INTERIM CLINICAL STUDY REPORT SYNOPSIS: EP0034

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, Long-Term Extension Study to Investigate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Pediatric Subjects with Epilepsy with Partial-Onset Seizures

Investigators: This is an ongoing multicenter study; 96 investigators have enrolled subjects as of the clinical cutoff date of 01 Nov 2016.

Study sites: As of the clinical cutoff date, 96 sites have enrolled subjects in the study.

Publications (references): None.

Study period: This study is ongoing. Study duration from the first subject enrolled to the clinical cutoff date is approximately 2 years and 2 months. **First subject enrolled:** 13 Aug 2014 **Last subject completed:** This study is ongoing. The clinical cutoff date for this interim report was 01 Nov 2016.	**Phase of development:** Phase 3

Objectives: The primary objective of this study is to assess the long-term safety and tolerability of LCM in pediatric subjects.

The secondary objective of this study is to assess the efficacy of LCM during long-term exposure in pediatric subjects.

The other objectives of this study are to assess behavior, cognition, quality of life, and development during long-term LCM exposure in pediatric subjects.

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: EP0034 is an ongoing Phase 3, multicenter, open-label, extension study to obtain long-term safety and efficacy data in pediatric subjects with epilepsy with partial-onset seizures treated with LCM oral solution or LCM tablets as adjunctive therapy.

Subjects who participated in SP0967 or SP0969, meet the eligibility requirements of this open-label extension study, and those who consent or whose legal representative consents to

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participation could enroll into EP0034 for a maximum duration of approximately 2 years per subject. However, subjects in EP0034 who originated from SP0967 are excluded from the safety data presentations in this submission because these subjects are outside of the target age group for this submission.

EP0034 includes a Treatment Period, Taper Period, and Safety Follow-up Period, which are summarized in the following subsections.

Treatment Period

After completion of the blinded Transition Period in the primary study, all subjects are transitioned to 1 of the following LCM doses according to their weight at Baseline of the primary study: LCM 10mg/kg/day (oral solution) for subjects weighing <30kg, LCM 6mg/kg/day (oral solution) for subjects weighing ≥30kg to <50kg, and LCM 300mg/day (tablets) for subjects weighing ≥50kg. Subjects remained on this dose during at least their first week in the Treatment Period of EP0034. After 1 week in EP0034, the investigator may have adjusted the LCM dose during the Treatment Period within a range of 2mg/kg/day to 12mg/kg/day for the oral solution and 100mg/day to 600mg/day for the tablets. Regardless of formulation, the maximum dose allowed is 600mg/day or 12mg/kg/day, whichever is lower based on body weight. Subjects may take either oral solution or tablets during the Treatment Period, based on clinical judgment, regardless of their weight. Subjects may have been allowed to switch from 1 formulation to the other formulation during the Treatment Period based on clinical judgment.

At the completion of the study, or at the Early Termination Visit (ETV) for subjects who prematurely discontinue the study, investigators are to discuss treatment options with the subject and/or their legal representative(s) to best manage the subject's epilepsy. Taper of LCM may not be required for some subjects, depending on the treatment option selected by the investigator in consultation with the subject and/or legal representative(s).

Subjects who do not undergo taper of LCM should complete Visit 13/Termination Visit or the ETV and then complete the Safety Follow-up (SFU) Telephone Contact 30 days (-1/+3 days) after the final dose of LCM. The SFU Visit is not required for subjects who complete the study and who do not undergo taper of LCM. Subjects who do undergo taper of LCM should complete Visit 13/Termination Visit or the ETV and enter the Taper Period.

Taper Period

The Taper Period (up to 4 weeks, depending on dose level achieved) is required for subjects who complete the study or withdraw from treatment during the study if the following doses are achieved: LCM ≥3mg/kg/day for subjects receiving oral solution or LCM ≥150mg/day for subjects taking tablets; lower doses do not require a taper. A Taper Visit will be completed at the end of the Taper Period. A slower taper is permitted, if medically necessary. In case of an

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emergency, a faster taper is permitted after discussion with the Medical Monitor, whenever possible.

End of Study and SFU Period

Subjects who complete the study or withdraw prematurely from the study, and who discontinue use of LCM, should complete a SFU Visit 2 weeks (±2 days) after the final dose of LCM. A SFU Telephone Contact is required for all subjects (those who complete the study as planned or withdraw prematurely from the study). This telephone contact will occur 30 days (-1/+3 days) after the final dose of LCM.

Unscheduled visits may be conducted at the discretion of the investigator.

Number of subjects (planned and analyzed): Approximately 500 subjects from SP0967 and SP0969 may be eligible to enroll in this open-label extension study. Data from subjects previously enrolled in SP0967 are not included in this interim report because these subjects are outside of the target age group for this submission. As of the 01 Nov 2016 clinical cutoff date for this interim CSR, 283 subjects from SP0969 had been enrolled and received at least 1 dose of LCM.

Diagnosis and main criteria for inclusion: This study enrolled male and female subjects aged 4 to ≤17 years with a diagnosis of epilepsy with partial-onset seizures who had completed the Transition Period of SP0967 or SP0969 and were expected to benefit from participation in an open-label extension study with LCM, in the opinion of the investigator.

Test product, doses and mode of administration, batch numbers: Investigational medicinal product is provided as LCM oral solution (LCM 10mg/mL) and LCM tablets (LCM 50mg and LCM 100mg).

The oral solution formulation is colorless to pale yellow in appearance.

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.

For LCM oral solution, the following batch numbers were used as of the clinical cutoff date: BX1011063, BX1011064, BX1011065, BX1011066, BX1012414, BX1012413, BX102710, and BX1012711, BX1013589, BX1013590, BX1013591, and BX1013592.

For LCM tablets, the following batch numbers were used as of the clinical cutoff date: 50mg bottles: BX1011002, BX1012445, BX1012792, and BX1013472; 100mg bottles: BX1011003, BX1012446, BX1012793, and BX1013473.

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Duration of treatment: The maximum duration of LCM administration per subject during EP0034 will be approximately 2 years.

Reference therapy, doses and mode of administration, batch numbers: Not applicable.

Criteria for evaluation:

Efficacy: Efficacy assessments are not included in this interim CSR.

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

- Adverse event (AE) reporting
- Safety laboratory tests (hematology; biochemistry including hepatic monitoring of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyltransferase; endocrinology for all subjects; and urinalysis for subjects ≥5 years of age)
- Electrocardiograms (ECGs)
- Physical (including Tanner Stage, if applicable depending on subject's developmental status) and neurological examinations
- Vital signs (blood pressure and pulse rate)
- Body weight and height

Statistical methods: EP0034 is an ongoing study. The database for this interim CSR is based on a clinical cutoff date of 01 Nov 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 health outcomes measures 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, median, minimum, and maximum.

In general, summaries are presented overall for all subjects and additionally based on the subject's age at time of entry into study EP0034, using the following age groups: 1 to <6 months; 6 months to <1 year; 1 to <2 years; 2 to <4 years; total <4 years; 4 to <12 years; 12 to <16 years;

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total 4 to <16 years; and ≥16 years.

All summaries are descriptive; no statistical hypothesis testing is planned.

For the interim CSR based on a clinical cutoff date of 01 Nov 2016, the only analysis set applicable from the protocol is the Safety Set (SS). The SS consists of all enrolled subjects who took at least 1 dose of LCM in this long-term extension study. All safety analyses were performed on the SS.

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 EP0034: <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.

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.

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.

Summary and conclusions:

Subject disposition: As of the clinical cutoff date for this interim CSR, 284 subjects from SP0969 had been screened and 283 subjects had been enrolled in EP0034 at 96 sites. This includes 138 subjects aged 4 to <12 years, 103 subjects aged 12 to <16 years, and 42 subjects aged ≥16 years. A total of 232 subjects (82.0%) were ongoing as of the clinical cutoff date for this interim CSR and 9 subjects (3.2%) had completed the study. The majority of ongoing subjects (153 subjects [54.1%]) have completed <12 months. Of the ongoing subjects, a total of 79 subjects (27.9%) have completed ≥12 months, including 34 subjects (24.6%) aged 4 to <12 years, 28 subjects (27.2%) aged 12 to <16 years, and 17 subjects (40.5%) aged ≥16 years.

A total of 42 subjects (14.8%) aged ≥4 years discontinued from the study, including 23 of 138 subjects (16.7%) aged 4 to <12 years, 14 of 103 subjects (13.6%) aged 12 to <16 years, and 5 of 42 subjects (11.9%) aged ≥16 years. Overall, the most common reason for discontinuation was lack of efficacy (14 subjects [4.9%]), followed by consent withdrawn (11 subjects [3.9%]), AE (9 subjects [3.2%]), and "other" (8 subjects [2.8%]).

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Efficacy results: Efficacy was not evaluated for this interim CSR.

Safety results: The safety observations in EP0034 were consistent with the known safety profile of LCM in adults. Observations in EP0034 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 170 subjects (60.1%) experienced treatment-emergent AEs (TEAEs) during the study. Treatment-emergent AEs were most common in the SOCs of Infections and infestations (85 subjects [30.0%]), Nervous system disorders (60 subjects [21.2%]), and Gastrointestinal disorders (55 subjects [19.4%]). The most common TEAEs overall (by PT) were vomiting (21 subjects [7.4%], upper respiratory tract infection (20 subjects [7.1%]), and pharyngitis (19 subjects [6.7%]).
  - A similar incidence of TEAEs was observed in the 4 to <12 years, 12 to <16 years, and ≥16 years age groups (79 subjects [57.2%], 65 subjects [63.1%], and 26 subjects [61.9%], respectively).
  - Treatment-emergent AEs were observed in 46 subjects (54.1%), 53 subjects (63.9%), and 45 subjects (61.6%) in the 4 to <16 years of age group in the <30kg, ≥30kg to <50kg, and ≥50kg weight bands, respectively.
  - The incidence of TEAEs was similar across 3 month time intervals from ≤3 months through >12 months to ≤15 months (range: 30.7% to 39.6%), and then slightly lower across 3-month time intervals from >15 months to ≤18 months through ≥24 months (range: 7.7% to 19.1%)
- The majority of subjects overall experienced TEAEs with a maximum intensity of mild (78 subjects [27.6%]) or moderate (81 subjects [28.6%]). Eleven subjects (3.9%) experienced 22 severe TEAEs, half of which were serious, and the majority of which were not related to study medication (17 of 22 events) and did not lead to discontinuation from the study (20 of 22 events). The incidence of severe TEAEs was balanced across age groups (range: 2.4% to 5.9%).
- A total of 60 subjects (21.2%) experienced TEAEs considered by the investigator to be related to LCM (ie, drug-related). These drug-related TEAEs were observed at similar incidences across age groups (range: 18.1% and 25.2%). The most common drug-related TEAEs were vomiting, somnolence, and dizziness (11 subjects [3.9%], 10 subjects [3.5%], and 9 subjects [3.2%], respectively), and were observed at similar incidences across age

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groups. The only serious drug-related TEAEs were nausea, vomiting, and dyspepsia (1 subject each).

- One death was reported prior to the clinical cutoff date (cause of death unknown) and one death was reported after the clinical cutoff date (status epilepticus and infection); neither was considered related to LCM by the investigator.
- Twenty-six subjects (9.2%) experienced a total of 45 serious TEAEs. The incidence of serious AEs (SAEs) was similar in the 12 to <16 and ≥16 years age groups (6 subjects [5.8%] and 3 subjects [7.1%]) and slightly higher in the 4 to <12 years age group (17 subjects [12.3%]). The only PTs reported by more than 1 subject were convulsion (4 subjects [1.4%]), and dengue fever, status epilepticus, and vomiting (2 subjects [0.7%] each). The only SAEs considered related to study medication were vomiting, nausea, and dyspepsia (1 subject each).
  - In subjects aged 4 to <16 years, the incidence of SAEs was 9.4% (8 subjects) in the <30kg weight band, 12.0% (10 subjects) in the ≥30kg to <50kg weight band, and 6.8% (5 subjects) in the ≥50kg weight band.
  - Nine subjects experienced SAEs during the first 3 months of EP0034; 10 subjects experienced SAEs >3 to ≤6 months, and 11 subjects experienced SAEs after the first 6 months of EP0034.
- A total of 9 subjects (3.2%) experienced 12 TEAEs leading to discontinuation. The only PT observed in more than 1 subject was convulsion (2 subjects [0.7%]).
  - Seven of the subjects (5.1%) experiencing TEAEs leading to discontinuation were in the 4 to <12 years age group, 1 subject (1.0%) was in the ≥12 to <16 years age group, and 1 subject (2.4%) was in the ≥16 years age group.
  - The incidence of TEAEs leading to discontinuation was low and similar for subjects 4 to <16 years of age across the 3 weight bands (4 subjects [4.7%] <30kg, 3 subjects [3.6%] ≥30kg to <50kg, and 1 subject [1.4%] ≥50kg).
  - All TEAEs leading to discontinuation occurred within 9 months of initiating LCM treatment in EP0034.
- Four other significant TEAEs (3 suicidal ideation and 1 suicide attempt) were observed during the study in a 10-year-old subject and a 17-year-old subject.

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- Two subjects reported a positive response for suicidal ideation on the C-SSRS and 1 subject reported a positive response for suicide attempt; the events were not related to study medication by the investigator and resolved. The suicide attempt led to discontinuation from the study. In addition, 2 subjects reported a positive response for suicidal behavior.
- Few TEAEs of relevance to the partial-onset seizure population were observed.
  - Nineteen subjects experienced seizure-related TEAEs during the study (10 events of convulsion, 2 events of epilepsy, 2 events of status epilepticus, 2 events of partial seizures with secondary generalization, 2 events of complex partial seizures, 1 event of petit mal epilepsy, 1 event of febrile convulsion, and 1 event of seizure cluster).
  - Two subjects experienced a body weight change TEAE (weight increased).
  - No TEAEs related to memory impairment, amnesia, cognitive disorders, or psychotic disorders were observed.
- Twelve subjects experienced TEAEs related to pediatric growth, neurodevelopment, behavior, or endocrine function during the study (8 events of aggression, 2 events of emotional disorder of childhood, 1 event of disturbance in attention, 1 event of learning disorder, 1 event of gynecomastia, 1 event of irritability, 1 event of psychomotor hyperactivity, 1 event of hypothyroidism, and 1 event of psychomotor retardation).
- There were no pregnancies reported in this study.
- No consistent or clinically relevant mean 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 administration of LCM.

Conclusions: The interim results from this ongoing long-term extension 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: 17 Mar 2017