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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

Vimpat

lacosamide

Procedure no: EMEA/H/C/000863/P46/025

Note

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

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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 19 February 2015, the MAH submitted completed paediatric studies for Vimpat, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This procedure concerns the final report for the following study in accordance with Article 46 of Regulation (EC) No 1901/2006:

SP847 A multicenter, open-label study to investigate the safety, tolerability, and pharmacokinetics of LCM oral solution (syrup) as adjunctive therapy in children with partial-onset seizures

SP1047 A multicenter, open-label study to investigate the pharmacokinetics of commercial LCM oral formulation as therapy in children (aged 1 month to 17 years) with epilepsy

A short critical expert overview has also been provided.

Therefore, this PAM submission is aimed at fulfilling the requirement of reporting pediatric data as outlined in Article 46, which requires MAH to submit information on studies conducted in children (<18 years of age) treated with lacosamide (LCM).

2. Scientific discussion

2.1. Information on the development program

Vimpat 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.

The MAH stated that the submitted studies SP847 and SP1047 are part of a paediatric development program.

MAH is currently not seeking to expand the label in paediatrics. The limited preliminary safety and efficacy data of LCM in paediatric subjects from these studies do not provide a basis for adding any significant information in the VIMPAT EU Product Information according to the MAH. Furthermore, according to the MAH, the data do not influence the benefit-risk balance of LCM to require any regulatory action on the marketing authorization of VIMPAT.

2.2. Information on the pharmaceutical formulation used in the studies

The oral solution (syrup) is used in the pediatric subjects. Bioequivalence has been shown between the tablet and oral solution (syrup) formulations, comparing 2 tablets of LCM 100mg and the oral solution (syrup) containing LCM 200mg, after single-dose administration in healthy adult subjects. The PK of LCM and its main metabolite (SPM 12809) in plasma, urine, and saliva were identical or very similar after single oral doses of LCM 200mg administered as tablets or as oral solution (syrup).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- SP847: A multicenter, open-label study to investigate the safety, tolerability, and pharmacokinetics of LCM oral solution (syrup) as adjunctive therapy in children (aged 1 month to 17 years, inclusive) with partial onset seizures;
- SP1047 A multicenter, open-label study to investigate the pharmacokinetics of commercial LCM oral formulation as therapy in children (aged 1 month to 17 years, inclusive) with epilepsy;

2.3.2. Clinical studies

Study SP847

Description

SP847 was a multicenter, open-label, safety, tolerability, and pharmacokinetic (PK) dose-titration study investigating LCM oral solution (syrup) (LCM 2mg/kg/day up to LCM 12mg/kg/day) as adjunctive therapy in pediatric subjects aged ≥1 month to ≤17 years, inclusive, with uncontrolled partial-onset seizures.

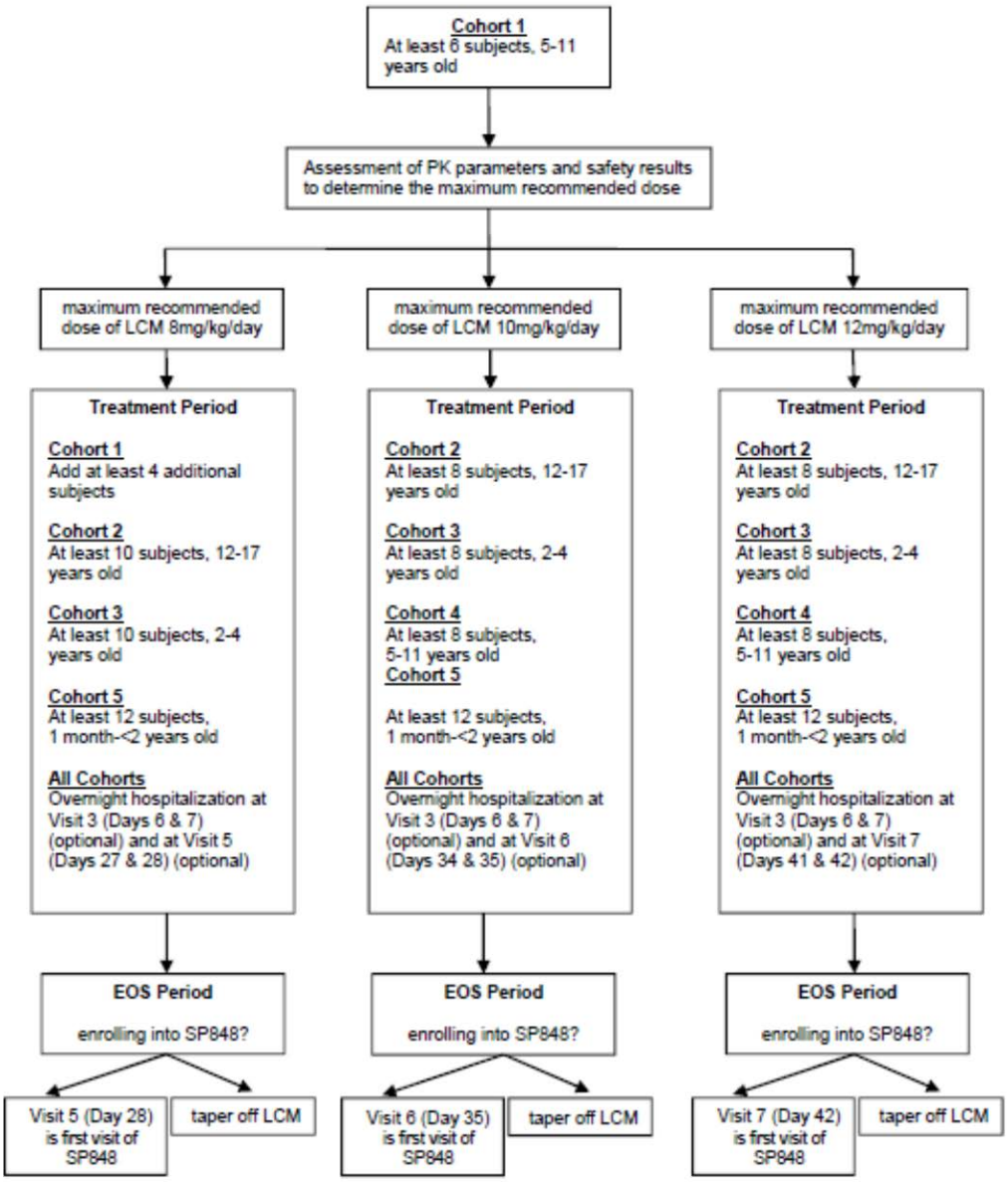
Methods

The objectives of this study were: To evaluate the safety, tolerability, and PK of LCM when added to 1 to 3 concomitant AEDs in children aged 1 month to 17 years with a diagnosis of uncontrolled partial-onset seizures and to obtain preliminary efficacy data on seizure frequency,

Study design

Subjects were to be taking a stable dosage regimen of at least 1 but no more than 3 antiepileptic drugs (AEDs). The study included a Screening Period (up to 14 days), Treatment Period (up to 4 weeks), and End-of-Study Period (up to 35 days after the last dose of LCM). The study enrolled 5 cohorts based on age: Cohort 1 (≥5 to <12 years), Cohort 2 (≥12 to ≤17 years), Cohort 3 (≥2 to <5 years), Cohort 4 (≥5 to <12 years), and Cohort 5 (≥1 month to <2 years) (Figure 1).

Figure: Overview of Treatment and End-of-Study Periods



EOS=End-of-Study; LCM=lacosamide; PK=pharmacokinetics
Note: Cohort 4 was not enrolled if the maximum recommended dose did not exceed LCM 8mg/kg/day.

Cohort 1 received a maximum dose of LCM 8mg/kg/day. After the determination of the planned dose range based on Cohort 1, additional cohorts of subjects were enrolled and doses titrated up to the maximum recommended dose (set to LCM 12mg/kg/day or LCM 600mg/day based on body weight, whichever was lower) or the maximum dose each subject was able to tolerate for at least 3 days. Doses started at 2mg/kg/day and were to be titrated in weekly increments of LCM 2mg/kg/day up to a target dose of either LCM 8mg/kg/day or LCM 12mg/kg/day (based on cohort), where target dose was to be maintained for 1 week. Dose reduction was permitted for tolerability concerns. If a subject required a dose reduction for any reason, the dose could not be increased again.

The duration of the study per subject was up to approximately 13 weeks.

Lacosamide was orally administered bid (at approximately 12-hour intervals, once in the morning and once in the evening). The LCM dose was measured and orally administered via a dosing syringe.

Blood samples for the assessment of LCM and the major metabolite SPM 12809 plasma concentrations were collected at various timepoints. In addition, 12-hour urine collection was performed for some 5- to 17-year-old subjects in order to assess urinary excretion of LCM and SPM 12809.

At the end of the Treatment Period or at the time of early discontinuation, the subject may have entered the SP848 open-label extension study or tapered off LCM. Subjects who withdrew or those who completed the Treatment Period and chose not to enroll in the open-label extension study were to be tapered off LCM.

Results

Recruitment / Number analysed

A total of 47 subjects started the study, which included 15 subjects aged ≥1 month to <4 years, 23 subjects aged ≥4 years to <12 years, and 9 subjects aged ≥12 years to ≤17 years. A total of 24 subjects (51.1%) completed the study, including 9 of 15 subjects (60.0%) aged ≥1 month to <4 years, 14 of 23 subjects (60.9%) aged ≥4 years to <12 years, and 1 of 9 subjects (11.1%) aged ≥12 years to ≤17 years.

All 47 subjects (100%) had blood samples taken for PK analysis at steady-state at 2 separate visits to fulfill the requirements for the PK objective of the study

Per the design of the study, if the subject met the study obligations (achieved MTD; collected plasma samples for determination of LCM concentration), the subject was required to discontinue the study. All 47 subjects in the study completed the required PK assessments; however, due partially to the design of the study, only 24 subjects (51.1%) completed the entire study. Subjects who discontinued were eligible to continue LCM treatment by participating in the long-term follow-up study (SP848) at the final reduced LCM dose achieved in SP847.

There were approximately equal percentages of male (48.9%) and female subjects (51.1%) in the safety set (SS). The mean age of the enrolled subjects was 7.03 years (range: 0.5 to 17.0 years); 15 subjects were <4 years of age and 32 subjects were 4 to 17 years of age. Most of the subjects were white (63.8%) and not Hispanic/Latino (55.3%). Mean weight, height, and body mass index (BMI) were 26.60kg, 115.46cm, and 17.48kg/m2, respectively. The mean time from diagnosis of epilepsy to enrollment in SP847 was 4.28 years. At study entry, 8 subjects (17.0%) were taking 3 concomitant AEDs, 29 subjects (61.7%) were taking 2 concomitant AEDs, and 10 subjects (21.3%) were taking 1 concomitant AED, with the majority of subjects in each age group taking 2 concomitant AEDs.

Overall, the mean historical seizure count for all seizures was 34.0 seizures per 28 days. The mean historical seizure count for simple partial seizures, complex partial seizures, and partial, secondary generalized seizures were 53.8 seizures per 28 days, 35.3 seizures per 28 days, and 10.1 seizures per 28 days, respectively. No subjects reported any unclassified epileptic seizures.

Pharmacokinetic data

Plasma Ctrough values for LCM increased from Visit 3, Day 7 (839.9ng/mL) to Visit 5, Day 28 (4541.2ng/mL) as subjects titrated their dose to their MTD. After Visit 5, Day 28 plasma Ctrough values remained relatively constant throughout the remainder of the study. Plasma Ctrough values for SPM12809 increased from Visit 3, Day 7 (839.9ng/mL) through Visit 7, Day 42 (1725.8ng/mL).

Safety results

Partially due to the predefined requirements of the study (if a subject required a dose reduction for any reason, the dose could not be increased again. Once the dose was reduced and having met the study obligations [achieving maximum tolerated dose; collection of plasma sample for determination of LCM concentration], the subject was required to discontinue SP847), 23 subjects (48.9%) discontinued the study (Table 1).

Table 1: Summary of subject disposition and discontinuation reasons by age group (SS)

		≥4 to ≤17 years			
Disposition	≥1 month to <4 years N=15 n (%)	≥4 to <12 years N=23 n (%)	≥12 to ≤17 years N=9 n (%)	Total N=32 n (%)	All subjects N=47 n (%)
Started study	15 (100)	23 (100)	9 (100)	32 (100)	47 (100)
PK completer	15 (100)	23 (100)	9 (100)	32 (100)	47 (100)
Completed study	9 (60.0)	14 (60.9)	1 (11.1)	15 (46.9)	24 (51.1)
Discontinued	6 (40.0)	9 (39.1)	8 (88.9)	17 (53.1)	23 (48.9)
Primary reason for discontinuation					
Adverse event	5 (33.3)	8 (34.8)	6 (66.7)	14 (43.8)	19 (40.4)
Lack of efficacy	0	1 (4.3)	0	1 (3.1)	1 (2.1)
Protocol violation	0	0	0	0	0
Lost to follow up	0	0	0	0	0
Consent withdrawn	0	0	0	0	0
Other	1 (6.7)	0	2 (22.2)	2 (6.3)	3 (6.4)
Planned to enter SP848	12 (80.0)	21 (91.3)	7 (77.8)	28 (87.5)	40 (85.1)

PK=pharmacokinetic; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Percentages were based on the number of subjects in the SS.
Note: Pharmacokinetic completer was defined as a subject who had blood samples taken for PK analysis at steady-state at 2 separate visits. Completed study was defined as a subject who finished the study per the protocol.
Note: Subject [redacted] in the ≥4 years to <12 years age group had a primary reason for discontinuation of lack of efficacy; however, the subject also experienced a TEAE leading to discontinuation (sedation) and therefore is included in the count of subjects with TEAEs leading to discontinuation in Section 8.5 (n=20).
Data sources: Table 1.4.1; Listing 1.4.1

Mean study medication duration was 40.4 days overall and was similar for each age group (range: 37.6 days to 41.4 days). Mean daily dose for the Treatment Period was 5.82mg/kg/day overall and was also similar for each age group (range: 5.09mg/kg/day to 6.26mg/kg/day). The mean daily dose increased by visit as subjects titrated dose (from 2.00mg/kg/day at Visit 3 to 11.76mg/kg/day at Visit 7), and the increases observed at each visit were similar across the age groups.

A total of 42 subjects (89.4%) reported treatment-emergent adverse events (TEAEs) during the study, with a similar percentage reported across age groups (range: 82.6% to 100%)(Table 2).

Table 2: Overview of TEAEs by age group (SS)

	≥1 month to <4 years N=15 n (%) [#]	≥4 to ≤17 years			All subjects N=47 n (%) [#]
		≥4 to <12 years N=23 n (%) [#]	≥12 to ≤17 years N=9 n (%) [#]	Total N=32 n (%) [#]	
Any TEAE	14 (93.3) [37]	19 (82.6) [82]	9 (100) [36]	28 (87.5) [118]	42 (89.4) [155]
Serious TEAEs	3 (20.0) [4]	3 (13.0) [3]	0	3 (9.4) [3]	6 (12.8) [7]
Discontinuation due to TEAEs	5 (33.3) [5]	9 (39.1) [11]	6 (66.7) [11]	15 (46.9) [22]	20 (42.6) [27]
Drug-related TEAEs	6 (40.0) [12]	14 (60.9) [32]	8 (88.9) [23]	22 (68.8) [55]	28 (59.6) [67]
Severe TEAEs	1 (6.7) [1]	0	0	0	1 (2.1) [1]
All deaths	0	0	0	0	0

AE=adverse event; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: Percentages were based on the number of subjects in the SS.
Note: [#]=number of individual occurrences of the AE in that category.
Note: Drug-related TEAEs were those with a relationship of "related," "possibly related," or those with missing responses.
Data source: Table 9.1.1

By weight band, a higher percentage of subjects ≤30kg reported TEAEs (93.8%) compared with subjects >30kg to ≤50kg (77.8%) and >50kg (83.3%). The most commonly reported TEAEs overall (by PT) were vomiting (10 subjects [21.3%]), diarrhea (7 subjects [14.9%]), and somnolence (6 subjects [12.8%]). The incidence of TEAEs reported was generally similar across the age groups (Table 3). Analysis of the most common TEAEs by dose at onset suggests that the incidences were not dose related.

Table 3: Incidence of most common TEAEs (with an incidence of at least 5% overall) by age group (SS)

MedDRA SOC PT	≥1 month to <4 years N=15 n (%) [#]	≥4 to ≤17 years			All subjects N=47 n (%) [#]
		≥4 to <12 years N=23 n (%) [#]	≥12 to ≤17 years N=9 n (%) [#]	Total N=32 n (%) [#]	
Any TEAE	14 (93.3) [37]	19 (82.6) [82]	9 (100) [36]	28 (87.5) [118]	42 (89.4) [155]
Gastrointestinal disorders	5 (33.3) [8]	10 (43.5) [19]	4 (44.4) [7]	14 (43.8) [26]	19 (40.4) [34]
Vomiting	1 (6.7) [3]	7 (30.4) [7]	2 (22.2) [2]	9 (28.1) [9]	10 (21.3) [12]
Diarrhoea	2 (13.3) [2]	4 (17.4) [7]	1 (11.1) [1]	5 (15.6) [8]	7 (14.9) [10]
Constipation	1 (6.7) [1]	1 (4.3) [1]	1 (11.1) [1]	2 (6.3) [2]	3 (6.4) [3]
General disorders and administration site conditions	5 (33.3) [6]	6 (26.1) [9]	3 (33.3) [4]	9 (28.1) [13]	14 (29.8) [19]
Irritability	3 (20.0) [3]	1 (4.3) [1]	1 (11.1) [1]	2 (6.3) [2]	5 (10.6) [5]
Pyrexia	2 (13.3) [2]	3 (13.0) [4]	0	3 (9.4) [4]	5 (10.6) [6]
Gait disturbance	0	2 (8.7) [2]	1 (11.1) [1]	3 (9.4) [3]	3 (6.4) [3]
Infections and infestations	6 (40.0) [8]	7 (30.4) [12]	2 (22.2) [2]	9 (28.1) [14]	15 (31.9) [22]
Otitis media	0	3 (13.0) [3]	0	3 (9.4) [3]	3 (6.4) [3]
Pharyngotonsillitis	3 (20.0) [3]	0	0	0	3 (6.4) [3]
Nervous system disorders	4 (26.7) [4]	11 (47.8) [21]	6 (66.7) [8]	17 (53.1) [29]	21 (44.7) [33]
Somnolence	2 (13.3) [2]	3 (13.0) [3]	1 (11.1) [1]	4 (12.5) [4]	6 (12.8) [6]
Dizziness	0	3 (13.0) [4]	2 (22.2) [2]	5 (15.6) [6]	5 (10.6) [6]
Balance disorder	0	1 (4.3) [2]	2 (22.2) [2]	3 (9.4) [4]	3 (6.4) [4]
Status epilepticus	2 (13.3) [2]	1 (4.3) [1]	0	1 (3.1) [1]	3 (6.4) [3]
Skin and subcutaneous tissue disorders	1 (6.7) [1]	4 (17.4) [4]	2 (22.2) [2]	6 (18.8) [6]	7 (14.9) [7]
Rash	1 (6.7) [1]	1 (4.3) [1]	2 (22.2) [2]	3 (9.4) [3]	4 (8.5) [4]

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: MedDRA version 16.1 was used.
Note: n=number of subjects reporting at least 1 TEAE within SOC/PT.
Note: Percentages were based on the number of subjects in the SS.
Note: [#]=number of individual occurrences of the TEAE.
Data source: Table 9.3.1

Assessors comments

The reported most common TEAEs are all identified as “common” or” very common” in the current SmPC, or expected in the included population of children and young patients with partial-onset seizures (i.e. pyrexia, otitis media, pharyngotonsillitis and status epilepticus).

The majority of subjects reported TEAEs with a maximum intensity of mild (19 subjects [40.4%]) or moderate (22 subjects [46.8%]). Only 1 subject (2.1%) reported a severe TEAE (Table 2).

A total of 28 subjects (59.6%) experienced TEAEs considered by the investigator to be related to study medication (Table 2). The most commonly reported drug-related TEAEs were diarrhea and pyrexia (each reported by 5 subjects [10.6%] overall).

No deaths were reported during this study.

A total of 6 subjects (12.8%) reported 7 treatment-emergent serious adverse events (SAEs). Status epilepticus was the most common SAE, reported by 3 subjects (6.4%). In one of the patient the investigator reported that the subject had experienced similar episodes of long lasting convulsive seizures. The subject did not experience an increase in seizure frequency, new seizure types, new or different prodromal symptoms or other symptoms of concern. In the other two patients nothing were reported about any previous episode of status epilepticus.

Assessors comments

Status epilepticus is not uncommon in the included patient population. Therefore no conclusion regarding any potential increased risk of status epilepticus can be drawn from the 3 reported SAEs in this small study but status epilepticus should be followed in ongoing/upcoming studies.

No other SAE was reported by more than 1 subject (dehydration, pneumonia viral, gastrointestinal inflammation, and viral upper respiratory tract infection were each reported by 1 subject). Two SAEs were considered related to study medication by the investigator (2 events of status epilepticus). All 7 SAEs were reported by subjects <12 years of age and ≤30kg.

A total of 20 subjects (42.6%) experienced TEAEs leading to discontinuation (Table 2). The most common TEAEs leading to discontinuation were vomiting (4 subjects [8.5%]), gait disturbance, dizziness, and somnolence (3 subjects [6.4%] each). By weight band, there was a lower incidence of TEAEs leading to discontinuation for subjects ≤30kg (37.5%) compared with subjects >30kg to ≤ 50kg (55.6%) and subjects >50kg (50.0%). Of the 20 subjects experiencing TEAEs leading to discontinuation, 5 subjects had received a maximum dose of LCM 12mg/kg/day, 3 subjects had received a maximum dose of 10mg/kg/day, 7 subjects had received a maximum dose of 8mg/kg/day, 4 subjects had received a maximum dose of 6mg/kg/day, and 1 subject had received a maximum dose of 4mg/kg/day.

Assessors comments

By weight band, there was a lower incidence of TEAEs leading to discontinuation for subjects ≤30kg (37.5%) compared with subjects >30kg to ≤50kg (55.6%) and subjects >50kg (50.0%). However, a higher percentage of subjects ≤30kg reported TEAEs (93.8%) compared with subjects >30kg to ≤ 50kg (77.8%) and >50kg (83.3%) by weight band. These contradictory findings are consequently interpreted as chance findings by the assessor.

No other significant TEAEs were reported during the study.

Three subjects reported seizure related TEAEs during the study (3 events of status epilepticus) and 1 subject reported a body weight change TEAE (weight decreased). No TEAEs related to memory impairment, amnesia, cognitive disorders, or psychotic disorders were reported.

One subject (a 2-year-old female) experienced a TEAE of drug induced liver injury and shifts in liver function test parameters (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase). Test results for ALT (slightly above upper limit normal at baseline) and AST were substantially increased above upper limit normal 7 days after first dose of Vimpat, but normalized to the baseline values after discontinuation of Vimpat. Bilirubin did not increase.

Assessors comment

“Liver function test abnormal” is reported as “Uncommon” in the current SmPC, i.e. identified as an AE.

No clinically significant changes in mean body weight, overall or for any age group, were observed at any post-Baseline visit. However, 7 subjects (14.9%) were reported as <3% of the normal body weight growth curve range and 5 of these 7 subjects continued to have abnormally low weights at Visit 7/Early Termination.

Assessors overall comments on safety findings

Partially due to the predefined requirements of the study a substantial number of included patients discontinued the study (48.9%), mainly due to AEs. The reported most common TEAEs are all expected from the known AE profile of Vimpat, or expected in the included young patient population. There was a similar percentage of TEAEs reported across age groups during the study.

The most common TEAEs leading to discontinuation are all “common” according to the current SmPC.

No conclusion regarding any potential increased risk of status epilepticus can be drawn from this small study but status epilepticus should be followed in ongoing/upcoming studies.

Overall, the safety findings do not raise any new concerns in the studied population.

Efficacy results

At Screening, subjects/caregivers (including parent/legal guardian) were asked how many and the type of seizures the subject had in the previous 4 weeks; this served as a historical Baseline.

Seizure data were to be collected in diaries provided to subjects/caregivers (including parent/legal guardian). Each subject/caregiver (including parent/legal guardian) kept a diary to note daily seizure activity (seizure type and seizure frequency) from the Screening Visit until the end of study participation.

The percent change in seizure frequency per 28 days by seizure type and by age group and overall is summarized for the FAS in Table 4.

Table 4: Percent change in seizure frequency per 28 days by seizure type and by age group (FAS)

Seizure type	Statistic	≥1 month to <4 years N=14	≥4 to ≤17 years			All subjects N=46
			≥4 to <12 years N=23	≥12 to ≤17 years N=9	Total N=32	
Total	n	14	23	9	32	46
	Mean (SD)	18.94 (111.44)	18.38 (88.16)	34.59 (92.45)	22.94 (88.18)	21.72 (94.59)
	Median	-6.57	-8.81	-4.61	-8.57	-8.57
	Min, max	-100.0, 320.0	-87.1, 242.3	-57.0, 190.9	-87.1, 242.3	-100.0, 320.0
Simple partial seizures (IA)	n	3	2	1	3	6
	Mean (SD)	1.73 (40.02)	96.19 (242.47)	-84.85	35.85 (200.80)	18.79 (130.84)
	Median	18.12	96.19	-84.85	-75.26	-12.88
	Min, max	-43.9, 31.0	-75.3, 267.6	-84.8, -84.8	-84.8, 267.6	-84.8, 267.6
Complex partial seizures (IB)	n	7	18	8	26	33
	Mean (SD)	61.07 (149.51)	9.18 (106.76)	19.84 (97.46)	12.46 (102.15)	22.77 (112.92)
	Median	40.73	-23.34	-20.52	-20.68	-16.05
	Min, max	-88.1, 366.6	-86.8, 350.7	-63.6, 194.0	-86.8, 350.7	-88.1, 366.6
Partial, secondary generalized seizures	n	4	7	2	9	13
	Mean (SD)	-0.95 (88.76)	39.37 (72.67)	-35.78 (27.97)	22.67 (71.81)	15.40 (74.41)
	Median	-18.23	45.45	-35.78	0.00	-15.04
	Min, max	-89.5, 122.2	-57.4, 158.6	-55.6, -16.0	-57.4, 158.6	-89.5, 158.6

FAS=Full Analysis Set; Max=maximum; min=minimum; SD=standard deviation
Note: Percent change was from Baseline to Treatment Period in seizure frequency per 28 days.
Data source: Table 6.3.1

Use of historical seizure data for Baseline values contributed to a wide variation in reported seizure rates at Baseline. Overall, and in each age group, increases in mean percent change in seizure frequency per 28 days were observed (overall: 21.72% increase in seizures per 28 days).

Similar results were observed overall and for most age groups for simple partial seizures (overall: 18.79% increase in seizures per 28 days), complex partial seizures (overall: 22.77% increase in seizures per 28 days), and partial, secondary generalized seizures (overall: 15.40% increase in seizures per 28 days).

The response to treatment per 28 days by age group and response level is summarized for the FAS in Table 5.

Table 5: Response to treatment per 28 days by age group (FAS)

		≥4 to ≤17 years			
Disposition	≥1 month to <4 years N=14 n (%)	≥4 to <12 years N=23 n (%)	≥12 to ≤17 years N=9 n (%)	Total N=32 n (%)	All subjects N=46 n (%)
≥75%	3 (21.4)	3 (13.0)	0	3 (9.4)	6 (13.0)
≥50%	4 (28.6)	4 (17.4)	2 (22.2)	6 (18.8)	10 (21.7)
≥50% to <75%	1 (7.1)	1 (4.3)	2 (22.2)	3 (9.4)	4 (8.7)
≥25% to <50%	1 (7.1)	5 (21.7)	1 (11.1)	6 (18.8)	7 (15.2)
No change	3 (21.4)	6 (26.1)	2 (22.2)	8 (25.0)	11 (23.9)
Increase in frequency	6 (42.9)	8 (34.8)	4 (44.4)	12 (37.5)	18 (39.1)

FAS=Full Analysis Set
Note: Response categories reflect reduction in seizure frequency per 28 days. No change reflects a reduction in seizure frequency per 28 days of less than 25% or an increase in seizure frequency per 28 days less than 25%. Increase in frequency reflects an increase in seizure frequency per 28 days greater than or equal to 25%.
Data source: Table 6.4.1

A similar percentage of subjects overall reported a ≥25% reduction in seizure frequency (17 subjects [37.0%]) as subjects who reported a ≥25% increase in seizure frequency (18 subjects [39.1%]), while 11 subjects (23.9%) reported no change in response to treatment. Similar results were observed in each age group.

The majority of subjects overall and in each age group were reported as having an improved status after LCM treatment based on both clinician-rated assessment and caregiver-rated assessment (78.3% to 100%).

Assessors comments

Efficacy data from this study are of limited value due to the limited sample size, the open-label design of the study, the short duration of LCM treatment at the maximum dose (1 week), and the use of historical seizure data for Baseline values. Overall, the results do not raise concern that Vimpat would be less effective in subjects aged 1 month to 17 years compared to adults, given the limitation in study design.

Study SP1047

Description

This was an open-label, multicenter study evaluating the PK of LCM in 32 children (aged 1 month to 17 years, inclusive) with epilepsy. SP1047 was conducted to augment the PK data obtained from SP847 by collecting sparse samples from paediatric subjects (aged 1 month to 17 years) who were prescribed VIMPAT for the treatment of epilepsy.

Methods

The objective of this study was to evaluate the PK of LCM in children with epilepsy, aged 1 month to 17 years.

The study consisted of a Screening Period, a Treatment and Evaluation Period, and a Follow-up Period. Subjects must have been taking prescribed VIMPAT (ie, LCM) for the treatment of epilepsy for at least 1 month prior to study entry. During the 1-day Treatment and Evaluation Period, subjects were to receive VIMPAT oral tablets or oral solution at the dose prescribed

Blood samples for LCM and SPM 12809 concentration determination was taken at 3 scheduled time points: 0 to 1 hour predose, 12 minutes to 1 hour postdose, and 1 to 2 hours postdose,

Results

A total of 32 subjects were enrolled and completed the study. They were enrolled in the following age groups: 10 subjects in the ≥1 month to <4 years age group, 13 subjects in the ≥4 to <12 years age group, and 9 subjects in the ≥12 to ≤17 years age group. Overall, the mean age of all subjects was 8.93 years (range: 0.6 to 17.3 years). The mean age of subjects by age group was 2.78, 8.99, and 15.66 years in the ≥1 month to <4 years, ≥4 to <12 years, and ≥12 to ≤17 years age groups, respectively.

Based upon consistent safety and PK modeling results from the studies SP847 and SP1047, a weight-based dosing scheme for LCM pediatric studies was established. With agreement from the European Medicines Agency Paediatric Committee (PDCO), SP1047 was terminated upon completion of SP847. At the time of completion of SP847, 2 of the planned minimum of 8 subjects were enrolled in the ≥1 month to <2 years age category and it was agreed that further enrollment of subjects <2 years of age in SP1047 was not warranted.

Pharmacokinetic results

Geometric mean plasma concentrations of LCM and SPM 12809 increased from predose (2.82µg/ml and 0.81µg/ml, respectively) to 0.2 to 1h postdose (5.82µg/ml and 0.92µg/ml, respectively) and 1 to 2h postdose (6.37µg/ml and 1.03µg/ml, respectively

Efficacy results

Efficacy was not evaluated.

Safety results

A total of 32 subjects were enrolled in the study and all 32 enrolled subjects completed the study.

Two AEs were reported for 1 subject in the ≥1 month to <2 years stratification age group during the conduct of the study (flatulence and irritability); both AEs were nonserious and considered to be not related to study medication by the investigator. No other AEs were reported during the conduct of the study.

2.3.3. Discussion on clinical aspects

The pharmacokinetic data collected in these studies are based on sparse sampling. This is in order to use the data for populations PK modelling. Without the Population PK modelling data it is impossible to draw any conclusion from the spares exposure data presented in the submitted

studies. However, the Population PK modelling of the combined data from SP1047 and SP847 are reported separately (CL0177) and were used to support weight-based dosing scheme for the Phase 3 paediatric program.

The safety data reported in the studies do not raise any new concerns in the paediatric population when comparing to the established safety profile of Vimpat in adults.

No conclusion regarding any potential increased risk of status epilepticus can be drawn from this small study but status epilepticus should be followed in ongoing/upcoming studies.

Overall, the efficacy results in study SP847 do not raise concern that Vimpat would be less effective in subjects aged 1 month to 17 years compared to adults, given the limitation in study design.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

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.

Recommendation

X Fulfilled:

No regulatory action required.

Additional clarifications requested

Not applicable.