at baseline (OL) to an abnormal value at endpoint occurred in fewer than 23.1% of patients per laboratory parameter. For any laboratory parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of creatine kinase, activated by N-acetyl cysteine (clinically significant for 5 patients [3.3%]), GGT (clinically significant for 15 patients [9.9%], and leukocytes (clinically significant for 6 patients [3.9%]).

● The majority of the 148 patients who had post-baseline measurements of sodium levels, had normal sodium levels: 14 patients (9.2%) had low sodium levels and no patients had high sodium levels. Most

of the patients (12/14) with low sodium levels had values >130 to 135 mmol/L, and the other patients had values ≤130 mmol/L. However, none of these sodium levels were considered clinically significant.

● No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index, head circumference, sexual maturation assessment, and ECG during Part III–V.

The proportion of patients with exacerbation of seizure frequency (increase of ≥ 25%) compared to baseline part III-V was 26.6%. The proportions of patients with exacerbation showed no consistent trend over time.

It is stated that no clinically relevant changes in the total score of the Hague seizure severity scale were seen during part III-V.

Rapporteur's comment:
According to the study report, no patients experienced a TEAE that led to treatment discontinuation. However, in 1 patient who withdrew during study part III the reason for discontinuation was specified as "adverse event".

Whereas hyponatremia (common), leukopenia, transaminases increased and liver disorder, respectively are labelled AEs of Zebinix in the approved adult indication, increased creatine kinase can often be found after generalised tonic-clonic seizures.

No serious AE was considered related to the study medication and a causal relationship of the death case with the study medication is considered remote.

No new unique safety concerns occurred within this study. Update or change of product information is therefore not considered necessary at this point.

1. Discussion on clinical aspects

In part I of study 305 no superior efficacy of ESL over placebo could be shown as adjunctive treatment in children ≥ 2 years of age with refractory partial onset seizures. The only statistically significant difference in favour of ESL compared to placebo (in an analysis of the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III) resulted from a post-hoc analysis. Although it is reassuring that overall efficacy results of study part III-V compared favorably not only to baseline of study part I but also to baseline of study part III-V, i.e. the last 4 weeks of treatment during open-label extension part II, no robust conclusions of efficacy of ESL in the evaluated population can be drawn from the open extension parts of the study.

Efficacy results of study 305 appear contradictory to the results of study 208, submitted during variation EMEA/H/C/988/II/41 in which ESL as adjunctive treatment was statistically significantly different from placebo with respect to the primary efficacy endpoint (improvement in standardized seizure frequency) as well as with respect to further efficacy parameters in paediatric patients with partial onset seizures.

No new unique safety concerns occurred within study 305. Update or change of product information is therefore not considered necessary at this point.

Rapporteur’s overall conclusion and recommendation

Overall conclusion

The applicant does not propose any amendment of the product information and further states, that the data submitted do not influence the benefit-risk balance for Zebinix and therefore do not require taking further regulatory action on the marketing authorization for Zebinix.

Study 305 (including part III-V) does not allow for conclusion of efficacy of ESL as adjunctive treatment in paediatric patients with refractory partial onset seizures and the current information given in the PI of Zebinix, that efficacy of eslicarbazepine acetate in children has not yet been established is considered further valid.

No new unique safety concerns occurred within this study. Update or change of product information regarding safety is therefore not considered necessary at this point.

Recommendation

☒ **Fulfilled**

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable