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Committee for Medicinal Products for Human Use (CHMP)

Vimpat

(lacosamide)

Procedure No. EMEA/H/C/000863/P46 021

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

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

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1. INTRODUCTION

On 06 December 2012 the MAH submitted a safety study report for study SP0961 including very limited paediatric data (3 subjects who were 17 years old at the time of inclusion) for Vimpat, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A short critical expert overview has also been provided.

2. SCIENTIFIC DISCUSSION

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

Lacosamide tablets (50mg, 100mg, 150mg, and 200mg), solution for infusion (10mg/ml), and syrup (10mg/ml) are indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16 to 18 years) patients with epilepsy.

2.2. Clinical aspects

2.2.1. Introduction

The current study (SP0961) is an open label pilot study to assess the safety of lacosamide in subjects with uncontrolled PGTC seizures, and contains paediatric data.

In the study oral lacosamide was administered to a target dose of a maximum of 400 mg/day after titration was completed.

The MAH is submitting the final report for study SP0961 with the title “An open-label pilot study to assess the safety of oral lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy”.

2.2.2. Clinical study(ies)

Description

SP 0961 “An open-label pilot study to assess the safety of oral lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy” was a phase 2 study with 49 subjects enrolled at 19 sites in the US.

Methods

The objectives of the study were to assess the safety of lacosamide in subjects with uncontrolled primary generalised tonic-clonic (PGTC) seizures with idiopathic generalized epilepsy (IGE). Safety was assessed through the collection of adverse events (AEs), electrocardiograms (ECGs), clinical laboratory data, vital sign measurements, body weight, physical and neurological examination findings, as well as electroencephalogram (EEG) recordings for the evaluation of spike wave discharges. In addition, subjects kept a diary to record daily seizure activity. The pharmacokinetics of lacosamide were also accessed via measurements of drug plasma concentrations.

The study design was a multi center opel label pilot study. The baseline phase (4-week prospective) began with subject screening at Visit 1 (Week 0). Visit 1 was conducted to evaluate subject eligibility for enrolment into the study. Seizure frequency and type eligibility were verified by reliably

documented seizure history collected (eg, in a seizure diary) over the 12 weeks prior to the baseline phase. A study seizure diary was dispensed to subjects to record seizure frequency during the baseline phase.

Subjects were contacted via telephone 2 weeks following Visit 1 to assess continued eligibility and were reminded of the importance of accurate seizure diary completion. Subjects returned to the clinic the morning of the day prior to Visit 2 (end of week 4) to begin 24-hour ambulatory EEG recordings. Subjects returned to the clinic approximately 24 hours later (Visit 2) for removal of the scalp electrodes and recording device return. The EEG recording was completed before subjects received their first dose of lacosamide.

At the end of the baseline phase (completion of Visit 2), subjects commenced a 3-week titration phase. Dose titration began at lacosamide 100 mg/day (50 mg bid approximately 12 hours apart) for 1 week. Subjects returned to the clinic for Visit 3 (end of week 5), Visit 4 (end of week 6), and Visit 5 (end of week 7) and were instructed to increase their daily dose to lacosamide 200mg/day, lacosamide 300 mg/day, and the target dose of lacosamide 400 mg/day, respectively, if deemed clinically appropriate.

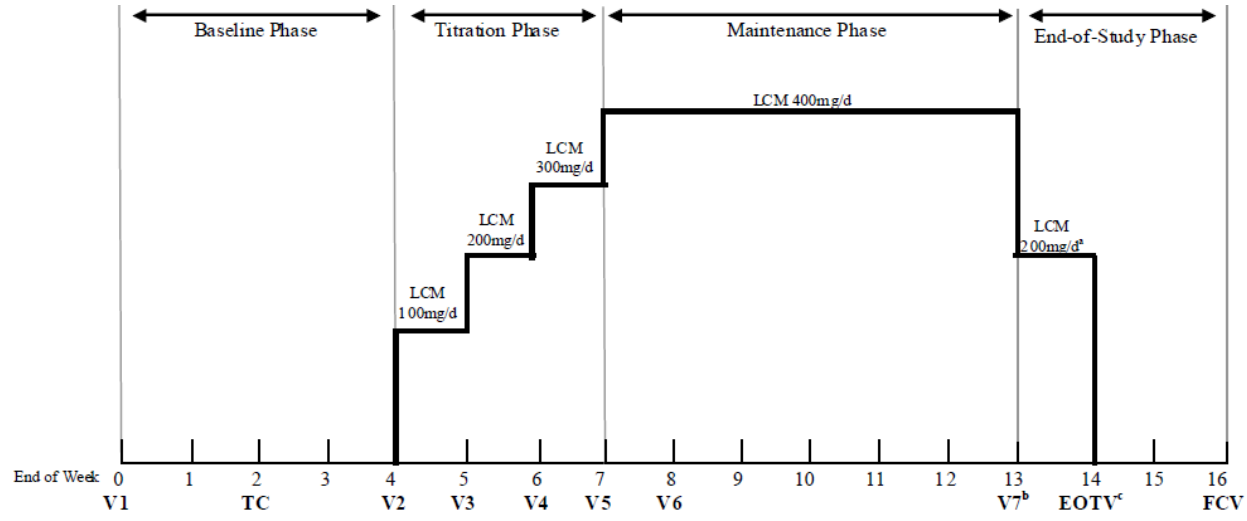
At the end of the titration phase (completion of Visit 5), the 6-week maintenance phase began.

During the maintenance phase, Visit 6 (end of Week 8) and Visit 7 (end of Week 13; termination Visit) were conducted. Subjects returned to the clinic the morning of the day prior to Visit 6 to begin 24-hour ambulatory EEG recordings. Subjects returned to the clinic approximately 24 hours later (Visit 6) for removal of the scalp electrodes and recording device return.

Subjects returned to the clinic for a termination visit (Visit 7) at the end of Week 13. Subjects who completed the maintenance phase were given the opportunity to take part in the open-label extension study (SP0962). Subjects who did not qualify for, or chose not to participate in, the open-label extension study (SP0962) began a 3-week End-of-Study phase after completion of the maintenance phase. If subjects discontinued prematurely from the study, an early Termination visit occurred, when the same assessments as the Termination visit (Visit 7) were performed. These subjects were not eligible to participate in the open-label extension study (SP0962). During the early termination visit, subjects were instructed to taper their lacosamide dose as appropriate.

During the End-of-Study phase, those subjects on lacosamide 300 mg/day or lacosamide 400 mg/day were tapered gradually at a recommended decrease rate of lacosamide 200 mg/day per week (ie, lacosamide 400 mg/day to lacosamide 200 mg/day or lacosamide 300 mg/day to lacosamide 100 mg/day). At the end of week 14, subjects returned to the clinic for an End-of-Taper visit. A final clinic visit was conducted 2 weeks after the subject's last lacosamide dose (end of week 16).

Figure 1: Sp 0961 study schematic diagram



bid=twice daily; d=day; EOTV=End-of-Taper Visit; FCV=Final Clinic Visit; LCM=lacosamide; TC=telephone contact; V=Visit

A total of 49 subjects were recruited into the study. Of these 3 subjects were below 18 years (all were 17 years old). A total of 9 subjects prematurely discontinued during the study. The reasons for discontinuation were adverse events (AE) (5 subjects) and withdrawn consent (4 subjects). All subjects who discontinued were over 18 years old.

The primary variables for assessing safety within SP0961 were:

Change in seizure days with absence seizures from baseline phase to the maintenance phase

Change in seizure days with myoclonic seizures from baseline phase to the maintenance phase

Results

- **Pharmacokinetics (PK)**

Sparse blood sampling for PK analyses was performed, but the results were only presented as plasma concentrations listed by subject and no PK parameters were calculated. Thus, no PK results are presented in this assessment report.

- **Safety**

Absence seizures

The change in the number of days with absence seizures per 28 days from baseline phase to titration and treatment phases are shown in the table below:

Table 1 Change in the number of days with absence seizures per 28 days from baseline phase (4 week prospective) to titration and treatment phases

Subgroup	Actual Value				Change from Baseline			
Phase	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
All subjects								
Baseline	49	4.65 (±8.48)	0.00	0.0, 28.0				
Titration	49	4.91 (±8.42)	0.00	0.0, 28.0	49	0.26 (±3.67)	0.00	-12.1, 12.7
Treatment	49	4.89 (±8.60)	0.00	0.0, 28.0	49	0.25 (±4.26)	0.00	-10.4, 12.7

Max=maximum; Min=minimum; SD=standard deviation; SS=Safety Set

Note: Baseline is defined as the 4-week prospective Baseline Phase

The mean (±SD) number of days with absence seizures per 28 days was 4.65 (±8.48) in the Baseline Phase and 4.91 (±8.42) in the Titration Phase. The mean (±SD) change in number of days with absence seizures per 28 days from the Baseline Phase to the Titration Phase was 0.26 (±3.67). The median change in number of days with absence seizures per 28 days from the Baseline Phase to the Titration Phase was 0.00.

The MAH has analysed change in number of days with absence seizures per 28 days from baseline to titration and from baseline to treatment phase by age of onset of diagnoses with subsets of <2, 2 to <5, 5 to <10, 10 to <15, 15 to <20, and ≥20 years. The evaluation of some of the age at onset of diagnosis subsets were found to be difficult to interpret due to the limited number of subjects. For the subsets with a larger number of subjects (5 to <10, 10 to <15, and 15 to <20 years), the MAH could find no clinically meaningful effect of age of onset on the change in number of days with absence seizures per 28 days from the baseline to the titration or from baseline to treatment phase.

The MAH has also analysed the change in number of days with absence seizures per 28 days from baseline phase to titration phase and from baseline phase to treatment phase by concomitant AED use subsets (valproate, lamotrigine and other AEDs). The evaluation of subsets showed no clinical meaningful effect on the change in the number of days with absence seizures per 28 days from the baseline phase to titration phase and from baseline phase to treatment phase. 69% of the subjects had 2 or 3 concomitant AEDs.

As there was an increase in absence seizures in some subjects going from baseline to treatment phase in the study the MAH has summarized the absence in treatment by numbers as follows:

Table 2 Summary of absence seizures occurring during treatment phase that had not occurred in the baseline phase

Absence in Treatment (n)	Subject Numbers
With Absence at Baseline (16)	1150, 1129, 1141, 1138, 1153, 1156, 1165, 1116, 1112, 1122, 1130, 1152, 1149, 1144, 1114, 1160
Without Absence at Baseline (6)	1120, 1127, 1133, 1134, 1154, 1163[a]
History of Absence prior to SP0961 (4)	1120, 1127, 1133, 1154
Absence in Titration (4)	1127, 1133, 1134, 1154
Absence in Maintenance (1)	1120

[a] Subject 01163 was incorrectly reported to have absence seizures during the Maintenance Phase who did not have absence at Baseline.

Sixteen subjects (32.7%) who had absence seizures during the baseline phase also had absence seizures during the treatment phase. Six subjects (12.2%) had absence seizures during the treatment phase who did not have absence seizures during the baseline phase. Due to a CRF transcription error, 1 of the 6 subjects was incorrectly reported to have absence seizures during the maintenance phase who did not have absence during the baseline phase. All in all 5 subjects (10.2%) had absence seizures during the treatment phase without having absence seizures during the baseline Phase. Four of the 5 subjects had a history of absence seizures prior to enrolment in SP0961.

One additional subject who did not have absence seizures during the baseline phase or during treatment phase, terminated the study prematurely with an episode reported as petit mal status.

Four of the 5 subjects had absence seizures during the titration phase and 1 subject had absence seizures during the maintenance phase. Three subjects experienced 21.64, 2.55, and 1.33 days, respectively, with absence seizures per 28 days during the titration phase, but none in the maintenance phase. One subject experienced 5.89 days with absence seizures per 28 days during the titration phase before discontinuing the study prematurely due to hallucinations. One subject did not have absence seizures in the titration phase and experienced 3.68 days with absence seizures per 28 days in the maintenance phase.

Assessment comment: The percentage of subjects who experienced an increase in absence seizures is around 10% (5 subjects). One additional subject who did not have absence seizures during the baseline phase or during treatment phase, terminated the study prematurely with an episode reported as petit mal status. It is acknowledged that the study is a small open study exploratory in nature, and it is therefore difficult to draw any firm conclusions from these findings. However it cannot be excluded that lacosamide has caused a worsening of absence seizures in a minority of subjects. It is noted that all of the 5 patients; were 18 yrs and older.

Myoclonic seizures

The change in the number of days with myoclonic seizures per 28 days from baseline phase to titration and treatment phases are shown in the table below:

Table 3 Change in the number of days with myoclonic seizures per 28 days from baseline phase (4 week prospective) to titration and treatment phases

Subgroup	Actual Value				Change from Baseline			
Phase	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
All subjects								
Baseline	49	4.66 (±7.98)	0.00	0.0, 27.0				
Titration	49	3.37 (±7.00)	0.00	0.0, 28.0	49	-1.29 (±6.26)	0.00	-23.9, 10.3
Treatment	49	2.75 (±6.25)	0.00	0.0, 27.6	49	-1.91 (±6.34)	0.00	-25.2, 8.0

Max=maximum; Min=minimum; SD=standard deviation; SS=Safety Set

Note: Baseline is defined as the 4-week prospective Baseline Phase.

The mean (±SD) number of days with myoclonic seizures per 28 days was 4.66 (±7.98) in the baseline phase and decreased to 3.37 (±7.00) in the titration phase. The mean (±SD) change in number of days with myoclonic seizures per 28 days from the baseline phase to the titration phase was -1.29 (±6.26). (The median change in number of days with myoclonic seizures per 28 days from the baseline phase to the titration phase was 0.00.). The mean (±SD) number of days with myoclonic

seizures per 28 days was 4.66 (±7.98) in the baseline phase and decreased to 2.75 (±6.25) in the treatment phase. The mean (±SD) change in number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase was -1.91 (±6.34). The median change in number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase was 0.00

The change in the number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase by age at onset of diagnosis subsets <2, 2 to <5, 5 to <10, 10 to <15, 15 to <20, and ≥20 years was evaluated. The evaluation of some age at onset of diagnosis subsets were found to be difficult to interpret due to the limited number of subjects. For the subsets with a larger number of subjects (5 to <10, 10 to <15, and 15 to <20 years) there was no clinically meaningful effect of age of onset on the change in number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase.

The change in the number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase by concomitant AED use subsets (valproate, lamotrigine, and other AEDs [including all epileptic drugs except valproate and lamotrigine]) was evaluated. The evaluation of the subsets based on AED use showed no clinically meaningful effect on the change in the number of days with myoclonic seizures per 28 days from the baseline phase to the treatment phase. 69% of subjects were taking 2 or 3 concomitant AEDs

Assessment comment: The study is a small open study exploratory in nature. Also due to the nature of this type of epilepsy and patient population it is acknowledged that no firm conclusions from the results on myoclonic seizures can be drawn.

Other safety

The MAH evaluated the change in PGTC seizures for exploratory purposes only as the 9 week treatment phase was not considered long enough to draw conclusions on efficacy. The mean (±SD) change in number of PGTC seizures per 28 days from the combined baseline phase to the maintenance phase was -0.27 (±1.05) and from the combined baseline phase to the treatment phase 0.04 (±2.40). The median change in the number of PGTC seizures per 28 days from the combined baseline phase to the maintenance phase was -0.35 and from the combined baseline phase to the treatment phase was -0.25.

Overall, 43 subjects (87.8%) reported at least 1 TEAE during the study. TEAEs were similar to those seen in POS studies with the exception of those that are unique to the PGTC class of seizures (reported terms for petit mal epilepsy). Frequently reported TEAEs (>15%) were dizziness (19 subjects [38.8%]), nausea (13 subjects [26.5%]), headache (8 subjects [16.3%]), and somnolence (8 subjects [16.3]).

No subjects died during the study. One serious TEAE of petit mal epilepsy (reported term: petit mal status) was reported during the study.

A total of 9 subjects prematurely discontinued the study. The AEs leading to discontinuation included dizziness (1 subject); grand mal convulsion (reported term: increased generalized tonic-clonic seizures [1 subject]); petit mal epilepsy (reported term: increased absence seizures [1 subject]); vertigo, diplopia, gait disturbance, hallucination, nausea, sedation, vision blurred (1 subject); and petit mal epilepsy (reported term: petit mal status [1 subject]). The only “other significant TEAE” reported was alanine aminotransferase increased which occurred in 1 subject (again in a subject older than 18 years of age).

The median values for haematology, clinical chemistry, and urinalysis parameters remained within the normal range, and the changes from baseline were not of clinical relevance.

Assessment of or ECG parameters, vital sign parameters (pulse rate, blood pressure [systolic and diastolic blood pressure]), body weight, and results from physical and neurological examinations did not reveal any clinically relevant findings.

Assessment comment: The pattern of Adverse Events in general for this small study seem to be in line with what is seen in patients treated with adjunctive Vimpat for partial-onset seizures which is the currently approved indication

2.2.3. Discussion on clinical aspects

The MAH has submitted data from a small open study assessing safety in uncontrolled PGTC seizures. The paediatric data from this small study consists of only 3 subjects who were all 17 years old at the time of inclusion.

Although not significant it is of interest to note there seem to be a small increase in absence seizures in the study population during the titration phase of the study. None of the 5 subjects is below 18 yrs, and no conclusions can be drawn from these findings. There are reports in the literature of seizure exacerbation in juvenile IGE (Gelisse et al, Epilepsia 2004;45:1282-1286 and Perucca et al Epilepsia,39 (1):5-17,1998) in subjects treated with anti-epileptics.

Assessment comment: The small increase in absence seizures in the study population could be of potential interest as none of the 5 subjects had absences at baseline. The MAH is asked to discuss this in more detail.

Additional CHMP comments:

Overall, the conclusions are endorsed. In particular, the MAH should specify the epileptic syndrome of each patient who developed/experienced increase in absence seizures and discuss the possible evolution/worsening of seizure in the context of the specific epileptic syndrome.

According to the Art.46 of Reg(EC)N.1902/2006, the MAH submitted available paediatric data from SP0961 study. This study includes a very limited number of paediatric subjects (only 3 out of 49 were 17 years old at the time of inclusion), however a discussion on these subject's results might have been useful.

The primary objective of SP0961 was to assess the safety of lacosamide in subjects with uncontrolled PGTC seizure with IGE, whereas the efficacy in the reduction of PGTC seizure frequency was only evaluated for exploratory purposes. Overall, the results indicate that there was a small reduction in absence seizures and myoclonic seizures frequency from the baseline phase to the maintenance phase. However, it is of note that around 10% of the subjects experienced an increase in absence seizures during the treatment phase (including titration phase and maintenance phase) without having absence seizures during the baseline phase (one subject had no history of absence seizures prior to enrolment in SP0961). Due to the small number of subjects, the study results do not allow to draw conclusions either on efficacy or on safety in the paediatric population.

2.3. Rapporteur's Overall Conclusion and Recommendation

The post-authorisation measure is considered fulfilled. However, further action is required as detailed below.

2.4. ADDITIONAL CLARIFICATIONS REQUESTED

1. The small increase in absence seizures in the study population could be of potential interest as none of the 5 subjects had absences at baseline. The MAH is asked to discuss this in more detail and specify the epileptic syndrome of each patient who developed/experienced increase in absence seizures and discuss the possible evolution/worsening of seizure in the context of the specific epileptic syndrome
2. This study includes a very limited number of paediatric subjects (only 3 out of 49 were 17 years old at the time of inclusion), the applicant is however requested to provide a discussion on these subject's results.

This information was requested to be provided and will be assessed in the context of Periodic Safety Update Report (PSUR) #6.