CLINICAL STUDY REPORT SYNOPSIS: SP847

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 Safety, Tolerability, and Pharmacokinetics of Lacosamide (LCM) Oral Solution (Syrup) as Adjunctive Therapy in Children with Partial-Onset Seizures

Investigators: This was a multicenter study.

Study sites: This study was a multicenter study conducted at 30 sites in the USA, Belgium, and Mexico; 17 sites enrolled subjects.

Publications (references): None

Study period: 4 years, 9 months, 22 days **First subject enrolled:** 04 Nov 2009 **Last subject completed:** 26 Aug 2014	**Phase of development:** Phase 2

Objectives: The objectives of this study were:

- To evaluate the safety, tolerability, and pharmacokinetics (PK) of LCM when added to 1 to 3 concomitant antiepileptic drugs (AEDs) in children aged 1 month to 17 years with a diagnosis of uncontrolled partial-onset seizures
- To obtain preliminary efficacy data on seizure frequency

Methodology: SP847 was a multicenter, open-label, 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 with uncontrolled partial-onset seizures.

There were 3 periods in the study: Screening Period, Treatment Period, and End-of-Study Period. The study enrolled 5 cohorts.

The Screening Period assessments were to be conducted up to 14 days prior to the first administration of LCM.

Cohort 1 was to enroll at least 6 subjects aged ≥5 to ≤11 years. During the Treatment Period, the subjects' doses were to be titrated to LCM 8mg/kg/day over a period of 4 weeks, and subjects were to be maintained at this dose for at least 3 days to ensure subjects were at steady-state. Subjects who did not achieve a maximum dose of LCM 8mg/kg/day because of tolerability

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issues, but did complete the Treatment Period (ie, the collection of blood samples for PK analysis during Visit 3 and Visit 5 [or the Early Termination Visit {ETV}]) contributed toward the 6 subjects needed for the determination of the maximum recommended dose for subsequent cohorts. Completion of the Treatment Period was defined as any subject who achieved steady-state at LCM ≥4mg/kg/day and completed ETV or Visit 5 procedures.

When the 6 subjects in Cohort 1 completed the Treatment Period, PK parameters were calculated using noncompartmental methods, based on the blood samples collected during the 2 separate overnight stays. These PK parameters were evaluated (alone and compared with adult PK parameters), in combination with the safety results, to determine the maximum recommended dose moving forward (not to exceed LCM 12mg/kg/day [or LCM 600mg/day based on body weight, whichever was lower]), which approximated the same exposure that was previously evaluated in adults. Clinical interpretation of the tolerability of LCM as well as plasma concentration data from Cohort 1 determined the maximum recommended dose. Based on the maximum recommended LCM dose selected (LCM 8, 10, or 12mg/kg/day), the number of subsequent cohorts was determined and enrollment was initiated.

After the determination of the planned dose range based on Cohort 1, 4 additional cohorts were enrolled (Cohort 2: at least 8 subjects aged 12 to 17 years, Cohort 3: at least 8 subjects aged ≥2 to ≤4 years, Cohort 4: at least 8 subjects aged ≥5 to ≤11 years, and Cohort 5: at least 12 subjects aged ≥1 month to <2 years), and doses titrated up to the maximum recommended dose (not to exceed 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. Subjects were to be on each LCM dose for at least 5 days before the dose was titrated up to the next dose.

After at least 3 days on the maximum recommended dose (not to exceed LCM 12mg/kg/day [or LCM 600mg/day based on body weight, whichever was lower]) or the maximum dose the subject was able to tolerate (for subjects in Cohorts 2 to 5 only), blood samples were to have been collected for PK analysis. Subjects who withdrew from the study prior to completion of the Treatment Period must have completed an ETV. Blood samples were to be collected at the ETV for the maximum tolerated dose (MTD) achieved by the subject.

One LCM 2mg/kg/day dose reduction of LCM was allowed if the subject had achieved a dose of at least LCM 4mg/kg/day. However, once the LCM dose had been reduced, it could not be increased. After a dose reduction occurred, titration to the target dose of LCM no longer continued and the subject should have terminated early from the study. For the purposes of PK sampling, once a dose reduction occurred, the subject needed to remain on study medication for an adequate duration (ie, stable dosing for a minimum of 3 days) in order to achieve

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steady-state levels of LCM at his/her MTD. An additional (second) dose reduction would have required an immediate return to the clinic for an ETV regardless of the status of LCM plasma levels.

Subjects who withdrew from SP847 due to a dose reduction may have chosen to enroll in the open-label extension study (SP848), provided that eligibility requirements were met.

During the End-of-Study Period, subjects may have entered the open-label extension study (SP848) or tapered off LCM, via weekly decrements of LCM 4mg/kg/day. A final End-of-Study Visit occurred 2 weeks after the final dose of LCM. A Safety Follow-Up telephone contact was performed 28 to 35 days after the final dose of LCM.

Number of subjects (planned and analyzed): The population design of SP847 was optimized using the software PFIMOPT® 3.0, based on the expression of the population Fisher information matrix in nonlinear mixed effects models using the simplex algorithm. The optimization results indicated that 24 subjects and 6 PK samples per subject (ie, 3 samples for each of the planned 2 visits with PK sampling) were appropriate for determining the structural PK parameters of LCM with good precision (about 3% mean Relative Standard Error [RSE] on clearance, 7% RSE on distribution volume, and 25% RSE for rate constant of absorption).

However, the actual precision may have been poorer and for this reason the target number of subjects was originally increased to 30 subjects.

With the addition of Cohort 5 (aged ≥1 month to <2 years) with 12 subjects, the planned sample size was approximately 42 subjects.

A total of 47 subjects started the study, which included 15 subjects aged ≥1 month to <4 years (including 12 subjects aged ≥1 month to <2 years), 23 subjects aged ≥4 years to <12 years, and 9 subjects aged ≥12 years to ≤17 years.

Diagnosis and main criteria for inclusion: Subjects were male or female between 1 month (ie, 4 weeks after full term [37 weeks gestational age]) and 17 years of age, inclusive, with a diagnosis of epilepsy with partial-onset seizures who were on a stable dosage regimen of 1 to 3 AEDs.

Test product, doses and mode of administration, batch numbers: Beginning with Protocol Amendment 4, the oral solution (syrup) formulation of LCM used in this study contained 10mg/mL of drug substance (formerly containing 15mg/mL of drug substance) and was colorless to pale yellow in appearance. The manufacturer for the LCM oral solution was Unither

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Manufacturing LLC (formerly known as UCB Manufacturing, Inc.; Rochester, NY).

Lacosamide was orally administered twice daily (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.

Batch numbers used in this study were:

- 15mg/mL: BX1002757, BX1004529, BX1005465, BX1005915
- 10mg/mL: 1081031-01, BX1009382, BX1009178, BX1006877, BX1009172

Duration of treatment: The maximum duration of treatment for an individual subject was up to approximately 13 weeks (due to the maximum allowed visit windows and if a slower taper of 2mg/kg/day per week was necessary). This consisted of a Screening Period conducted up to 14 days prior to the first administration of LCM and a 4- to 6-week Treatment Period (where subjects were titrated to a maximum dose of LCM 8mg/kg/day [Cohort 1] or LCM 12mg/kg/day [Cohorts 2 to 5] in increments of LCM 2mg/kg/day). Once subjects completed the Treatment Period, they entered the 2-week End-of-Study Period, during which subjects may have entered the open-label extension study (SP848) or tapered off LCM. In addition, there was a telephone contact 28 to 35 days after last LCM dose.

Reference therapy, doses and mode of administration, batch numbers: None

Criteria for evaluation:

Safety: Safety and tolerability were assessed using the following primary variables:

- Incidence of adverse events (AEs) reported spontaneously by the subject and/or caregiver (including parent/legal guardian), or observed by the investigator
- Subject withdrawal due to AEs
- Changes in hematology, clinical chemistry, endocrinology (follicle-stimulating hormone, luteinizing hormone, tri-iodothyronine, thyroxine, thyroid-stimulating hormone, testosterone), and urinalysis parameters
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital sign measurements (ie, blood pressure [BP] and pulse)
- Physical and neurological examination findings
- Changes in body weight, height, and calculated body mass index

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- Changes in Tanner Stage (if applicable)

Pharmacokinetics: Plasma concentrations of LCM and its major metabolite SPM 12809 were determined for characterization of steady-state PK of LCM and SPM 12809 using population PK methods.

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.

Efficacy: The efficacy variables were to be presented for descriptive purposes only and included:

- Seizure counts, which were assessed using subject diaries
- Clinical Global Impression of Change (GIC) at the end of the Treatment Period
- Caregiver GIC at the end of the Treatment Period

Statistical methods: Safety variables were summarized for the Safety Set (SS).

Adverse events were tabulated by Medical Dictionary for Regulatory Affairs (MedDRA) system organ class (SOC) and preferred term (PT) for each age group and overall; select tables were also presented by weight band, by maximum dose, or by treatment cohort. For analyses based on dose at onset, the denominator for each dose was the number of subjects who received that dose at any time during the Treatment Period.

For continuous laboratory variables (hematology, clinical chemistry, endocrinology, and urinalysis [continuous]) and vital signs, summary statistics of the actual values and their change from Baseline were presented by age group and visit. In addition, summary statistics for the actual value and change from Baseline were presented by age group for the last visit, and minimum and maximum post-Baseline values obtained during the Treatment Period. For categorical urinalysis parameters, the number and percentage of subjects identified as "negative," "trace," "1+," "2+," and "3+" were presented by visit and age group. A shift table that cross-tabulated Baseline versus maximum values during the Treatment Period was presented by age group for live function tests. The number and percentage of subjects with treatment-emergent marked laboratory abnormalities (hematology and clinical chemistry) were summarized by laboratory parameter, visit, and age group. The number and percentage of subjects with abnormal vital signs during the Treatment Period were presented by age group.

For quantitative ECG measurements (heart rate [HR], RR interval, PR interval, QRS duration, QT interval, QT interval corrected by Fridericia's formula [QTcB], and QT interval corrected by

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Fridericia's formula [QTcF]), summary statistics of the actual and change from Baseline values were presented by visit and age group. In addition to Baseline and each post-Baseline visit, the last visit, and minimum and maximum post-Baseline values were presented. Frequency tables for categorized QTc values were presented. The number and percentage of subjects with treatment-emergent ECG abnormalities were presented by visit and age group.

A population PK model was developed using the LCM plasma concentrations and dosing records, as well as demographic covariates and the presence of concomitant AEDs. Population PK modeling is reported separately (CL0177). Descriptive statistics for the LCM and SPM 12809 concentrations were presented by visit.

All seizure frequency tables were based on the Full Analysis Set (FAS) and Evaluable Set (EVS). All other presentations for efficacy parameters were based on the FAS except where otherwise noted.

Descriptive statistics for the seizure frequency per 28 days and per 7 days were presented by age group and overall for Baseline and the Treatment Period, in addition to the change from Baseline in 28-day and 7-day seizure frequency during the Treatment Period. Descriptive statistics for percent change from Baseline in 28-day seizure frequency during the Treatment Period were presented by age group and overall. Descriptive statistics for percent change from Baseline in 28-day seizure frequency during the Treatment Period were also presented for each age group and overall by Baseline seizure type. A frequency table summarizing the proportion of subjects reporting each of the following categories of percent change from Baseline in 28-day seizure frequency during the Treatment Period was presented by age group and overall. The number and percentage of subjects within each response category for the Clinical GIC were summarized by visit, age group, and overall. Additionally, the number and percentage of subjects who improved (Clinical GIC<4), had no change (Clinical GIC=4), and worsened (Clinical GIC>4) were also provided.

Summary and conclusions:

Subject disposition: 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. All 47 subjects (100%) had blood samples taken for PK analysis at steady-state at 2 separate visits and were therefore considered PK completers. 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.

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Doses in this study were titrated in increments of LCM 2mg/kg/day at weekly intervals, with a dose reduction permitted for tolerability concerns. If a subject required a dose reduction for any reason, the dose could not be increased again. 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 based on the study design. However, the 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 in SP847.

Partially due to these predefined requirements of the study, 23 subjects (48.9%) discontinued the study, including 6 of 15 subjects (40.0%) aged ≥1 month to <4 years, 9 of 23 subjects (39.1%) aged ≥4 years to <12 years, and 8 of 9 subjects (88.9%) aged ≥12 years to ≤17 years. Overall, the most common reason for discontinuation was AE (19 subjects [40.4%]), followed by "other" (3 subjects [6.4%]) and lack of efficacy (1 subject [2.1%]).

The majority of subjects overall (40 subjects [85.1%]) and in each age group (range: 77.8% to 91.3%) planned to enter the long-term follow-up study (SP848).

Safety results: The safety observations in SP847 were consistent with the known safety profile of LCM in adults and no new safety concerns were identified.

- 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%). 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.
  - 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%).
  - Analysis of the most common TEAEs by dose at onset suggests that the incidences were not dose related.
- 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.
- A total of 28 subjects (59.6%) experienced TEAEs considered by the investigator to be related to study medication. The most commonly reported drug-related TEAEs were diarrhea and pyrexia (each reported by 5 subjects [10.6%] overall).

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- 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%). 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. 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.
- 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.
- There were no pregnancies reported in this study.
- No consistent or clinically relevant mean or median changes from Baseline after LCM treatment were observed for hematology, clinical chemistry, endocrinology, or urinalysis parameters.
  - One subject (Subject SP847[redacted]; a [redacted]-year-old female) experienced a TEAE of drug-induced liver injury and shifts in liver function test parameters (alanine

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aminotransferase, aspartate aminotransferase, and alkaline phosphatase).

- No clinically significant changes in mean body weights, 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.
- There was no evidence for any effect of LCM treatment on vital signs, 12-lead ECGs, or physical examinations.
- One subject reported a positive response for suicidal ideation on the Columbia-Suicide Severity Rating Scale prior to initiating treatment (Subject SP847[redacted]). The subject did not have any other positive responses during the study.

Pharmacokinetics results: Population PK modeling results are reported separately (CL0177).

Efficacy results:

- 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 and by individual seizure type were observed. Reductions in seizure frequency were observed in the ≥12 years to ≤17 years age group for simple partial seizures and the ≥1 month to <4 years and the ≥12 years to ≤17 years age groups for partial, secondary generalized seizures.
- A similar percentage of subjects overall, and in each age group, reported a ≥25% reduction in seizure frequency (17 subjects [37.0%] overall) as subjects who reported a ≥25% increase in seizure frequency (18 subjects [39.1%] overall), while 11 subjects (23.9%) overall reported no change in response to treatment.
- 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%).

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Conclusions: The results of this study support the safety of adjunctive LCM treatment for pediatric subjects with uncontrolled partial-onset seizures and the weight-based dosing scheme to be used in future studies of LCM. The TEAE profile was generally consistent with that observed in previous LCM studies in adults, and no new safety concerns were identified.

The limited interpretation of the efficacy data supports a potential beneficial effect of LCM on seizure reduction and clinical- and caregiver-rated assessments of improvement in this pediatric population.

Report date: 03 Dec 2014