20 August 2015
EMA/583608/2015
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

Vimpat

International non-proprietary name: lacosamide

Procedure No. EMEA/H/C/000863/P46 026

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Invented name of the medicinal product:	Vimpat
INN (or common name) of the active substance(s):	Lacosamide
MAH:	UCB Pharma S.A.
Currently approved Indication(s)	Epilepsy
Pharmaco-therapeutic group (ATC Code):	N03AX18
Pharmaceutical form(s) and strength(s):	Film coated tablet (50 mg, 100 mg, 150 mg, 200 mg), Solution for infusion (10 mg) Syrup (10 mg)

1. Introduction

On 5th June 2015, the MAH submitted the results of a completed study (SP904) for Lacosamide (Vimpat), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, as it included 3 subjects who were <18 years old at the time of study entry.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study "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 number(s)" (Study no SP904) is part of a clinical development program. The extension application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by January/16. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Lacosamide was supplied as white, oval, immediate-release, film-coated tablets in strengths of 50 and 100mg.

2.3. Clinical aspects

2.3.1. Introduction

Lacosamide was first approved by the European Medicines Agency in 2008 and is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16 to 18 years) patients with epilepsy.

2.3.2. Clinical study

This document summarizes disposition and treatment emergent adverse events (TEAEs) for the 3 subjects from SP904 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 SP904 are provided for comparison in the accompanying CSR (Module 5.3.5.1). As SP904 was primarily a safety study, no efficacy variables were assessed.

Description

SP904 (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).

Methods

Objective(s)

- Obtain information about the percentage of subjects who remained on lacosamide (LCM) monotherapy and the duration of LCM monotherapy treatment
- Obtain information about the long-term safety of LCM when used as monotherapy or adjunctive therapy in subjects with partial-onset seizures

Study design/Study population

SP904 was a multicenter, open label extension study to assess the long term use of LCM monotherapy and safety of LCM monotherapy and adjunctive therapy in subjects with partial onset seizures (with and without secondary generalization) who were previously enrolled in SP902. SP902 was a historical controlled, multicenter, double blind, randomized, conversion to monotherapy study to assess the efficacy and safety of LCM 400mg/day monotherapy in subjects 16 to 70 years of age with partial onset seizures. Subjects who entered the Maintenance Phase of SP902 and either completed SP902 or met an exit criterion in SP902 (with the exception of subjects enrolled at sites in Germany) were eligible to enroll in this open label extension study. Subjects enrolled in SP902 at sites in Germany who entered the Maintenance Phase but were withdrawn due to meeting an exit criterion were not eligible to participate in SP904.

Visits 1 through 3 occurred at 4 week intervals; Visits 4 through 6 occurred at 8 week intervals. Beginning at Visit 7, visits were performed at 12 week intervals (Visit 7 through the Termination Visit), with telephone contacts required at 4 week intervals to obtain information regarding concomitant medication use, adverse events, diary completion, and compliance with the study medication schedule.

The maximum duration of a subject's study participation was 2 years after Visit 1 in SP904.

Treatments

At the termination of the previous study, SP902, subjects received a dose of LCM 300 or 400mg/day. At the beginning of this extension study, the investigator may have adjusted or maintained the LCM dose so that a subject began the study at a dose of LCM 200, 300, or 400mg/day for subjects who were receiving LCM 300mg/day at the end of SP902, or LCM 300, 400, or 500mg/day for subjects who were receiving LCM 400mg/day at the end of SP902. The investigator was to increase the dose no faster than LCM 100mg/day per week up to maximum LCM 800mg/day.

During the study, investigators were allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. A clinic visit (scheduled or unscheduled) was required for all LCM dose increases. For subjects receiving LCM monotherapy at the time of study entry, the addition of up to 2 concomitant AEDs was allowed to optimize tolerability and seizure reduction. Concomitant AEDs should have been added only when the subject had not optimally or adequately responded to a maximum tolerated dose of LCM monotherapy.

For subjects who entered the study on both LCM and other concomitant AED therapy, concomitant AED(s) may have been carefully tapered and discontinued to achieve LCM monotherapy.

At the end of treatment, or if subjects discontinued the study prematurely, a Termination Visit was performed. Subjects receiving LCM ≥300mg/day should have been tapered off gradually at a

recommended decrease rate of LCM 200mg/day per week. Clinic visits were not required for LCM dose adjustments during the Taper Phase. Subjects receiving LCM 100 or 200mg/day did not require a taper. A Final Visit was performed 2 weeks after the final dose of study medication.

Taper of LCM was not required for subjects who completed or withdrew from the study and who, in consultation with the investigator, chose to initiate treatment with commercial LCM. The last scheduled study visit for subjects continuing on commercial LCM should have been the Termination Visit.

Outcomes/endpoints

As this was primarily a safety study, seizure frequency and seizure freedom were not analyzed. Long-term use of LCM monotherapy was assessed using the following primary variables:

- Percentage of subjects on LCM monotherapy
- Duration of LCM monotherapy treatment

Long-term safety of LCM monotherapy or adjunctive therapy was assessed using the following secondary variables:

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

Other safety variables included the following:

- Changes in hematology, blood chemistry, and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (eg, blood pressure, pulse)
- Changes in physical or neurological examination findings
- Changes in body weight

Results

Number analysed

A total of 3 subjects were <18 years old at SP904 study entry. Details regarding these subjects are provided below.

Efficacy results

As this was primarily a safety study, seizure frequency and seizure freedom were not analyzed.

Safety results

Subject 1 was a 17 year old white female (SP904 CSR Listing 3.1.1). Treatment emergent AEs reported during the study were pyrexia, anxiety, panic attack, fall, arthropod bite, headache, and dizziness postural. All TEAEs were mild or moderate in intensity and none were serious. None of the TEAEs led to discontinuation from the study or a dose reduction, and none of the TEAEs were considered related to study drug by the investigator (SP904 CSR Listing 9.1.1). The subject used the concomitant AED carbamazepine during the study (SP904 CSR Listing 5.1.1). The subject

discontinued from the study prematurely (due to lack of efficacy) after 250 days of treatment with LCM in SP904 (SP904 CSR Listing 2.1.1).

Subject 2 was a 17 year old black male (SP904 CSR Listing 3.1.1). Treatment emergent AEs reported during the study were upper respiratory tract infection and pyrexia. All TEAEs were mild or moderate in intensity and none were serious. None of the TEAEs led to discontinuation from the study or a dose reduction, and none of the TEAEs were considered related to study drug by the investigator (SP904 CSR Listing 9.1.1). No concomitant AED use was reported during the study (SP904 CSR Listing 5.1.1). The subject completed the study after 726 days of treatment with LCM in SP904 (SP904 CSR Listing 2.1.1).

Subject 3 was a 16 year old white male (SP904 CSR Listing 3.1.1). No TEAEs (SP904 CSR Listing 9.1.1) or concomitant AED use (SP904 CSR Listing 5.1.1) were reported for this subject during the study. The subject completed the study after 763 days of treatment with LCM in SP904 (SP904 CSR Listing 2.1.1).

2.3.3. Discussion on clinical aspects

Treatment emergent AEs (TEAEs) reported during the study SP904 for the included 3 subjects <18 years old were mild or moderate in intensity and none were serious. None of the TEAEs led to discontinuation from the study or a dose reduction, and none of the TEAEs were considered related to study drug by the investigator. Overall, the limited number and the character of the reported TEAEs in the 3 subjects do not raise any new safety concerns.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The limited number and the character of the reported TEAEs in the 3 subjects <18 years old included in study SP904 do not raise any new safety concerns.

This study is being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU Summary of Product Information for VIMPAT are being proposed by the MAH based on the analysis of the TEAEs in 3 subjects <18 years old, which is supported.

Recommendation

X Fulfilled:

No regulatory action required.

Additional clarifications requested

Not applicable.

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

Clinical studies

Product Name: Vimpat Active substance: Lacosamide

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

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
A Historical-controlled, Multicenter, Double-blind, Randomized Trial to Assess the Efficacy and Safety of Conversion to Lacosamide 400mg/day Monotherapy in Subjects with Partial-onset Seizures	SP902	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	Q3 2015	As per Regulation (EC) No 1901/2006 at the latest by LPLV date + 6 months
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)	~ 2016	As per Regulation (EC) No 1901/2006 at the latest by LPLV date + 6 months
Planned Phase 3, multicenter,open-label, follow-up to SP0994	SP1042 (Follow-up of SP0994)	~ 2018	As per Regulation (EC) No 1901/2006 at the latest by LPLV date + 6 months