EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/261700/2020
Human Medicines Division

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/P46/037

Note

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

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1. Introduction

In the EU, lacosamide (LCM) is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide; previously referred to as harkoseride) is a functionalised amino acid. The precise mechanism of its antiepileptic effects in humans is not fully elucidated, but in vitro electrophysiological studies have indicated a selective enhancement of slow inactivation of voltage-gated sodium channels with ensuing stabilization of hyperexcitable neuronal membranes.

On 5th of December, 2019, the MAH submitted an Article 46 paediatric dossier for study SP0060, which was completed on 28th of June 2019, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

EP0060 was a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of i.v. LCM infusions in pediatric patients ≥1 month to <17 years of age with epilepsy. The study also assessed the pharmacokinetics (PK) of LCM use in this population. The MAH has provided the final CSR based on the completed study.

The study EP0060 aimed at enrolling a total of approximately 100 paediatric patients.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product was provided as LCM 10mg/mL intravenous solution.

2.3. Clinical aspects

2.3.1. Introduction

For the current report, the MAH submitted a clinical overview addendum, summarizing the disposition and TEAEs for the 103 participants from EP0060, all within the age ranges from 1 month to <17 years old at the time of study entry, in order to fulfil the requirement of reporting paediatric data as outlined in Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The MAH also submitted a final clinical study report for study SP0982 providing data from the overall participant population.

2.3.2. Clinical study

EP0060: ***Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric study participants ≥1 month to <17 years of age with epilepsy.participants ≥ 4 years of age with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs.***

Description

Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of i.v. LCM infusions in pediatric study participants ≥1 month to <17 years of age with epilepsy, and in addition, pharmacokinetic (PK) data regarding the use of the i.v. LCM formulation either as replacement for oral LCM or for adjunctive LCM treatment initiation. No efficacy data were collected.

Methods

Objective

The primary objective of this study was to evaluate the safety and tolerability of i.v. LCM infusion(s) in paediatric study participants ≥1 month to <17 years with epilepsy. Evaluation of the PK of i.v. LCM in paediatric patients was considered an additional objective.

Study design

As described above, EP0060 was a phase 2/3, multicenter, open-label safety and tolerability study to evaluate i.v. LCM infusions in pediatric study participants ≥1 month to <17 years of age with epilepsy. The study population of some 100 patients from approximately 30 sites was to consist of following patient groups eligible for the study:

- Open-label lacosamide (OLL) patients: patients receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study) upon EP0060 enrollment.
- Patients on prescribed lacosamide (RxL) (eg. VIMPAT) patients: patients who were receiving prescribed oral LCM from commercial supply (eg. VIMPAT) as adjunctive or monotherapy upon EP0060 enrollment.
- Initiating iv lacosamide (IIL) patients: patients who were not receiving LCM prior to EP0060 enrollment and received iv LCM as adjunctive treatment in EP0060. LCM monotherapy was not permitted in IIL study participants.

For all patients, the screening, baseline, treatment period, and the final visit occurred in 1 day, provided the patient only required 1 i.v. infusion, results of examinations were available to allow verification of eligibility prior to infusion, and the time permitted completion of final visit assessment. Should more time be necessary for screening assessments or to obtain results, the screening period could last up to 7 days. For OLL and RxL patients, oral LCM was administered during this time according to their open-label study or prescribed LCM dosage regimen, whereas IIL patients were not administered LCM during this period. If time did not permit completing the end-of-study/final visit assessments on the same day, it was conducted on the day following the last dose of iv LCM. The safety follow-up (SFU) telephone contact 1 occurred 1 to 3 days after the final visit for all study participants.

EP0060 was to begin with Cohort 1 with completion of treatment of the first 20 patients, followed by a review of the safety and tolerability data by the Independent Data Monitoring Committee (IDMC) before further enrollment. IDMC review was performed similarly after completion of 20 patients in Cohort 2.

Study population /Sample size

EP0060 was designed to include up to 2 age-based cohorts:

- Cohort 1 including a minimum of 40 patients who were ≥8 to <17 years of age, with at least 20 patients being at least 12 years old and at least 20 patients in the age range ≤8 to <12.
- Cohort 2 including approximately 44 study participants who were ≥1 month to <8 years of age, with 20 patients in the age range ≥4 to <8 years, 12 patients in the range ≥2 to <4 years, and 12 patients in the range ≥1 month to <2 years of age.

Treatments

At least 1 dose of i.v. LCM was administered during the treatment period. In case more than 1 infusion was given, they were administered twice daily (bid) at approximately 12-hour intervals for up to 10 doses (or up to 5 days) according to the clinical need (e.g. undergoing surgery) or up to 2 consecutive doses (over approximately 24 hours) for elective administration (initiation of LCM treatment). For OLL and RxL patients, the daily dose of i.v. LCM equalled the patient's current stable daily dose of oral LCM (2 to 12mg/kg/day or 100 to 600mg/day). The maximum dose permitted in this study for OLL and RxL study participants was 12mg/kg/day or 600mg/day, whichever was lower. For IIL study participants, the i.v. LCM dose was 1mg/kg bid (weight <50kg) or 50mg bid (weight ≥50kg). The total LCM daily dose for IIL patients was 2mg/kg/day (weight <50kg) or 100mg/day (weight ≥50kg) and remained constant for at least 7 days prior to an increase.

For the first 20 patients in Cohort 1, i.v. LCM was to be infused over a duration of 30-60 minutes. After IDMC review and acceptance, the infusions could be given within 15-30 minutes if needed.

Outcomes/endpoints

The primary safety variables for assessment of safety and tolerability:

- adverse events reported spontaneously by the patient and/or caregiver (including parent/legal guardian) or observed by the investigator
- patient withdrawal due to AEs

Other safety variables:

- changes in 12-lead ECGs
- changes in vital sign measurements (BP and pulse rate)
- changes in physical examinations
- changes in neurological examinations

PK variables:

- LCM concentration in plasma
- SPM 12809 concentration in plasma (the main metabolite of LCM)

There were no efficacy variables as no efficacy data were collected.

Statistical Methods

All safety and demographic variables were summarized by descriptive statistics. All summaries remained purely descriptive, as no statistical hypothesis testing was planned.

CHMP comment

The study EP0600 was focused primarily on the safety and tolerability of intravenously administered LCM in paediatric population with epilepsy (mostly as add-on treatment). The design was staged with intervening safety monitoring and carried out in two age-based cohorts.

Results

Recruitment/ Number analysed

A total of 103 patients (100%) started and completed the study, with 48 patients in Cohort 2 (≥1 month to <8 years of age) and 55 patients in Cohort 1 (≥8 to <17 years of age).

The patient subgroups are shown in the table below ***(Table 1):***

	OLL and RxL 15 to 30 minutes		OLL and RxL 30 to 60 minutes		IIL 15 to 30 minutes		IIL 30 to 60 minutes		Overall		
Disposition	Cohort 2 ≥1 mo to <8 yrs N=1 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%)	Cohort 2 ≥1 mo to <8 yrs N=5 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=16 n (%)	Cohort 2 ≥1 mo to <8 yrs N=7 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%)	Cohort 2 ≥1 mo to <8 yrs N=35 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=25 n (%)	Cohort 2 ≥1 mo to <8 yrs N=48 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=55 n (%)	All Study Participants N=103 n (%)
Started study	1 (100)	7 (100)	5 (100)	16 (100)	7 (100)	7 (100)	35 (100)	25 (100)	48 (100)	55 (100)	103 (100)
Completed study	1 (100)	7 (100)	5 (100)	16 (100)	7 (100)	7 (100)	35 (100)	25 (100)	48 (100)	55 (100)	103 (100)
Discontinued from study	0	0	0	0	0	0	0	0	0	0	0

ECG=electrocardiogram; IIL=initiating intravenous lacosamide; iv=intravenous; LCM=lacosamide; mo=month; OLL=open-label lacosamide; PK=pharmacokinetic; SS-iv=Safety Set-intravenous; RxL=prescribed lacosamide; yrs=years
Note: Completed study was defined as completed at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG).
Note: Percentages were based on the number of study participants in the SS-iv.
Data source: Table 1.4.2

The majority of patients were in the IIL group (71.8% [n=74]), followed by the RxL group (25.2% [n=26]). The predominance of IIL group was more accentuated in Cohort 2 compared to Cohort 1 (87.5% [n=42] vs. 58.2% [n=32]) whereas there were fewer patients in the RxL group (12.5% [n=6] vs. 36.4% [n=20]). The OLL study participants were all in Cohort 1 (5.5% [n=3]).

Baseline data

A summary of patient disposition and baseline characteristics is given in the table below ***(Table 2):***

Variable	Cohort 2 ≥1 mo to <8 yrs N=48	Cohort 1 ≥8 yrs to <17 yrs N=55	All Study Participants N=103
Age (years) n [a]	48	55	103
Mean (SD)	3.840 (2.329)	12.662 (2.409)	8.551 (5.013)
Median (min, max)	3.875 (0.17, 7.92)	12.583 (8.33, 16.58)	8.500 (0.17, 16.58)
Age [b], n (%)			
≥1 mo to <2 yrs	12 (25.0)	0	12 (11.7)
≥2 to <12 yrs	36 (75.0)	20 (36.4)	56 (54.4)
≥12 to <17 yrs	0	35 (63.6)	35 (34.0)
Age [c], n (%)			
≥1 mo to <2 yrs	12 (25.0)	0	12 (11.7)
≥2 to <4 yrs	14 (29.2)	0	14 (13.6)
≥4 to <8 yrs	22 (45.8)	0	22 (21.4)
≥8 to <12 yrs	0	20 (36.4)	20 (19.4)
≥12 to <17 yrs	0	35 (63.6)	35 (34.0)
Study participant group, n (%)			
OLL	0	3 (5.5)	3 (2.9)
EP0034	0	2 (66.7)	2 (66.7)
SP848	0	1 (33.3)	1 (33.3)
RxL	6 (12.5)	20 (36.4)	26 (25.2)
IIL	42 (87.5)	32 (58.2)	74 (71.8)

(Table 2 contd.)

Variable	Cohort 2 ≥1 mo to <8 yrs N=48	Cohort 1 ≥8 yrs to <17 yrs N=55	All Study Participants N=103
Target infusion duration, n (%)			
15 to 30 minutes	8 (16.7)	14 (25.5)	22 (21.4)
30 to 60 minutes	40 (83.3)	41 (74.5)	81 (78.6)
Subgroup (study participant group/target infusion duration)			
OLL/15 to 30 minutes	0	0	0
OLL/30 to 60 minutes	0	3 (5.5)	3 (2.9)
RxL/15 to 30 minutes	1 (2.1)	7 (12.7)	8 (7.8)
RxL/30 to 60 minutes	5 (10.4)	13 (23.6)	18 (17.5)
IIL/15 to 30 minutes	7 (14.6)	7 (12.7)	14 (13.6)
IIL/30 to 60 minutes	35 (72.9)	25 (45.5)	60 (58.3)
Gender, n (%)			
Male	22 (45.8)	24 (43.6)	46 (44.7)
Female	26 (54.2)	31 (56.4)	57 (55.3)
Weight (kg)	48	55	103
Mean (SD)	15.84 (6.83)	49.73 (21.36)	33.93 (23.48)
Median (min, max)	16.05 (4.8, 31.8)	46.40 (18.2, 111.9)	27.20 (4.8, 111.9)
Weight group, n (%)			
0 to <30kg	47 (97.9)	13 (23.6)	60 (58.3)
≥30 to <50kg	1 (2.1)	16 (29.1)	17 (16.5)
≥50kg	0	26 (47.3)	26 (25.2)
Height (cm)	48	54	102
Mean (SD)	98.46 (20.71)	149.39 (15.89)	125.43 (31.38)
Median (min, max)	99.50 (57.0, 131.0)	150.25 (114.0, 180.0)	127.50 (57.0, 180.0)
BMI (kg/m^2)	48	54	102
Mean (SD)	15.55 (2.15)	21.62 (6.27)	18.76 (5.66)
Median (min, max)	15.15 (11.2, 20.5)	20.10 (13.1, 38.6)	17.15 (11.2, 38.6)
Country, n (%)			
US	3 (6.3)	23 (41.8)	26 (25.2)
Hungary	12 (25.0)	9 (16.4)	21 (20.4)
Italy	1 (2.1)	4 (7.3)	5 (4.9)
Poland	5 (10.4)	4 (7.3)	9 (8.7)
Ukraine	27 (56.3)	15 (27.3)	42 (40.8)

Patient population was slightly female-dominant (55.3% [n=57]). A majority of the were white (93.2% [n=96]).

Table 3: History of seizure characteristics in the patient cohorts

Parameter	Cohort 2 ≥1 mo to <8 yrs N=48	Cohort 1 ≥8 yrs to <17 yrs N=55	All Study Participants N=103
Age at first diagnosis (yrs), n	48	55	103
Mean (SD)	1.69 (1.71)	6.29 (4.51)	4.15 (4.17)
Median (min, max)	1.15 (0.0, 5.6)	6.30 (0.0, 15.9)	3.00 (0.0, 15.9)
Time since first epileptic seizure (yrs), n [a]	48	54	102
Mean (SD)	2.52 (2.02)	6.61 (4.64)	4.68 (4.17)
Median (min, max)	2.35 (0.1, 7.4)	6.55 (0.3, 16.2)	3.55 (0.1, 16.2)
History of withdrawal seizures, n (%)	6 (12.5)	4 (7.3)	10 (9.7)
History of status epilepticus, n (%)	4 (8.3)	5 (9.1)	9 (8.7)
Time since last status epilepticus (yrs), n [a]	4	5	9
Mean (SD)	1.10 (1.80)	4.62 (4.99)	3.06 (4.14)
Median (min, max)	0.25 (0.1, 3.8)	1.50 (1.1, 12.5)	1.30 (0.1, 12.5)

max=maximum; min=minimum; mo=month; SD=standard deviation; SS-iv=Safety Set-intravenous; yrs=years
Note: Percentages were based on the number of study participants in the SS-iv.
[a] Relative to the date of informed consent.
Data source: Table 2.4

Table 4: Historical seizure types in the patient cohorts

Parameter	Cohort 2 ≥1 mo to <8 yrs N=48 n (%)	Cohort 1 ≥8 yrs to <17 yrs N=55 n (%)	All Study Participants N=103 n (%)
Partial seizures (I)	44 (91.7)	30 (54.5)	74 (71.8)
Simple partial seizures (IA)	2 (4.2)	6 (10.9)	8 (7.8)
Complex partial seizures (IB)	21 (43.8)	18 (32.7)	39 (37.9)
Partial evolving to secondary generalized (IC)	26 (54.2)	13 (23.6)	39 (37.9)
Generalized seizures (II)	1 (2.1)	11 (20.0)	12 (11.7)
Absence (IIA)	0	1 (1.8)	1 (1.0)
Myoclonic (IIB)	0	1 (1.8)	1 (1.0)
Clonic (IIC)	1 (2.1)	0	1 (1.0)
Tonic (IID)	1 (2.1)	2 (3.6)	3 (2.9)
Tonic-clonic (IIE)	0	7 (12.7)	7 (6.8)
Atonic (IIF)	0	1 (1.8)	1 (1.0)
Unclassified (III)	2 (4.2)	0	2 (1.9)

IIL=initiating intravenous lacosamide; mo=month; OLL=open-label lacosamide; RxL=prescribed lacosamide; SS-iv=Safety Set-intravenous; yrs=years
Note: Historical seizures experienced by IIL and RxL study participants during 4 weeks prior to the Screening Visit.
Note: Percentages were based on the number of study participants in the SS-iv.
Data source: Table 2.3

Actual duration of infusion ranged from 28 to 55 minutes in Cohort 2 and from 21 to 60 minutes in Cohort 1. Infusion times below 30 minutes were only evaluated in 4 study participants, including 2 study participants below 4 years of age.

The majority of patients (99.0% [n=102]) used a concomitant anti-epileptic drug (AED) during the treatment period. The most common concomitant AEDs by chemical subgroup were other antiepileptics

(63 patients [61.2%]), fatty acid derivatives (46 patients [44.7%]), and carboxamide derivatives (34 patients [33.0%]).

The use of AEDs by medication name was generally similar between cohorts, with the exception of valproic acid, used by a higher percentage of study participants in Cohort 2 (≥1 month to <8 years of age) compared with Cohort 1 (≥8 to <17 years of age), and levetiracetam and LCM, used by a lower percentage of study participants in Cohort 2 compared with Cohort 1.

CHMP comment

The subgrouping is strongly weighted towards lacosamide-naïve patients, especially in the Cohort 2. In the baseline seizure characteristics, the partial-onset seizures dominate, in line with the presently approved indication of LCM, whereas 12 patients (11.7%) were reported to have had generalized seizures. The main infusion rate under scrutiny (in 96%) is within the range 30-60 minutes. The concomitant antiepileptic medications were acceptable in combination, and the differences of concomitant AEDs between the cohorts are expected.

Efficacy results

N/A

Safety results

A total of 79 patients (76.7%) received 1 infusion, 20 patients (19.4%) received 2 infusions, 1 patient (1.0%) received 3 infusions, and 3 patients (2.9%) received 10 infusions. In Cohort 2 (≥1 month to <8 years of age) compared with Cohort 1 (≥8 to <17 years of age), a lower proportion of study participants received 1 infusion (60.4% [n=29] compared with 90.9% [n=50]) and a higher proportion of study participants received 2 infusions (39.6% [n=19] compared with 1.8% [n=1]). All study participants that received 3 infusions or 10 infusions were in Cohort 1.

Summary of TEAEs

A summary of the incidence of TEAEs in participants <18 years of age is presented in the table below ***(Table 5)***.

Category	OLL and RxL 15 to 30 minutes		OLL and RxL 30 to 60 minutes		IIL 15 to 30 minutes		IIL 30 to 60 minutes		Overall		
	Cohort 2 ≥1 mo to <8 yrs N=1 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=5 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=16 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=7 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=7 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=35 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=25 n (%) [#]	Cohort 2 ≥1 mo to <8 yrs N=48 n (%) [#]	Cohort 1 ≥8 yrs to <17 yrs N=55 n (%) [#]	All Study Participants N=103 n (%) [#]
Any TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Nonserious TEAEs	0	1 (14.3) [2]	0	1 (6.3) [1]	1 (14.3) [1]	0	2 (5.7) [3]	0	3 (6.3) [4]	2 (3.6) [3]	5 (4.9) [7]
Study participant discontinuation due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Permanent withdrawal of study medication due to TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related TEAEs	0	0	0	0	0	0	0	0	0	0	0
Drug-related serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0	0	0	0	0	0
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0	0	0	0

AE=adverse event; IIL=initiating intravenous lacosamide; mo=month; OLL=open-label lacosamide; RxL=prescription lacosamide; SS-iv=Safety Set-intravenous; TEAE=treatment-emergent adverse event; yrs=years
Note: n is the number of study participants that reported at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: Percentages are based on the number of study participants in the SS-iv.
Data source: Table 5.1

Five patients (4.9%) reported a total of 7 treatment-emergent adverse events (TEAEs) following treatment with iv LCM, including 3 patients (6.3%, 4 TEAEs) in Cohort 2 (≥1 month to <8 years of age) and 2 patients (3.6%, 3 TEAEs) in Cohort 1 (≥8 to <17 years of age). All of the TEAEs were nonserious. None of the TEAEs were considered related to study medication, led to discontinuation, led to permanent withdrawal of study medication, were severe, or led to death. Subgroup analysis of study participant groups (OLL and RxL, combined, and IIL) and target infusion duration (15 to 30 minutes, and 30 to 60 minutes) by cohort showed no meaningful trends.

The only TEAEs by SOC that occurred in >1 patient were Infections and infestations and Investigations (2 patients [1.9%] each). Four patients reported AEs during oral intake of LCM; all but one of the AEs were considered not related to study medication, and the one (pyrexia) was considered treatment emergent.

TEAEs of Interest

No TEAEs of specific interest were reported (significant arrhythmias, syncopes or loss of consciousness, serious hypersensitivity reactions, worsening of epilepsy, or sign of significant hepatic injury).

Vital sign measurements, ECG and laboratory findings

Vital signs or 12-lead electrocardiographic observations yielded no consistent or clinically relevant changes from baseline. ECG changes deemed clinically not relevant were small for PR interval, QRS duration, QTcF, and QTcB changes with no evidence of QT, QTcB, or QTcF prolongation following LCM treatment, and no ECG-related TEAEs were reported.

No hematological TEAEs were reported. Treatment-emergent AEs of increased blood triglycerides were reported by 2 patients (1.9%) as well as increased blood cholesterol in one patient (1.0%), Investigations by SOC.

The pharmacokinetic data display a high postdose variability. PK data is indicated by the MAH to be reported separately.

CHMP comment

The overall incidence of TEAEs, especially drug-related, appears low in this setting, and does not raise any new concerns about the intravenous administration in the paediatric population.

The pharmacokinetic data shows variability, which may not be unexpected, but the pharmacological conclusion is missing. The separate population PK report is not provided with the dossier. In order to evaluate whether data on exposure in paediatric subjects below 4 years of age are relevant for section 5.2, in accordance with the paediatric legislation, the population PK report should be submitted.

2.3.3. Discussion on clinical aspects

A total of 103 patients ≥1 month and <17 years old were included in study EP0060, which constituted the total population under study. The open-label study was designed to probe safety and tolerability aspects of i.v. administered LCM, which was used either as a replacement for oral administration during a procedure or for adjunctive, elective treatment initiation. The clinical contexts prompting i.v. administration are not further discussed.

A small minority of the patients reported TEAEs (5 subjects; 4.9 %). None of the events were serious or led to discontinuation of the medication. No such safety findings were reported that would fall outside the known safety profile of LCM or raise a safety concern.

The safety profile of lacosamide in the paediatric population is currently reflected in the SmPC. No new safety concerns were identified, and consequently, there is no need to update the product information based on this dataset at present; however, in order to evaluate whether data on exposure in paediatric subjects below 4 years of age are relevant for section 5.2, in accordance with the paediatric legislation, the population PK report should be submitted, as well as a clarification of how the dose was determined in the study at hand.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of EP0060 in order to fulfil the requirement of reporting paediatric data as outlined in accordance with Article 46 of regulation (EC) no 1901/2006, as amended. The limited number and the character of the reported TEAEs in subjects ≤18 years of age does not raise new safety concerns.

The MAH does not propose any changes of the currently approved SmPC based on the present data, which is supported.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is requested to provide the separate population pharmacokinetic report containing the clinical pharmacology conclusions.

2. Since LCM is not licensed in children below 4 years of age, the MAH should clarify how the dose used in the age group ≥ 1 month to 4 years was determined.

3. The i.v. LCM formulation was used in the study either as a replacement for oral administration or for adjunctive treatment initiation. The MAH is asked to briefly summarize the clinical contexts that are thought to raise the need for the use of i.v. LCM as an adjunctive treatment or as a replacement for oral use.

MAH responses to Request for supplementary information

1. The MAH have acknowledged the Agency's comment and provided the following response. The prior LCM population PK model (CL0447 Part II, submitted in sequence LC0257) was extended with data from i.v. dosed paediatric study participants from EP0060 (CL0447 Part III). CL0447 Part II contained PK data from 9 orally dosed studies EP0008, SP754, SP755, SP847, SP1047, SP848, SP0969, SP0966, SP0982. The CL0447 Part III report was provided as requested.

The modeling and simulation study aimed to update an existing population pharmacokinetic (PK) model of lacosamide (LCM), with intravenous (iv) administered data in paediatric study participants from EP0060 in order to assess the degree of similarity in exposure for the i.v. and oral routes of administration. Simulations of the proposed dosing schedule of 6 mg/kg bid for weight <30 kg, 4

mg/kg bid for weight ≥30 kg and weight <50 kg, and 200 mg bid for weight ≥50 kg [1, 2], resulted in paediatric exposures in line with adult exposures as illustrated below:

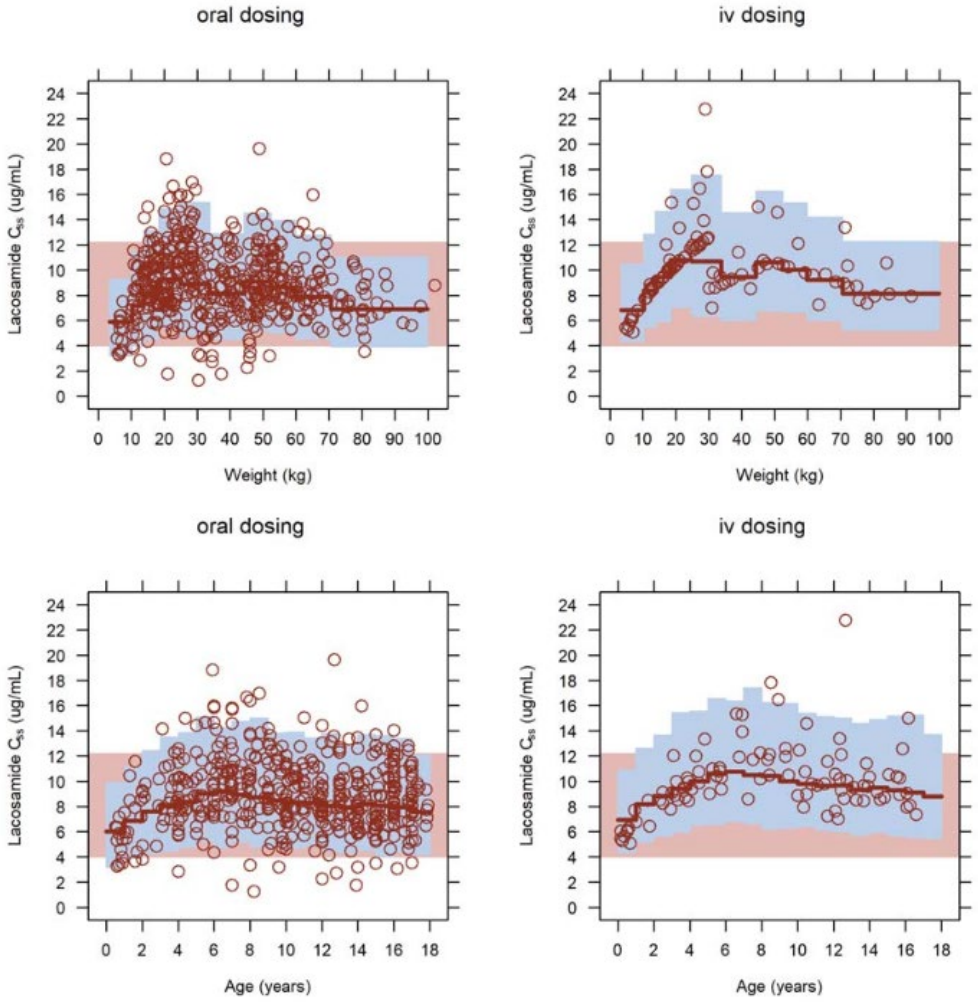

Figure: Predicted LCM Css for a 6 mg/kg bid dose for weight <30kg, a 4 mg/kg bid dose for 30≤weight<50 kg, and a 200 mg bid dose for weight ≥50 kg vs. age (bottom row) and weight (top row) for children, using the final LCM population PK model (run107) Css: average steady state concentration. Red line and blue area: median and 90% of simulated LCM Css values for study participants <18 years sampled from the Nhanes database for oral dosing (left column) and iv dosing (right column). Red circles: individual predicted LCM Css values. Pink area: 90% of simulated LCM Css values for adult study participants after oral dosing in all graph panels.

The oral dosing scheme was mostly positioned in the model-predicted range, which was interpreted as showing adequacy of the model predictions. The MAH concluded that the proposed dosing scheme results in uniform exposure across the investigated age and weight ranges in paediatric study participants, and oral dosing can be replaced with i.v. dosing without further dose-adaptation.

CHMP comment

The population PK report has been submitted with its conclusions. The supplementary information may be considered sufficient and the conclusion acceptable. The average steady state concentrations given the i.v. administration are largely similar to the concentration range given the oral administration for all body weights and ages. Hence no update of the SmPC is warranted. Issue resolved.

2. Since LCM licensing does not cover children less than 4 years of age, the MAH was asked to clarify how the dosing was determined in the age group ≥ 1 month to 4 years. The MAH responded as follows:

Acknowledging the Rapporteur's question, the rationale below is provided for dose selection:

i) A weight-based LCM dosing scheme for paediatric subjects has been or is being evaluated in Phase 3 double-blinded, placebo-controlled studies and targets similar LCM plasma concentrations as those observed in adults given 400mg/day. As such, the target doses of LCM for the Phase 3 studies are 8 to 12mg/kg/day; however, subjects entering EP0060 can be on a wider range of LCM doses based on the ranges of doses allowed in the long-term, open-label studies (2 to 12mg/kg/day or 100to 600mg/day). Thus, the i.v. LCM doses being evaluated in EP0060 will range from 2 to 12mg/kg/day or 100 to 600mg/day for open-label lacosamide (OLL) and prescribed lacosamide (RxL) subjects, with a maximum dose of 12mg/kg/day or 600mg/day, whichever is lower. For initiating intravenous lacosamide (IIL) subjects, this range of doses above also includes the paediatric starting dose of 2mg/kg/day (subjects <50kg) or 100mg/day (subjects ≥50kg), which is the same as those used in the Phase 3 paediatric LCM studies. The LCM dose at initiation of treatment should remain constant for at least 7 days prior to a LCM dose increase. The applied doses were derived from CL0177 report (submitted within sequence LC0186) and related publication (provided in Module 5.4), studied in EP0060 and confirmed in CL0447 part III report (provided in Module 5.3.3.5).

ii) The modeling and simulation study CL0447 part III aimed to update an existing population pharmacokinetic (PK) model of lacosamide (LCM), with intravenous (iv) administered data in paediatric study participants from EP0060, with the intent to assess the degree of similarity in exposure for the iv and oral route of administration. These results suggest that the proposed dosing schedule of 6 mg/kg dosed twice daily (bid) for weight <30 kg, 4 mg/kg bid for weight ≥30 kg and weight <50 kg, and 200 mg bid for weight ≥50 kg, results in uniform exposures across the investigated age and weight ranges in paediatric study participants, and oral dosing can be replaced with iv dosing without further dose-adaptation.

iii) The dose used in the age group ≥ 1 month to 4 years was also based on UCB Phase 3 study SP0967 (for paediatric patients from ≥ 1 month to 4 years of age). Using the same mg-per-mg intravenous dose as by the oral route when patients switch from oral to IV and back is justified by the complete bioavailability (F) of lacosamide (Foral:100%). The intravenous dosing regimen is also supported by prior paediatric intravenous PK modeling and simulation (CL0266 report submitted within sequence LC0186).

iv) Furthermore, EP0060 was designed to include up to 2 age-based cohorts with Cohort 1 including at least 40 study participants who were ≥8 to <17 years and Cohort 2 including approximately 44 study participants who were ≥1 month to <8 years. Within Cohort 1, at least 20 study participants were to be ≥12 to <17 years of age and at least 20 study participants were to be ≥8 to <12 years of age. Within

Cohort 2, every attempt was to be made to enroll 20 study participants ≥4 to <8 years of age, 12 study participants ≥2 to <4years of age, and 12 study participants ≥1 month to <2 years of age. An IDMC reviewed the safety and tolerability data for each cohort to make the following recommendations: the progression of the Cohort 1, including iv infusion durations to be evaluated, and initiation of enrollment in the next cohort (Cohort 2). In conclusion and considering the above, UCB considered that sufficient data were available to apply this dose regimen in the age group ≥ 1 month to 4 years.

CHMP comment

The rationale of dose determination in the youngest patient group has been acceptably clarified.

3. As the i.v. LCM formulation was used in the study either as a replacement for oral administration or for adjunctive treatment initiation, the MAH was asked to briefly summarize the clinical contexts that are thought to raise the need for the use of i.v. LCM as an adjunctive treatment or as a replacement for oral use.

In response, the MAH explained that intravenous formulations are particularly helpful as short-term replacement of oral formulations for patients unable to take oral products (e.g. preoperative and postoperative patients, patients with acute gastrointestinal disorders). Such formulations allow patients to be maintained on the same AED on their stable dose when they are unable to take the drug orally. Intravenous formulations may also be helpful in the initiation of treatment in certain situations when the patient is unable to take oral medications.

CHMP comment

The potential clinical contexts have been acknowledged and briefly summarized in the response, which is accepted.