CLINICAL STUDY REPORT SYNOPSIS: SP1047

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Lacosamide	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide, LCM)	**Page:** Not applicable	

Title of study: A Multicenter, Open-Label Study to Investigate the Pharmacokinetics of Commercial Lacosamide Oral Formulation as Therapy in Children (Aged 1 Month to 17 Years) With Epilepsy

Investigators: This was a multicenter study.

Study sites: This study was a multicenter study conducted at 9 sites in the [redacted] 5 sites enrolled subjects.

Publications (references): None

Study period: 3 years, 3 months, 19 days **First subject enrolled:** 11 Apr 2011 **Last subject completed:** 29 Jul 2014	**Phase of development:** Phase 1

Objective: The objective of this study was to evaluate the pharmacokinetics (PK) of lacosamide (LCM) in children with epilepsy, aged 1 month to 17 years.

Methodology: This was an open-label, multicenter study evaluating the PK of LCM in pediatric subjects (aged 1 month to 17 years) prescribed VIMPAT for epilepsy.

The study consisted of the following:

Screening Period (up to 8 days; Day -7 to Day 1): Subjects must have been prescribed VIMPAT (ie LCM) for the treatment of epilepsy for at least 1 month prior to study entry. Subjects must have been on a stable LCM dose and dose regimen as prescribed by a physician for at least 7 days prior to study entry with no missed doses within 3 days prior to PK sampling on Day 1. The Screening Period allowed the investigator to evaluate subjects for suitability for study enrollment. It was acceptable for screening to be conducted on more than 1 day, although it should not have extended over a period longer than 8 days (Day -7 to Day 1). It was acceptable for screening to occur on Visit 1/Day 1, the same day of the Treatment and Evaluation Period.

Treatment and Evaluation Period (1 day; Visit 1/Day 1): The Treatment and Evaluation Period consisted of a 1 day visit (Visit 1/Day 1) during which blood samples were to have been obtained for PK analysis. During Visit 1/Day 1, subjects should have received a single dose of LCM at the dose level currently prescribed by the subject's physician. Subjects should have used their own supply of prescription LCM (tablets or oral solution).

During the Treatment and Evaluation Period, blood samples for LCM and SPM 12809 concentration determination were to have been obtained via venous puncture or an indwelling

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catheter at 3 scheduled time points: 0 to 1 hour predose, 12 minutes to 1 hour postdose, and 1 to 2 hours postdose. There should have been at least 1 hour between collection of each postdose blood sample. For the plasma samples for PK analysis, the minimum total blood volume to be collected was 3mL (2 plasma samples at each of 3 scheduled time points, with a minimum of 0.5mL of plasma in each sample). Assessment of PK included analyzing plasma concentrations of LCM from sparse samples for characterization of steady-state PK of LCM using population PK methods.

Follow-up Period (7 to 10 days; Day 7 to Day 10): For subjects who completed the Treatment and Evaluation Period, a safety follow-up assessment should have been conducted via telephone during the Follow-up Period, 7 to 10 days after Visit 1/Day 1.

Number of subjects (planned and analyzed): Using the observed clearance and volume of distribution values for SP847 Cohort 1 (based on 5 subjects 5 to 11 years of age), SP1047 has been prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate of the geometric mean of clearance and volume of distribution. Therefore, the planned sample size was approximately 32 subjects. With agreement from 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.

A total of 32 subjects were enrolled in the study 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.

Diagnosis and main criteria for inclusion: Subjects were male or female between 1 month to 17 years of age, inclusive, with a diagnosis of epilepsy who had been prescribed LCM for the treatment of epilepsy for at least 1 month prior to Screening and had not been prescribed or maintained on LCM for the purposes of participating in this study. The LCM dose was stable for at least 7 days, and intake of the prescribed total daily dose confirmed for at least 3 days prior to participation. Subjects were also on a stable antiepileptic drug (AED) dosage regimen that had been kept stable for a period of at least 1 week (7 days) prior to participation.

Test product, dose(s) and mode of administration: Clinical trial supply was not provided in this study; instead, subjects were to be dosed using VIMPAT oral tablets (50mg, 100mg, 150mg or 200mg) or oral solution (10mg/mL) which the subject brought to the clinic at the dose prescribed. The investigator or designee should have confirmed that the correct product was in the possession of the subject and was used for dosing. During Visit 1, subjects should have

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received a single dose of LCM at the dose level prescribed by the subject's physician.

Duration of treatment: The maximum duration of treatment for an individual subject was up to 19 days. This consisted of a Screening Period up to 8 days, a 1 day Treatment and Evaluation Period (Visit 1/Day 1), and a safety follow-up assessment conducted via telephone during the Follow-up Period 7 to 10 days after Visit 1/Day 1.

Reference therapy, dose(s) and mode of administration, batch number(s): None

Criteria for evaluation:

Pharmacokinetics: Pharmacokinetic assessments were based on the analysis of plasma concentrations of LCM and its main metabolite, SPM 12809, from sparse samples for characterization of steady-state PK using population PK methods.

Safety: Safety and tolerability data were collected at Visit 1/Day 1 using the following variables:

- Incidence of adverse events (AEs) reported spontaneously by the subject and/or caregiver (including parent/legal guardian), or observed by the investigator
- Subject withdrawals due to AEs
- Changes in vital sign measurements (ie, blood pressure and pulse rate)
- Changes in 12 lead electrocardiograms (ECGs)
- Changes in neurological examination findings

Efficacy: No efficacy parameters were investigated in this PK study.

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Statistical methods: Pharmacokinetic data were summarized using the PK Per-Protocol Set (PK-PPS).

Descriptive statistics (n, n≥limit of quantification [LOQ]), geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, median, minimum, and maximum) for the LCM and SPM 12809 concentrations were presented by time point. Summary statistics were only calculated if at least two-thirds of data were above the lower LOQ. Values <LOQ were set to LOQ/2 for the determination of all summary statistics.

Safety variables were summarized for the Safety Set (SS).

Adverse events were tabulated by Medical Dictionary for Regulatory Affairs (MedDRA) version 16.1 system organ class (SOC) and MedDRA preferred term (PT) overall and by stratification age group. The number and percentage of subjects experiencing each event at least once were summarized. All summaries were sorted alphabetically by SOC and by frequency of events within PTs, starting with the most frequent event. All AEs reported during study conduct were to be considered treatment-emergent.

A subject data listing of all laboratory parameters (hematology, clinical chemistry, and urinalysis) collected prior to dosing was presented.

Summary statistics of the actual values and change from baseline values for vital sign parameters (systolic blood pressure, diastolic blood pressure, and pulse rate) were presented by visit. Repeated or unscheduled vital sign assessments during the study were not presented in summaries.

For quantitative ECG measurements (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT intervals using Bazett's and Fridericia's correction methods), summary statistics of the actual and change from baseline values were presented by visit. Repeated or unscheduled ECG assessments during the study were not presented in summaries.

Summary and conclusions:

Subject disposition: A total of 34 subjects were screened, 2 of whom were screen failures for reasons of ineligibility and lost to follow up (1 subject [2.9%] each). A total of 32 subjects were enrolled in the study 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.

All 32 enrolled subjects completed the study.

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Pharmacokinetics results:

- Plasma concentrations for LCM and SPM 12809 increased through 1 to 2 hours postdose. Population PK modeling of combined data from SP1047 and SP847 is reported separately (CL0177).

Safety results: The safety observations in SP1047 were consistent with the known safety profile of LCM in adults and no new safety concerns were identified.

- 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.
- No deaths were reported in this study.
- There were no AEs considered to be related to LCM by the investigator during study conduct.
- There were no AEs leading to discontinuations during study conduct.
- There were no serious adverse events (SAEs) during study conduct.
- There were no pregnancies during study conduct.
- There were no other significant AEs reported during study conduct.
- There was no evidence for any clinically significant effect of LCM treatment on vital signs, ECGs, physical examinations, or neurological examinations.

Efficacy results: There were no individual efficacy response data collected in this study.

Conclusions: Pharmacokinetic results from this study are consistent with the known PK profile of LCM. Population PK modeling of combined data from SP1047 and SP847 is reported separately (CL0177). No serious or drug related AEs were reported during the study.

Report date: 15 Sep 2017