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Procedure Management and Committees Support Division

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

Zebinix

eslicarbazepine acetate

Procedure no: EMEA/H/C/000988/P46/024

Note

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

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Introduction

On 5th October 2015, the MAH submitted the report for the study BIA-2093-208 (Part III), a double-blind, randomised, placebo-controlled, parallel-group, multicentre trial to evaluate efficacy and safety, including effect on cognitive function of eslicarbazepine acetate (ESL) as adjunctive therapy in paediatric patients with partial-onset seizures aged from 6 years to less than 16 years, with an open label (OL) extension phase (48 weeks), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The final report presented with the submission includes data from the additional two-year, OL extension of the study (Part III).

Scientific discussion

Information on the development program

The MAH stated that the Clinical Study Report (CSR) for the clinical trial code BIA-2093-208 (Part I and II) was submitted to the EMA on 6th December 2013. In addition this CSR was also part of the application submitted to the EMA on 30th June 2015 to extend the approved indication to the paediatric population. The double-blind (Part I) and one-year OL extension (Part II) are part of the PIP for ESL (P/0015/2015 issued on 30th January 2015). The subsequent OL extension period of the study (Part III) is not part of the PIP for ESL.

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

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

Zebinix is approved as immediate release tablets containing 200, 400, 600 and 800 mg of ESL. One additional formulation has been developed, an oral suspension (50 mg/mL), intended for use in children, and an extension application was submitted on 30th June 2015. Formulation used in study was white oblong tablets of 200 mg. The tablets are scored and can be broken into equal halves to allow dose adjustments.

Clinical aspects

1. Introduction

The MAH submitted the final report for:

- Study BIA-2093-208; Effects of Eslicarbazepine Acetate (BIA 2-093) on Cognitive Function in Children With Partial Onset Seizures: An Add-On, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial.

2. Clinical study

Description

The study reported here comprised only Part III since both Parts I and II were already reported. The objectives pertaining to the Part III OL extension of the study were to evaluate the safety, tolerability, and sustainability of the therapeutic effect of ESL for long-term use during an additional two-year OL extension.

Methods

- Objective and study design

The study consisted of three parts; the results from Part III are addressed in this clinical study report (CSR).

Part I was a multicenter, double-blind (DB), randomized, placebo-controlled, and parallel-group clinical study conducted in patients aged 6 to 16 years with a diagnosis of partial-onset seizures that were refractory to treatment with 1 to 2 anti-epileptic drugs (AEDs). Part I of the study comprised three periods: an observational baseline period of 4 weeks; a DB period of 12 weeks, with a 4-week up-titration period and an 8-week maintenance period; and a tapering-off period conducted in 2-week steps of down-titration. At the end of the observational baseline period, patients who met the selection criteria were randomly assigned in a 1:2 ratio to receive either placebo once daily (QD) or ESL 30 mg/kg/day QD (maximum 1200 mg). Cognitive, efficacy, and safety assessments were conducted at baseline and at specified time points throughout the study.

Part II consisted of a one-year, OL, uncontrolled period which started after completion of the last 2-week, 10 mg/kg/day down-titration step in Part I. All patients who entered this period initially received a dose of 10 mg/kg/day ESL, but this dose was titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). Patients entering the one-year OL extension attended the study clinic for 6 scheduled visits during Part II for ongoing safety monitoring and performance of study assessments. At the end of Part II, patients either entered a tapering-off/follow-up period or an additional two-year OL extension (Part III).

Part III was an additional two-year, OL extension adhering to an OL, uncontrolled design in which all patients received ESL. Patients could begin Part III on the same dose that they were taking at the Part II visit OL7. The dose range was 10 to 30 mg/kg/day (maximum allowed ESL dose of 1200 mg QD), and was titrated up or down by the investigator according to clinical response or in case of intolerable adverse events (AEs). Upon completion of this extension, patients were tapered off ESL in 10 mg/kg/day steps every 2 weeks.

ESL was provided as 200 mg tablets. Doses were rounded to the nearest 100 mg unit. Half tablets could be used. The total study duration was about 3.5 years for those patients who completed all three parts of the study.

- Study population /Sample size

Number of patients (randomized):

This international multicenter study was conducted in patients with partial-onset seizures that were refractory to treatment with 1 to 2 AEDs. A total of 133 patients were screened for eligibility to participate in Part I of the study, of these, 123 patients were randomized to study drug and were analyzed in the intent-to-treat (ITT) analysis population.

Of the 95 patients who completed the one-year OL extension period (Part II), a total of 42 patients entered the two-year OL extension (Part III). All 42 patients were included in the Safety Population, and 41 patients were included in Modified Efficacy ITT Population.

For Part III of the study, eligible participants had to meet the following inclusion criteria at the OL7 visit (baseline visit for Part III): 1) willingness to enter Part III based on seizure control and tolerability during the course of the study and 2) written informed consent and assent. No additional exclusion criteria were specified for this part of the study.

The following analysis sets were used in Part III of this study:

- Safety population – all patients who entered Part III and who received at least one dose of study treatment.
- Modified Efficacy Intent-to-Treat (ITT) population – all patients who entered Part III, who received at least one dose of study treatment and had at least one post-baseline Clinical Global Impression-Severity (CGI-S) scale assessment during Part III. Safety data were summarized for the Safety population, and efficacy data were summarized for the Modified Efficacy ITT population.

CHMP's comment:

Of the 95 patients who completed the one-year OL extension period (Part II), a total of only 42 patients entered the two-year OL extension (Part III). All 42 patients were included in the Safety Population, and 41 patients were included in Modified Efficacy ITT Population.

The Applicant is asked to clarify reasons, why more than half of the patients from Part II did not continue in the study.

• Treatments

ESL was provided as white oblong tablets of 200 mg that were scored so that they could be broken in half when necessary. The medication was taken orally. For patients who continued into Part II, the maximum duration of Part I was 20 weeks, while patients who opted not to enter Part II had an additional 4-week observational follow-up period with a ninth visit at the end, for a total maximum duration of 24 weeks. Duration of Part II was one year, and the duration of Part III was 2 years.

The total study duration was about 3.5 years for those patients who completed all three parts of the study.

• Outcomes/endpoints

Efficacy endpoints:

Efficacy endpoints for Part III included

1) Treatment retention time defined as actual time on treatment and

2) CGI-S scale change from baseline.

The **safety endpoints** for Part III were as follows:

- Treatment-emergent adverse events (TEAEs)
- Vital signs
- Body weight, height, and head circumference
- 12-lead ECG readings
- Physical and neurological examination

• Statistical Methods

The methods presented here refer to the analysis of data collected during the OL extension of the study (Part III). All demographic and baseline characteristics and medical history were taken from the screening or baseline visits at the start of Part I (i.e., V1 or V2). The baseline for the safety parameters was defined as data recorded at OL7 (i.e., the last visit of Part II). In addition, in order to assess the long-term safety of ESL, for patients who previously received ESL during Part I, the DB baseline for the safety parameters was defined as the baseline used for the Part I analysis. For efficacy (CGI-S scale endpoints), the baseline was defined as OL7 for the calculation of change from baseline during Part III. The baseline used for the Part I analysis was named “baseline (DB period)” and the baseline used for the Part III analysis was named “baseline (two-year OL extension)” in all tables. No formal inferential statistical analysis was performed on the Part III data; only descriptive statistics were presented. All statistical analyses were performed using SAS® Version 9.2.

Efficacy Analyses:

Treatment retention time (time to last dose) was summarized as actual time on treatment during Part III of the study using Kaplan-Meier methods, the estimates from which were presented in both tabular and graphical format. The CGI-S scale is a rating scale of 7 levels used to measure the severity of illness as assessed by the investigator based on their experience with the pediatric epilepsy patient population. The CGI-S scale was instituted only for Part III. During Part III, the CGI-S scale was completed at baseline (OL7) and all Part III visits (OL8 – OL13, EDV, and PSV). Both categorical and continuous summaries of the CGI-S scale were presented at each visit. CGI-S results were summarized at each time point by actual values (score) per individual patient and change from baseline. For all patients and by age group, the treatment retention time and the number and percentages of patients remaining on treatment, and categorical and continuous CGI-S results were summarized by previous DB treatment group and overall.

Safety:

All patients who received study treatment were evaluated for safety. AEs were summarized and listed by treatment received during the DB assessment period. TEAEs were defined as AEs with an onset date on or after the first dose of study drug in Part III up until 4 weeks after the last dose of study drug. TEAEs were summarized by treatment group, system organ class (SOC), and preferred term (PT).

Additionally, TEAEs were summarized by severity (intensity). Brief patient narratives were prepared for patients with serious adverse events (SAEs) and for patients who withdrew from the study due to AEs.

Vital signs variables were summarized for each treatment group by calculating summary statistics on the actual values and on the change from baseline at key time points. Shift tables were provided to summarize values that fell outside clinically significant limits. The number and percentage of patients with values outside the limits of clinical significance were summarized.

Shift tables for changes from baseline in ECG results (clinically relevant abnormalities) and in physical and neurological examinations to each post-baseline visit were presented by previous double-blind treatment group and overall. Separate summaries were presented based on the baseline defined for the Part III analysis and the baseline defined for the Part I analysis (ESL patients only).

Results

- Recruitment/ Number analysed

Disposition of patients

A total of 42 patients entered the two-year OL extension (Part III): 12 patients who received placebo in the previous DB period (Part I) and 30 patients who received ESL in the previous DB period (Part I).

Of the 42 patients, 31 patients (73.8%) completed the OL extension period (11 patients [91.7 %] with previous DB placebo; 20 patients [66.7%] with previous DB ESL).

Ten patients (23.8%) discontinued prematurely from the study (1 patient [8.3%] with previous DB placebo and 9 patients [30.0%] with previous DB ESL). The most common reason for premature discontinuation was patient/caregiver/parent request (6 [14.3%]).

The two treatment groups based on previous DB treatment were balanced for age, sex, and race. The mean age was 12.2 years; 33.3% of patients were 6 to 11 years of age, and 66.7% were 12 to 16 years of age. The percentage of male and female patients was equal. Caucasian was the predominant race (41/42 patients, 97.6%). Baseline height, weight, and BMI, as well as head circumference and IQ scores, were balanced between treatment groups based on previous DB treatment.

A total of 39 patients received at least one concomitant AED during the two-year OL extension. The most commonly used concomitant AEDs were valproate, carbamazepine, topiramate, lamotrigine, and levetiracetam. Overall, $\geq$ 50% of patients were taking at least one concomitant AED at any time point during the OL period. The proportion of patients who used at least one concomitant non-AED was similar in the patients who had received previous DB ESL (30.0%) and those who had received previous DB placebo (25.0%).

For the Safety population, the mean exposure to study drug was 681 days.

- Efficacy results

During Part III of the study, the efficacy was maintained and there was no worsening of disease severity.

The median treatment retention time was similar in the previous DB ESL treatment group (734 days) and the previous DB placebo group (739 days). The results of this analysis in each of the two age groups were similar to the overall results. Overall, 31 (75.6%) patients remained on treatment during Part III.

The mean values and the changes from baseline in CGI-S scale parameters during the two-year OL extension were similar in both previous DB treatment groups. Overall, at the last assessment, there was a slight mean reduction from baseline in the severity of illness (-0.5); all other categories were unchanged from baseline. Results overall and for each previous DB group were similar.

The results of the CGI-S analyses in each of the two age groups (6 to 11 years and 12 to 16 years) were similar to the overall results.

Overall, at the last assessment, there was a slight mean reduction from baseline in the severity of illness (-0.5); all other categories were unchanged from baseline.

- Safety results

There were no deaths during the study.

The incidence of SAEs was low overall (4.8%). A total of two patients reported one treatment-emergent SAE each (one patient in each previous DB treatment group): brain operation and complex partial seizures.

- Neither of these patients experienced an SAE that was considered by the investigator to be potentially related to study drug.
- No serious and potentially drug-related TEAEs of special interest (cutaneous, cardiovascular, or cerebrovascular) were reported during the study.

One patient who received previous DB placebo treatment had a TEAE of splenomegaly that led to premature discontinuation of study drug.

Overall, 7 patients (16.7%) experienced at least one TEAE during the two-year OL extension period. The proportion of patients who experienced at least one TEAE was the same in each previous DB treatment group (16.7%). Pyrexia and cough were reported in two patients each; all other TEAEs were reported by one patient each.

Most TEAEs were of mild or moderate intensity; two severe TEAEs, complex partial seizures and headache, occurred in one patient.

Overall, one patient (2.4%) reported a TEAE (splenomegaly) considered by the investigator as potentially related to study drug.

One patient in the previous DB placebo group experienced a post-treatment AE of nasopharyngitis that was considered non-serious, moderate in severity, and not related to study drug.

No patient had ECG changes from normal to abnormal during the study.

From DB baseline and OL baseline to the last assessment visit, no substantial shifts occurred in vital signs or in physical or neurological examinations.

1. Discussion on clinical aspects

Part III of the study was an additional long-term (two-year) extension offered to patients who completed Part II. Part III was designed to further evaluate safety, tolerability, and sustainability of the therapeutic effect of ESL in the paediatric population.

During Part III, efficacy endpoints included analyses of treatment retention time and CGI-S scale score during the two-year OL extension period to measure the effectiveness of the study treatment. The efficacy was maintained and there was no worsening of disease severity during Part III of the study. Median treatment retention time was similar in the previous DB ESL treatment group (734 days) and the previous DB placebo group (739 days). Overall, 75.6% of patients remained on treatment during Part III. The mean values and the changes from baseline in CGI-S scale parameters during the two-year OL extension were similar in both previous DB treatment groups. Overall, at the last assessment, there was a slight mean reduction from baseline in the severity of illness (-0.5); all other categories were unchanged from baseline.

CHMP's overall conclusion and recommendation

Overall conclusion

A majority of patients remained on treatment during the 2 year OL extension period. No new unique safety concerns occurred within this study. The AE profile was consistent with previous data on ESL.

Recommendation

☒ **Fulfilled –**

No regulatory action required

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable