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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

Vimpat

lacosamide

Procedure no: EMEA/H/C/000863/P46/027

Note

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

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1. Introduction

On 3rd of July 2017, the MAH submitted the results of SP0994 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), which requires UCB to submit information on studies conducted in children (<18 years of age) treated with lacosamide (LCM; VIMPAT®; SPM 927, previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037), which included data on 7 children who were <18 years of age.

A short critical expert overview has also been provided.

2. Scientific discussion

Information on the development program

The MAH stated that "A Multicenter, Double blind, Double dummy, Follow up Study Evaluating the Long term Safety of Lacosamide (200 to 600mg/day) in Comparison with Controlled release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects with Partial onset or Generalized Tonic clonic Seizures ≥16 Years of Age Coming from the SP0993 Study "(SP0994) is part of a clinical development program.

A line listing of all the concerned studies is annexed.

Information on the pharmaceutical formulation used in the study

The term "investigational medicinal product (IMP)" refers to LCM, CBZ-CR, and matching placebos administered in this study. LCM tablets (white, film-coated), in doses of LCM 100mg and LCM 50mg, LCM matching placebo tablets (white, film-coated) were used. CBZ-CR tablets overencapsulated in double-blind capsules size A (yellow, opaque) with an overfill (mix of magnesium stearate and avicel), in dose of CBZ-CR 200mg and CBZ-CR matching placebo double-blind capsules size A (yellow, opaque) with an overfill (mix of magnesium stearate and avicel) were administered.

2.1. Clinical aspects

Introduction

The MAH submitted a final report for:

Study SP0994 entitled "A Multicenter, Double blind, Double dummy, Follow up Study Evaluating the Long term Safety of Lacosamide (200 to 600mg/day) in Comparison with Controlled release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects with Partial onset or Generalized Tonic clonic Seizures ≥16 Years of Age Coming from the SP0993 Study "

Lacosamide was first approved by the European Medicines Agency in 2008 and is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy.

Clinical study

SP0994: "A Multicenter, Double blind, Double dummy, Follow up Study Evaluating the Long term Safety of Lacosamide (200 to 600mg/day) in

Comparison with Controlled release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects with Partial onset or Generalized Tonic clonic Seizures ≥16 Years of Age Coming from the SP0993 Study "

Description

SP0994 was a double-blind, double-dummy extension study for subjects who completed SP0993 or for subjects who experienced a seizure at the first or second target doses in the Maintenance Phase of SP0993.

Methods

Objective(s)

The objectives of this study were:

- To obtain information about the long-term safety of LCM in comparison with CBZ-CR when used as monotherapy in subjects with recently diagnosed partial-onset or generalized tonic-clonic seizures
- To allow subjects who completed the monotherapy study SP0993 to continue to receive LCM or CBZ-CR

Study design

SP0994 was a double-blind, double-dummy extension study for subjects who completed SP0993 or for subjects who experienced a seizure at the first or second target doses in the Maintenance Phase of SP0993. Following the database lock and unblinding of SP0993, SP0994 was unblinded and was closed for all subjects when follow-up access to LCM monotherapy was established outside of SP0994.

A clinic visit occurred approximately every 13 weeks relative to the SP0994 Visit 1 date with the exception of subjects requiring a higher target dose (ie, for dose optimization). Subjects requiring a higher target dose returned to the clinic for an Escalation Visit (ES) followed by a Stabilization Visit (SV); subsequent regularly scheduled visits occurred at 13-week intervals relative to the SV.

Visit 1 for SP0994 was the same as the second Maintenance Visit (MV2-1, MV2-2, or MV2-3) or the Early Termination Visit (ETV) for SP0993. The ETV of SP0993 as Visit 1 for SP0994 was applicable only for subjects on the first or second target dose. Subjects who were withdrawn from SP0993 while at the third target dose level were not allowed to participate in SP0994 with the exception of subjects who were terminated from SP0993 due to SP0993 Protocol Amendment 6.2.

Subjects who terminated from SP0993 due to Protocol Amendment 6.2 and who required taper were dispensed a taper kit in SP0994. Across the 2 studies (SP0993 and SP0994), subjects were allowed a maximum of 2 dose escalations due to the occurrence of a seizure and 1 dose reduction due to poor tolerability in accordance with the target dose levels defined in SP0993. If, in the opinion of the investigator, the subject's AEs indicated that the dose was at an intolerable level, the subject's dose may have been decreased. This dose reduction was managed via an Unscheduled Visit, phone call, or a regularly scheduled clinic visit. If the subject experienced a seizure at the first or second dose levels, the subject was to be brought in for a dose escalation visit.

This document summarizes disposition, subject demographics, history of epilepsy, extent of exposure, and treatment-emergent adverse events (TEAEs) for the 7 subjects from SP0994 who were <18 years old at the time of study entry in order to fulfill the requirement of reporting pediatric data as outlined

in Article 46. Data from the overall subject population in SP0994 are provided for comparison in the accompanying SP0994 final CSR (Module 5.3.5.1). The exploratory efficacy data in SP0994 were not summarized separately for subjects who were <18 years of age at the time of study entry."

- ***Study population /Sample size***

The study population of SP0994 consisted from subjects who had remained seizure free and completed SP0993 or subjects who experienced a seizure at the first or second target doses in the Maintenance Phase of SP0993. Subject was expected to benefit from participation in SP0994 in the opinion of the investigator.

- ***Treatments***

In SP0994, subjects received a dose of LCM 200mg/day, 300mg/day, 400mg/day, 500mg/day, or 600mg/day or a dose of CBZ-CR 400mg/day, 600mg/day, 800mg/day, 1000mg/day, or 1200mg/day. Study medication was orally administered twice daily (bid; at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses.

Treatment randomizations and subject numbers were assigned at the beginning of SP0993 and remained the same in SP0994.

- ***Outcomes/endpoints***

As this was primarily a safety study, only exploratory efficacy variables were assessed.

The primary safety variables were as follows:

- Adverse events reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- Serious AEs

The other safety variables were as follows:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and heart rate [HR])
- Changes in physical or neurological examination findings
- Changes in body weight

Efficacy evaluations were based on subject diaries where types, dates, and number of seizures were recorded. The exploratory efficacy variables were: 1) Percentage of subjects seizure free and 2) Time to discontinuation.

The exploratory health outcomes variables were: Health care resource use: Additional health care provider visits unforeseen by the protocol and hospitalizations.

Results

- ***Recruitment / Number analysed***

Among the 548 total subjects in the SS, 7 subjects were <18 years of age at the time of study entry.

- ***Efficacy results***

The exploratory efficacy variables were the percentage of subjects seizure free and time to discontinuation. Seizure control was maintained for most subjects in both treatment groups during the study.

- ***Safety results***

Of the 7 total subjects <18 years of age, 5 subjects (71.4%) completed the study and 2 subjects (28.6%) discontinued from the study. Overall, 6 subjects (85.7%) <18 years of age remained in SP0994 until SP0993 unblinding and 1 subject (14.3%) discontinued from SP0994 prior to SP0993 unblinding. Both subjects who discontinued from the study were in the CBZ-CR treatment group. The reasons for discontinuation were lack of efficacy (1 subject [14.3%] prior to SP0993 unblinding) and "other" (1 subject [14.3%] after SP0993 unblinding).

Among the small group of subjects <18 years of age, all 7 subjects were 17 years of age at entry into SP0994. There were 6 (85.7%) female subjects and 1 (14.3%) male subject. A total of 4 subjects (57.1%) were white and 3 subjects (42.9%) were Asian; no subjects were Hispanic or Latino. Mean weight, height, and BMI were 59.20kg, 163.83cm, and 22.03kg/m^2, respectively. There were no subjects with a BMI ≥30kg/m^2.

Among subjects <18 years of age in the LCM treatment group, the median age at diagnosis for subjects was 15.5 years and the median time since first diagnosis at SP0994 Visit 1 was 1.19 years. The median time since first seizure at SP0994 Visit 1 was 1.63 years. In the LCM treatment group, the median number of seizures in the past 3 months prior to SP0993 Visit 1 was 3.0 and the majority of subjects reported more than 2 seizures in the past year prior to SP0993 Visit 1. In the CBZ-CR treatment group, the median age at diagnosis for subjects was 16.0 years and the median time since first diagnosis at SP0994 Visit 1 was 1.17 years. The median time since first seizure at SP0994 Visit 1 was 1.23 years. In the CBZ-CR treatment group, the median number of seizures in the past 3 months prior to SP0993 Visit 1 was 2.0 and the majority of subjects reported 2 seizures in the past year prior to SP0993 Visit 1. One subject (25.0%) in the LCM treatment group and 1 subject (33.3%) in the CBZ-CR treatment group reported a temporal focus of localization at SP0993 Visit 1.

The median duration of exposure and subject-years exposed were longer in the LCM treatment group compared with the CBZ-CR treatment group (463.5 days [6.3 subject-years exposed] in the LCM treatment group compared with 354.0 days [3.7 subject-years exposed] in the CBZ-CR treatment group).

The median of the mean exposure to LCM per subject was 200.00mg/day and the median of the mean exposure to CBZ-CR per subject was 400.00mg/day during the Treatment Period, consistent with the overall observation for the study that most subjects remained at the first dose level (>100 to 200mg/day for LCM and >200 to 400mg/day for CBZ-CR). The maximum mean exposure to LCM per subject was 234.0mg/day and the maximum mean exposure to CBZ-CR per subject was 1050.4mg/day.

Among subjects <18 years of age at entry into SP0994, a total of 1 subject (25.0%) in the LCM treatment group reported 2 TEAEs and 2 subjects (66.7%) in the CBZ-CR treatment group reported 7 TEAEs during the study. One subject (25.0%) in the LCM treatment group and no subjects in the CBZ-CR treatment group reported TEAEs that were serious (Section 5.5.4). No subjects <18 years of age reported TEAEs leading to discontinuation, TEAEs considered related to study medication per the investigator, or severe TEAEs. There were no deaths among subjects <18 years of age.

Among subjects <18 years of age at entry into SP0994, the TEAEs reported in the LCM treatment group were appendicitis and postoperative wound infection (1 subject [25.0%] each). The TEAEs reported in the CBZ-CR treatment group were pyrexia, contusion, fall, fractured coccyx, road traffic accident, and weight decreased (1 subject [33.3%] each). The event of weight decreased was considered non-serious and did not lead to discontinuation.

One subject (25.0%, Subject [Protected Personal Data removed]) in the LCM treatment group reported 1 event of appendicitis that was serious, moderate in intensity, considered not related to study medication per the investigator, and that resolved.

Discussion on clinical aspects

All patients < 18 years old (n=4) treated with lacosamide in the SP0994 study were 17 years old at entry into the SP0994 study. All of them completed the study staying in the study for an average 463.5 days with the median of the mean exposure of 200mg/day. Based on these limited results long-term treatment with LCM was generally well tolerated in subjects < 18 years newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or tonic-clonic seizures at doses up to 600mg/day when used as monotherapy. The overall safety profile of LCM observed, including among subjects <18 years of age, is consistent with the currently-known safety profile of LCM and no new safety concerns were observed. However, due to small number of patients the results for subjects <18 years of age should be interpreted with caution.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of SP0994 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The limited number and character of the reported TEAEs in four subjects <18 years of age treated with lacosamide in the study SP0994 does not raise new safety concerns. The MAH does not propose any changes of the currently approved SmPC based on the presented data, which is supported.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Clinical studies part of the Vimpat clinical development program for monotherapy treatment of partial-onset seizures or generalized tonic-clonic seizures in patients ≥ 16 years

Study title	Study number	Date of completion	Date of submission of final study report
A Historical-controlled, Multicenter, Doubleblind, Randomized Trial to Assess the Efficacy and Safety of Conversion to Lacosamide 400mg/day Monotherapy in Subjects with Partial-onset Seizures	SP0902	Dec 2012	Nov 2013
A Multicenter, Open-label Extension Trial to Assess the Long-term Use of Lacosamide Monotherapy and Safety of Lacosamide Monotherapy and Adjunctive Therapy in Subjects with Partial-onset Seizures	SP904 (Follow-up of SP902)	Dec 2014	Jun 2015
A Multicenter, Double-blind, Double dummy, Randomized, positive controlled study comparing the Efficacy and Safety of Lacosamide (200 to 600mg/day) to controlled release Carbamazepine (400 to 1200mg/day), used as Monotherapy in Subjects (≥16 years) newly or recently diagnosed with epilepsy and experiencing partial-onset or generalized tonic-clonic seizures.	SP0993	Aug 2015	Jan 2016
A Multicenter, Double-blind, Double dummy Follow-up study Evaluating the long-term Safety of lacosamide (200 to 600mg/day) in comparison with controlled release carbamazepine (400 to 1200mg/day), used as Monotherapy in Subjects (≥16 years) newly or recently diagnosed with epilepsy and experiencing partial-onset or generalized tonic-clonic seizures coming from the SP0993 study	SP0994 (Follow-up of SP0993)	Jan 2017	July 2017
Planned Phase 3, multicenter,open-label, follow-up to SP0994	SP1042 (Follow-up of SP0994)	~ 2019	As per Regulation (EC) No 1901/2006 at the latest by LPLV date + 6 months