

INTERIM CLINICAL STUDY REPORT SYNOPSIS: SP848

Name of company: UCB Pharma	Individual study table referring to part of the dossier: Not applicable	<i>(For National Authority Use Only)</i>
Name of finished product: Lacosamide	Volume: Not applicable	
Name of active ingredient: SPM 927 (lacosamide [LCM])	Page: Not applicable	
Title of study: An Open-Label Study to Determine Safety, Tolerability, and Efficacy of Long-Term Oral Lacosamide (LCM) as Adjunctive Therapy in Children with Epilepsy		
Investigators: This is an ongoing multicenter study; 47 investigators have enrolled subjects as of the clinical cutoff date of 02 May 2016.		
Study sites: As of the clinical cutoff date, 47 sites have enrolled subjects in the countries of Belgium, France, Germany, Hungary, Japan, Mexico, Poland, and the US.		
Publications (references): None		
Study period: This study is ongoing. Study duration from the first subject enrolled to the clinical cutoff date is approximately 6 years and 5 months. First subject enrolled: 09 Dec 2009 Last subject completed: This study is ongoing. The clinical cutoff date for this interim report was 02 May 2016.		Phase of development: Phase 2
<p>Objectives: The objectives of this study are:</p> <ul style="list-style-type: none"> • To obtain information about the safety, tolerability, and pharmacokinetics (PK) of LCM during long-term exposure • To obtain preliminary efficacy data on seizure frequency during long-term exposure • To allow subjects who had participated in SP847 (or discontinued SP847 due to a dose reduction or status epilepticus) to continue receiving LCM • To allow subjects who had participated in other LCM pediatric clinical studies in epilepsy to continue receiving LCM • Beginning with Protocol Amendment 4, at selected sites, up to approximately 100 eligible pediatric subjects 4 to ≤17 years of age who had not previously received LCM were allowed to begin receiving LCM. Protocol Amendment 5.2 allowed approximately 46 additional eligible pediatric subjects ≥4 years to ≤17 years of age with partial-onset seizures who had not previously received LCM to directly enroll at approximately 9 sites in Japan. 		

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The purpose of this interim clinical study report (CSR) is to provide available long-term safety data in pediatric subjects with partial-onset seizures in support of a regulatory submission for LCM treatment of partial-onset seizures in pediatric subjects aged 4 years and above; therefore, only safety results are presented in this interim CSR.

Methodology: Subjects who completed SP847 (including discontinuation from SP847 due to a dose reduction or status epilepticus) or subjects from another applicable LCM pediatric clinical study (eg, SP0966) in epilepsy who chose to enter the open-label study, began on the LCM dose they had achieved in the primary study. Subjects were able to continue on LCM oral solution (syrup) or switch to LCM tablets. During the study, investigators were allowed to increase or decrease the dose of LCM and/or concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The maximum permitted LCM dose in SP848 was 12mg/kg/day or 600mg/day, whichever was lower. Increases in the LCM dose were to occur only during office visits. If the need arose to optimize tolerability and seizure reduction in selected subjects, concomitant AEDs could be carefully tapered and discontinued in order to achieve LCM monotherapy. New concomitant AEDs could be introduced as treatment if the medication was approved by the regulatory authorities in the country in which the subject lived. New concomitant AEDs could be added only when the subject had not optimally or adequately responded to a maximum tolerated dose of LCM. When subjects withdrew from the study, it was recommended that the study medication be tapered gradually in weekly decrements of 4mg/kg/day (oral solution [syrup]) or 200mg/day (tablets) for subjects who had achieved a dose of LCM ≥ 6 mg/kg/day (oral solution [syrup]) or ≥ 300 mg/day (tablet). A slower taper in weekly decrements of 2mg/kg/day (oral solution [syrup]) or 100mg/day (tablets) was permitted, if medically necessary. In case of an emergency, a faster taper was permitted after discussion with the Medical Monitor, whenever possible.

Subjects with epileptic syndromes associated with generalized seizures from SP0966 were also permitted to enroll into SP848; however, these subjects were excluded from this interim report, which presents only results for subjects with partial-onset seizures. The purpose of this interim report is to provide available long-term safety data in pediatric subjects with partial-onset seizures in support of a regulatory submission for LCM treatment of partial-onset seizures in pediatric subjects aged 4 years and above.

At selected sites, up to approximately 100 eligible pediatric subjects 4 to ≤ 17 years of age with partial-onset seizures (deemed appropriate for treatment with adjunctive LCM) who had not previously participated in an LCM clinical study were permitted to enroll directly into SP848. Following Screening, eligible subjects initiated treatment with LCM, and the LCM dose was titrated to a level to optimize tolerability and seizure control. Subjects could receive LCM oral

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<p>solution or LCM tablets for up to 2 years per subject as determined appropriate by the investigator.</p> <p>For sites in Japan, an additional 46 eligible pediatric subjects 4 to ≤17 years of age with partial-onset seizures who had not previously received LCM were also allowed to enroll directly into SP848. For these sites, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children or until the sponsor decides to discontinue the development of LCM in children in Japan.</p> <p>For sites in Japan, in order to include adequate numbers of subjects across the entire body weight range, 3 categories for body weight were defined: <30kg, ≥30kg to <50kg, and ≥50kg. At least 20% (≥10 subjects) of the Japanese subject population could enroll into each weight-based category. In order to balance each group size, the proportion of subjects assigned to each group was not to exceed 50% of the total Japanese subjects enrolled (≤23 subjects).</p> <p>The purpose of enrolling additional subjects from Japan directly into SP848 is to obtain additional long-term safety exposures in the age range from which adequate PK data have already been obtained in SP847; the additional long-term safety data will be included in planned LCM marketing applications for subjects aged 4 years and above.</p>		
<p>Number of subjects (planned and analyzed): Approximately 42 subjects from SP847 were eligible to enroll in this open-label study. Other subjects may be eligible to enroll as other LCM pediatric clinical studies in epilepsy are undertaken. In addition, at selected sites, beginning with Protocol Amendment 4, up to approximately 100 eligible pediatric subjects 4 to ≤17 years of age who had not previously participated in a LCM clinical study were permitted to enroll directly into SP848. Following the implementation of country-specific Protocol Amendment 5.2, sites in Japan were permitted to directly enroll additional eligible pediatric subjects (approximately 46 subjects) 4 to ≤17 years of age with partial onset seizures who have not previously received LCM. As of the clinical cutoff date for this interim CSR, a total of 198 subjects were screened at 47 sites and 177 subjects have started the study.</p>		
<p>Diagnosis and main criteria for inclusion: Subjects must have completed SP847 for the treatment of uncontrolled partial-onset seizures or have discontinued SP847 (due to a dose reduction or status epilepticus), or have participated in other LCM pediatric clinical studies in epilepsy and must have been expected to benefit from participation in the opinion of the investigator. Subjects who enroll directly into SP848 without previous participation in a LCM clinical study must be 4 to ≤17 years of age, have a diagnosis of epilepsy with uncontrolled partial-onset seizures after an adequate course of treatment with at least 2 AEDs, have been observed to have had at least 2 countable seizures in the 4 weeks prior to Screening, and</p>		

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currently be on a stable dosage regimen of 1 to 3 AEDs.		
<p>Test product, doses and mode of administration, batch numbers: Beginning with Protocol Amendment 3, the oral solution formulation contains 10mg/mL of drug substance (formerly 15mg/mL of drug substance) and is colorless to pale yellow in appearance. The oral solution (syrup) is packaged in amber polyethylene terephthalate bottles with a white, child-proof, polypropylene screw cap.</p> <p>The tablet formulation is supplied in doses of 50mg and 100mg. The 50mg tablets are light pink, oval, film coated tablets debossed with “SP” on 1 side and “50” on the other. The 100mg tablets are dark yellow, oval, film coated tablets debossed with “SP” on 1 side and “100” on the other. The tablets are packaged in high-density polyethylene bottles with a child-proof, polypropylene screw cap.</p> <p>Batch numbers used in this study as of the clinical cutoff date were:</p> <ul style="list-style-type: none"> • 10mg/mL oral solution: BX1006880, BX1006978, BX1006979, BX1009003, BX1009327, BX1010130, BX1010465, BX1011315, BX1012027, BX1012496, BX1013070, BX1013071 • 15mg/mL oral solution: 58396, BX1002728, BX1004528, BX1005502 • 50mg tablets: BX1002723, BX1003930, BX1005014, BX1006489, BX1008546, BX1009620, BX1010417, BX1011307, BX1012139, BX1012567, BX1013101 • 100mg tablets: BX1002724, BX1003933, BX1005016, BX1006490, BX1008238, BX1008547, BX1009621, BX1010418, BX1011309, BX1012140, BX1012568, BX1013102 		
<p>Duration of treatment: The maximum duration of LCM administration for an individual subject is to be approximately 2 years, with the exception of subjects in Japan. At the sites in Japan, the study will continue until the date of market approval for the partial-onset seizure indication for LCM in children in Japan or until the sponsor decides to discontinue the development of LCM for children in Japan.</p>		
<p>Reference therapy, doses and mode of administration, batch numbers: None</p>		
<p>Criteria for evaluation:</p> <p>Efficacy: Efficacy assessments are not included in this interim CSR.</p> <p>Pharmacokinetics: PK assessments are not included in this interim CSR.</p>		

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Safety: The safety variables evaluated in this interim CSR include the following:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, endocrinology, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (blood pressure and pulse)
- Physical and neurological examination findings
- Body weight, height, and calculated body mass index (BMI)
- Tanner Stage
- LCM palatability and ease of use questionnaire

Statistical methods: SP848 is an ongoing study. The database for this interim CSR is based on a clinical cutoff date of 02 May 2016; data reported after this date for the ongoing subjects were not included. Some safety measures are not included in this interim CSR (eg, Achenbach Child Behavior Checklist, Behavior Rating Inventory of Executive Function/Behavior Rating Inventory of Executive Function-Preschool Version, and Bayley Scales of Infant and Toddler Development-III); no efficacy or PK assessments are included in this interim CSR.

Descriptive statistics are displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category are presented. The denominator for percentages is based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. All summaries are descriptive; no statistical hypothesis testing is planned. This interim analysis only includes subjects with partial-onset seizures; therefore, subjects who entered SP848 from SP0966 were not included in the interim analysis data sets or summaries.

In general, Baseline is defined as the last nonmissing value collected prior to the first dose of LCM for safety and efficacy variables unless otherwise noted for a specific type of data. The Baseline values from SP847 are designated as Baseline values for SP848.

For the interim CSR based on a clinical cutoff date of 02 May 2016, the only analysis set applicable from the protocol is the Safety Set (SS). The SS consisted of all enrolled subjects who

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<p>took at least 1 dose of LCM in this long-term study. All safety analyses were performed on the SS.</p> <p>Adverse events are tabulated by Medical Dictionary for Regulatory Affairs (MedDRA) system organ class (SOC) and MedDRA preferred term (PT); select tables are also presented by weight band based on subject weight at time of entry into SP848: <30kg, ≥30 to <50kg, or ≥50kg. In addition, all AE summaries are presented by 3-month time intervals. The number and percentage of subjects experiencing each event at least once are summarized.</p> <p>Observed values of hematology, chemistry, endocrinology parameters, vital signs, and ECGs were summarized for each visit and the Last Visit. Change from Baseline for hematology, chemistry, and endocrinology parameters, vital signs, and ECGs were summarized for all post-Baseline visits and the Last Visit.</p> <p>The number and percentage of subjects with markedly abnormal laboratory or vital sign values are summarized at each post-Baseline visit and Last Visit. Percentages are relative to the number of subjects with a value at each time point. The number and percentage of subjects with treatment-emergent ECG abnormalities are presented for each post-Baseline visit and Last Visit.</p>		
<p>Summary and conclusions:</p> <p>Subject disposition: As of the clinical cutoff date for this interim CSR, a total of 177 subjects have started the study, which includes 12 subjects aged <4 years, 148 subjects aged 4 to <16 years (102 subjects aged 4 to <12 years and 46 subjects aged 12 to <16 years), and 17 subjects aged ≥16 years. A total of 56 subjects (31.6%) have completed the study (2 calendar years of treatment), which includes 8 subjects (66.7%) aged <4 years, 43 subjects (29.1%) aged 4 to <16 years, and 5 subjects (29.4%) aged ≥16 years. Of the 69 subjects (39.0%) who are ongoing in the study, 35 subjects (19.8%) have completed 12 months and 10 subjects (5.6%) have completed 24 months and are nearing completion in SP848.</p> <p>Overall, 52 subjects (29.4%) discontinued from the study, including 2 of 12 subjects (16.7%) aged <4 years, 48 of 148 subjects (32.4%) aged 4 to <16 years, and 2 of 17 subjects (11.8%) aged ≥16 years. The most common reason for discontinuation was lack of efficacy (21 subjects [11.9%]), followed by consent withdrawn (13 subjects [7.3%]) and AEs (10 subjects [5.6%]). Among the target age population of 4 to <16 years, a greater proportion of subjects aged 4 to <12 years (36.3%) discontinued from the study compared with subjects aged 12 to <16 years (23.9%); discontinuation reasons were generally similar between these age groups.</p>		

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Safety results: The safety observations in SP848 were consistent with the known safety profile of LCM in adults. Observations in SP848 were as expected for the pediatric population (eg, high incidence of infections and associated symptoms). No new safety concerns were identified based on the available data as of the clinical cutoff date.

- A total of 171 subjects (96.6%) experienced TEAEs as of the clinical cutoff date. Treatment-emergent AEs were most common in the SOCs of Infections and infestations (125 subjects [70.6%]), Nervous system disorders (115 subjects [65.0%]), and Gastrointestinal disorders (85 subjects [48.0%]). The most common TEAEs (by PT) were nasopharyngitis (57 subjects [32.3%]), vomiting (45 subjects [25.4%]), pyrexia (44 subjects [24.9%]), and dizziness (42 subjects [23.7%]).
 - The incidence of TEAEs was slightly lower in the 12 to <16 years age group (91.3%) compared with the other age groups (range: 98.0% to 100%).
 - Treatment-emergent AEs were observed in 98.6%, 93.9%, and 93.1% of subjects 4 to <16 years of age in the <30kg, ≥30kg to <50kg, and ≥50kg weight bands, respectively.
 - The majority of TEAEs during the study occurred during the first 3 months of treatment; a total of 150 of 177 subjects experienced TEAEs during this time interval, with lower incidence in the <4 years and 12 to <16 years age groups (66.7% and 73.9%, respectively) compared with the 4 to <12 years and ≥16 years age groups (91.2% and 88.2%, respectively).
- The majority of subjects overall experienced TEAEs with a maximum intensity of mild (83 subjects [46.9%]) or moderate (71 subjects [40.1%]). Overall, 17 subjects (9.6%) experienced severe TEAEs. The incidence of severe TEAEs was balanced across the age groups (range: 8.3% to 11.8%).
- A total of 96 subjects (54.2%) experienced TEAEs considered by the investigator to be related to study medication. Overall, the most common drug-related TEAEs were dizziness (31 subjects [17.5%]), somnolence (29 subjects [16.4%]), and vomiting (19 subjects [10.7%]).
 - Drug-related TEAEs were observed in 57.8%, 56.5%, and 64.7% of subjects in >4 years to <12 years, 12 to <16 years, and ≥16 years age groups, respectively; no drug-related TEAEs were observed in subjects in the <4 years age group.

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<ul style="list-style-type: none"> • No deaths were reported as of the clinical cutoff date for this interim CSR. • A total of 39 subjects (22.0%) experienced serious TEAEs up to the clinical cutoff date. Convulsion was the most common SAE by PT overall (17 subjects [9.6%]) and across the 4 to <12, 12 to <16, and ≥16 years age groups (range: 8.7% to 17.6%); subjects in the <4 years age group experienced no SAEs of convulsion. <ul style="list-style-type: none"> – The SAEs were observed with lower incidence by subjects in the 4 to <12 years and 12 to <16 years age groups (20.6% and 15.2%, respectively) compared with the <4 years and ≥16 years age groups (41.7% and 35.3%, respectively). – For subjects aged 4 to <16 years of age, the incidence of serious TEAEs was higher in the <30kg and ≥30kg to <50kg weight bands (14 subjects [20.0%] and 12 subjects [24.5%], respectively), compared with the ≥50kg weight band (2 subjects [6.9%]). – The incidence of serious TEAEs was consistently low and similar by time interval. There was no apparent trend for SAEs over time up to the clinical cutoff date. • A total of 11 subjects (6.2%) experienced TEAEs leading to discontinuation. The PTs of convulsion and dizziness were observed in 3 subjects (2.9%) each in the 4 to <12 years age group; the remaining PTs were observed in no more than 1 subject in any age group. <ul style="list-style-type: none"> – Nine of the subjects (8.8%) experiencing TEAEs leading to discontinuation were in the 4 to <12 years age group, 1 subject (2.2%) was in 12 to <16 years age group, and 1 subject (5.9%) was in the ≥16 years age group. – For subjects aged 4 to <16 years of age, TEAEs leading to discontinuation were evenly distributed across the 3 weight bands (4 subjects [5.7%] <30kg, 4 subjects [8.2%] ≥30kg to <50kg, and 2 subjects [6.9%] ≥50kg). – The incidence of TEAEs leading to discontinuation was consistently low across time intervals and was highest in the first 3 months of the study (5 subjects [3.4%]). At all subsequent time intervals, no more than 1 subject experienced a TEAE that led to discontinuation in subjects 4 to <16 years of age. • A total of 5 subjects overall (2.8%) experienced other significant TEAEs: 1 subject (8.3%) in the <4 years age group, 2 subjects (2.0%) in the 4 to <12 years age group, 1 subject (2.2%) in the 12 to <16 years age group, and 1 subject (5.9%) in the ≥16 years age group. Two subjects (1.1%) experienced bradycardia and 1 subject each (0.6%) experienced syncope, self-injurious behavior, and suicidal ideation. 		

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<ul style="list-style-type: none"> • The following TEAEs of relevance to the partial-onset seizure population were observed: <ul style="list-style-type: none"> – Forty-one subjects experienced seizure-related TEAEs: 26 subjects (14.7%) experienced convulsions, 6 subjects (3.4%) experienced status epilepticus, 3 subjects (1.7%) experienced epilepsy (worsening), 2 subjects each (1.1%) experienced complex partial seizures and seizure cluster, and 1 subject each (0.6%) experienced partial seizures and partial seizures with secondary generalization. – Two subjects (1.1%) experienced TEAEs of memory impairment. – One subject (0.6%) experienced a TEAE of amnesia. – Four subjects (2.3%) experienced TEAEs of weight decreased and 1 subject each (0.6%) experienced TEAEs of weight increased, obesity, and overweight. – No TEAEs of cognitive disorder or psychotic disorders were observed. • A total of 30 subjects experienced TEAEs related to pediatric growth, neurodevelopment, behavior or endocrine function: <ul style="list-style-type: none"> – Ten subjects (5.6%) experienced irritability. – Six subjects (3.4%) experienced abnormal behavior. – Three subjects (1.7%) experienced aggression. – Two subjects (1.1%) experienced psychomotor hyperactivity. – One subject (0.6%) each experienced developmental delay, autism spectrum disorder, impulse control disorder, impulsive behavior, personality change, cushingoid, growth hormone deficiency, tri-iodothyronine decreased, speech disorder developmental, attention deficit/hyperactivity, educational problem, hypothyroidism, blood thyroid stimulating hormone decreased, bilateral breast buds, and disturbance in attention. • There were no pregnancies reported as of the clinical cutoff date. • No consistent or clinically relevant mean or median changes from Baseline after LCM treatment were observed for hematology, clinical chemistry, or endocrinology parameters. • No clinically relevant changes from Baseline were observed for vital signs or 12-lead ECGs. • The incidence of shifts in neurological examination findings from normal at Baseline to abnormal, clinically significant at the Last Visit was low overall and for each age group after 		

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administration of LCM. <ul style="list-style-type: none"> • Overall and by age group, the majority of subjects responded to the palatability and ease of use questionnaire favorably for both the tablet and the syrup formulations of LCM. • Two subjects reported a positive response for suicidal ideation and 1 subject reported a positive response for suicidal behavior. None of the subjects had any other positive responses as of the clinical cutoff date. 		
Efficacy results: Efficacy was not evaluated for this interim CSR.		
Pharmacokinetic results: Pharmacokinetics were not evaluated for this interim CSR.		
Conclusions: The interim results from this ongoing long-term study are consistent with the known safety profile of LCM in adults; no new safety concerns have been identified. These results support the use of LCM in pediatric subjects aged 4 years and above with uncontrolled partial-onset seizures.		
Report date: 06 Oct 2016		