**CLINICAL STUDY REPORT SYNOPSIS: SP0994**

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<th>Name of company:</th>
<th>Individual study table referring to part of the dossier:</th>
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<td>UCB Pharma</td>
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<th>Name of finished product:</th>
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<th>Name of active ingredient:</th>
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<td>SPM 927 (lacosamide)</td>
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**Title of study:** A Multicenter, Double-blind, Double-dummy, Follow-up Study Evaluating the Long-term Safety of Lacosamide (200 to 600mg/day) in Comparison with Controlled-release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects with Partial-onset or Generalized Tonic-clonic Seizures ≥16 Years of Age Coming from the SP0993 Study

**Investigators:** A total of 149 investigators enrolled subjects.

**Study sites:** This was a multicenter study that included 156 sites.

**Publications (references):** None

**Study period:** This study is ongoing. Study duration from the first subject enrolled to the clinical data cutoff was approximately 3 years.

**First subject enrolled:** 16 May 2012

**Last subject completed:** This study is ongoing. The clinical data cutoff for this interim report was 22 May 2015.

**Phase of development:** Phase 3

**Objectives:** The objectives of this study are the following: to obtain information about the long-term safety of Lacosamide (LCM, Vimpat®, SPM 927, [R]-2-acetamido-N-benzyl-3-methoxypropionamide) in comparison with Carbamazepine (controlled release) (CBZ-CR) when used as monotherapy in subjects with recently diagnosed partial-onset or generalized tonic-clonic seizures and to allow subjects who completed the monotherapy study SP0993 to continue to receive LCM or CBZ-CR.

**Methodology:** SP0994 is a double-blind, double-dummy extension study for subjects who completed SP0993 or for subjects who experienced a seizure at the first or second target doses in the Maintenance Phase of SP0993.

A clinic visit occurs approximately every 13 weeks relative to the SP0994 Visit 1 date with the exception of subjects requiring a higher target dose (ie, for dose optimization). Subjects requiring a higher target dose return to the clinic for an Escalation Visit followed by a Stabilization Visit (SV); subsequent regularly scheduled visits occur at 13-week intervals relative to the SV. Visit 1 for SP0994 is the same as the second Maintenance Visit (MV) (MV2-1, MV2-2, or MV2-3) or the Early Termination Visit (ETV) for SP0993. The ETV of SP0993 as Visit 1 for SP0994.
SP0994 is applicable only for subjects on the first or second target dose. Subjects who were withdrawn from SP0993 while at the third target dose level were not allowed to participate in SP0994 with the exception of subjects who are terminated from SP0993 due to SP0993 Protocol Amendment 6.2. In SP0994, subjects are receiving a dose of LCM 200mg/day, 300mg/day, 400mg/day, 500mg/day, or 600mg/day or a dose of CBZ-CR 400mg/day, 600mg/day, 800mg/day, 1000mg/day, or 1200mg/day.

Subjects who terminated from SP0993 due to Protocol Amendment 6.2 and who required taper were dispensed a taper kit in SP0994. Across the 2 studies (SP0993 and SP0994), subjects were allowed a maximum of 2 dose escalations due to the occurrence of a seizure and 1 dose reduction due to poor tolerability in accordance with the target dose levels defined in SP0993. If, in the opinion of the investigator, the subject’s adverse events (AEs) indicate that the dose was at an intolerable level, the subject’s dose may have been decreased. This dose reduction was managed via an Unscheduled Visit, phone call, or a regularly scheduled clinic visit. If the subject experienced a seizure at the first or second dose levels, the subject was to be brought in for a dose escalation visit.

Number of subjects (planned and analyzed): Because this is a follow-up study and subjects continue into SP0994 based on their completion status of SP0993, no formal sample size determination has been performed. It was estimated that approximately 60% of subjects who enrolled in SP0993 would participate in SP0994, ie, approximately 60% of the 888 subjects who were randomized in SP0993 (533 subjects).

For this database snapshot with a clinical cutoff date of 22 May 2015, 525 subjects were included in the Safety Set (SS), which was defined as all subjects in the Enrolled Set who have received at least 1 dose of study medication prior to and including the cutoff date.

Diagnosis and main criteria for inclusion: This study enrolled subjects who had remained seizure free and completed the Maintenance Phase of the SP0993 monotherapy study, subjects who had experienced 1 or more seizures on the first or second target dose (ie, second target dose without a dose reduction) during the SP0993 Maintenance Phase, subjects who had been transferred from SP0993 to SP0994 as a result of SP0993 Protocol Amendment 6.2 (Bulgaria, Canada, Germany, Japan, Latvia, Lithuania, Mexico, Philippines, Romania, Russia, Slovakia, South Korea, Sweden, Ukraine, United States) or Czech Republic Amendment 6.3, and subjects who were expected to benefit from participation in SP0994 in the opinion of the investigator. Subjects enrolled in France who were covered by a judicial protection measure (ie, articles L.1121-6 and L.1121-8 of the French Public Health Code) were not eligible to participate in SP0994. Subjects with a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or had suicidal ideation in the past 6 months as indicated...
### Name of company:
UCB Pharma

### Individual study table referring to part of the dossier:
Not applicable

### Name of finished product:
VIMPAT®

### Volume:
Not applicable

### Name of active ingredient:
SPM 927 (lacosamide)

### Page:
Not applicable

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by a positive response (Yes) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening, or subjects who had a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS at Screening in the “Since Last Visit” version were not permitted to enroll in the study.

### Test product, doses and mode of administration, batch numbers:
Lacosamide is supplied as white, film-coated tablets in doses of 50mg and 100mg and matching placebo is supplied as white, film-coated tablets. The study medication is orally administered twice daily (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses.

For LCM tablets, the following batch numbers were used: BX1007780, BX1008174, BX1008178, BX1009105, BX1008181, BX1009104, BX1011762, BX1008180, BX1009106, BX1011772, BX1004314, BX1004341, BX1004347, BX1004340, BX1003096, BX1003095, BX1004348, BX1003098, BX1004418, BX1004418, BX1004471.

For LCM matching placebo, the following batch numbers were used: BX1008234, BX1008143, BX1008147, BX1008142, BX1008144, BX1011767, BX1011763, BX1011765, BX1008411, BX1006113, BX1004315, BX1004316, BX1004317, BX1004318, BX1004419, BX1004420, BX1005840, BX1004423, BX1005843.

### Duration of treatment:
Following the database lock and unblinding of SP0993, SP0994 was unblinded and will be closed for all subjects when follow-up access to LCM monotherapy is established. Subjects who are receiving CBZ-CR and wish to continue treatment after the close of SP0994 may receive prescribed CBZ (ie, not supplied by UCB BIOSCIENCES). Subjects who complete SP0994 and who were treated with LCM monotherapy have the option to enroll in SP1042, a long-term, open-label, follow-up study or EP0072, a Managed Access Program, following unblinding of SP0994 and approval of the respective follow-on program. Subjects who do not wish to continue LCM therapy after unblinding of SP0994 or subjects assigned to CBZ-CR treatment will be tapered off study medication and will not participate in the follow-on program.

### Reference therapy, doses and mode of administration, batch numbers:
Carbamazepine (controlled release) is supplied as yellow, opaque tablets overencapsulated in double-blind capsules size A with an overfill (mix of magnesium stearate and avicel) in a dose of CBZ-CR 200mg and matching placebo is supplied as yellow, opaque capsules size A with an overfill.

For CBZ-CR capsules, the following batch numbers were used: BX1008914, BX1010466, BX1012049, BX1012087, BX1004565, BX1004013, BX1004564, BX1005560, BX1005707, BX1006330, BX1006433, BX1005708.
For CBZ-CR matching placebo, the following batch numbers were used: BX1008919, BX1010467, BX1011995, BX1008432, BX1004567, BX1004569, BX1004566, BX1004012, BX1005559, BX1005706, BX1005754, BX1005559, BX1006406, BX1006522.

Criteria for evaluation: As the current report is an interim clinical study report (CSR), only subject (disposition and demographics) and key safety (based on AE reporting and electrocardiogram [ECG] data) information is presented in the results sections. The full analyses (including all safety variables, exploratory efficacy variables, other exploratory variables, and the pharmacokinetic [PK] variable) will be included in the final CSR when SP0994 is completed.

Efficacy: No exploratory analyses (including efficacy or health outcomes) are included in the 22 May 2015 clinical data cutoff analysis.

Pharmacokinetics/pharmacodynamics: No PK or pharmacodynamic results are included in the 22 May 2015 clinical data cutoff analysis.

Safety: The primary safety variables are as follows:

- Adverse events reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawals due to AEs
- Serious AEs (SAEs)

The other safety variables are as follows:

- Changes in hematology, chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure [BP] and heart rate [HR])
- Changes in physical or neurological examination findings
- Changes in body weight

Statistical methods: SP0994 is an ongoing study. The data for this interim CSR are based on a clinical data cutoff of 22 May 2015; data reported after this date for the ongoing subjects were not included. Not all analyses in the Statistical Analysis Plan were considered necessary for this interim CSR.

For categorical parameters, the number and percentage of subjects in each category were presented. The denominator for percentages was based on the number of subjects appropriate for
the purpose of analysis. For continuous parameters, descriptive statistics included n, mean, standard deviation, median, minimum, and maximum.

Unless otherwise specified, Baseline values for all parameters were the Baseline values in SP0993.

The Enrolled Set consists of all subjects who have given informed consent in SP0994. The SS consists of all subjects in the Enrolled Set who have received at least 1 dose of study medication in SP0994. All parameters were summarized using SS.

Treatment Period: the start of the Treatment Period is the date of Visit 1. The end of the Treatment Period is the date of the Termination Visit or ETV for subjects who are prematurely discontinued. For subjects who discontinued during the Treatment Period without an ETV, the end of the Treatment Period is the date of last known visit date (including unscheduled visits), the date of last dose, the date of premature termination, or the date of final contact, whichever is the latest.

End of Study Period: the day after the end of the Treatment Period to the Final Visit. Any additional data collected during the study, but after the Final Visit is also included in the End of Study Period.

The number of days of exposure (duration of exposure) during the Treatment Period was calculated as the treatment stop date minus the treatment start date during the Treatment Period plus 1 day. Days with unknown or zero doses that were prior to the date of last dose were included in the calculation.

Treatment-emergent AEs (TEAEs) were defined as AEs that started on or after the date of first dose of study medication in SP0994 and within 30 days following the date of last study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose. If the date of the last dose of study medication was unknown, any AEs occurring after the first dose of study medication were considered treatment-emergent.

Treatment-emergent AEs were assigned to an analysis period based on the AE onset dates. The AEs were tabulated by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term (PT). All summaries were sorted alphabetically by SOC and by frequency of events within SOCs, starting with the most frequent in the LCM treatment group.

Summaries of TEAEs and the incidence of TEAEs by dose at onset, SAEs and TEAEs leading to discontinuation (including incidence by dose at onset), and the incidence of other significant AEs during the Treatment Period were presented.

All laboratory parameters (hematology, clinical chemistry, urinalysis, and additional hormone...
and detailed information for BP, HR, body weight, and temperature were summarized in subject data listings. Twelve-lead ECG findings (QT intervals using Fridericia corrections [QTcF], PR and QRS interval, and HR values) were summarized.

### Summary and conclusions:

#### Subject disposition: At the time of the clinical cutoff date of 22 May 2015, 525 subjects were included in the SS. No subjects had completed the study, 452 subjects (86.1%) were ongoing, and 73 subjects (13.9%) had discontinued. Overall, the most common reasons for discontinuation were consent withdrawn (5.3%), AE (4.2%), and lack of efficacy (1.7%).

#### Safety results: As of the clinical cutoff date of 22 May 2015, long-term treatment with LCM was generally well tolerated in subjects newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or tonic-clonic seizures at doses up to 600mg/day when used as monotherapy for a mean duration of approximately 1 year when compared with CBZ-CR at doses up to 1200mg/day.

- The mean duration of exposure and subject-years exposed was comparable in the LCM and CBZ-CR treatment groups (378.8 days in the LCM treatment group compared with 359.4 days in the CBZ-CR treatment group and 275.9 subject-years exposed in the LCM treatment group compared with 254.8 subject-years exposed in the CBZ-CR treatment group, respectively).
- Overall, during the Treatment Period, 131 subjects (49.2%) and 121 subjects (46.7%) in the LCM and CBZ-CR treatment groups, respectively, experienced at least 1 TEAE. In the LCM and CBZ-CR treatment groups, respectively, SAEs occurred in 21 subjects (7.9%) and 19 subjects (7.3%), TEAEs leading to permanent discontinuation occurred in 11 subjects (4.1%) and 13 subjects (5.0%), and drug-related TEAEs occurred in 34 subjects (12.8%) and 31 subjects (12.0%).
- The most frequently reported TEAEs (incidence ≥3.0%) in the LCM treatment group were nasopharyngitis (4.9%) and headache (3.0%). The most frequently reported TEAEs (incidence ≥3.0%) in the CBZ-CR treatment group were nasopharyngitis (5.0%), headache (3.5%), and GGT increased and dizziness (3.1% for each).
- The incidences of the most common TEAEs (by PT) were similar between the LCM and CBZ-CR treatment groups.
- Among the small number of subjects receiving the highest doses (LCM up to 600mg/day and CBZ-CR up to 1200mg/day), the overall incidence of the most commonly reported TEAEs...
was not higher and no unexpected TEAEs were observed as compared with the lower doses.

- There were no SOCs leading to discontinuation with an incidence of ≥1% in the LCM treatment group and the most common SOCs leading to discontinuation with an incidence of ≥1% in the CBZ-CR treatment group were Injury, poisoning and procedural complications (1.2%), Nervous system disorders (1.2%), and Psychiatric disorders (1.2%).

- The most frequently reported SAEs in the LCM and CBZ-CR treatment groups were gastroenteritis (no subjects and 3 subjects [1.2%), respectively) and suicidal ideation (1 subject [0.4%] and 2 subjects [0.8%], respectively).

- Twelve cardiac-related TEAEs were reported by a total of 7 subjects in the LCM and CBZ-CR treatment groups during the Treatment Period. Ten events were reported by 5 subjects in the LCM treatment group and 2 events were reported by 2 subjects in the CBZ-CR treatment group, including sinus bradycardia (2 subjects [0.8%] and 1 subject [0.4%], respectively), atrial fibrillation (2 subjects [0.8%] in the LCM treatment group), bradycardia (1 subject [0.4%] in the LCM treatment group), and AV block second degree (1 subject [0.4%] in the CBZ-CR treatment group).

- Ten TEAEs related to suicidality were reported by a total of 5 subjects in the LCM and CBZ-CR treatment groups during the Treatment Period. Three events were reported by 2 subjects in the LCM treatment group and 7 events were reported by 3 subjects in the CBZ-CR treatment group, including suicidal ideation (2 subjects [0.8%] and 3 subjects [1.2%], respectively), suicide attempt (2 subjects [0.8%] in the CBZ-CR treatment group), suicidal behavior (1 subject [0.4%] in the LCM treatment group), and intentional overdose (1 subject [0.4%] in the CBZ-CR treatment group).

- Four subjects (1.5%) reported 4 TEAEs of syncope in the LCM treatment group and 1 subject (0.4%) reported 1 TEAE of syncope in the CBZ-CR treatment group during the Treatment Period.

- The incidence of TEAEs of relevance to the partial-onset seizure population was low.
  - The most frequently reported seizure-related TEAEs in the LCM treatment group were complex partial seizures and grand mal convulsion (2 subjects [0.8%] for each). One of the events of grand mal convulsion was considered serious and none of the events led to discontinuation. The most frequently reported seizure-related TEAEs in the CBZ-CR treatment group were complex partial seizures, grand mal convulsion, and convulsion (1 subject [0.4%] for each). The event of convulsion was considered serious.
and led to discontinuation.

- In the LCM treatment group, memory impairment and cognitive disorder were reported by 1 subject (0.4% for each). The event of cognitive disorder was considered serious and none of the events led to discontinuation. In the CBZ-CR treatment group, memory impairment and cognitive disorder were reported by 1 subject (0.4% for each); none of the events were considered serious and none led to discontinuation.

- There were no TEAEs of psychotic disorder, epileptic psychosis, or acute psychosis reported during the study.

- There were no TEAEs related to body weight change reported in the LCM treatment group. In the CBZ-CR treatment group 2 subjects (0.8%) reported weight decreased; none of the events were considered serious and none led to discontinuation.

- One subject in the LCM treatment group died as of the clinical cutoff date due to TEAEs of adenocarcinoma and acute renal failure, both were considered not related to study medication per the investigator.

- There were no notable differences in ECG parameters between the LCM and CBZ-CR treatment groups at Baseline. At all post-Baseline time points, there was no evidence of QRS, QT, or QTcF prolongation following treatment with either LCM or CBZ-CR. There were small mean increases from Baseline in both treatment groups in PR interval and there was a small incidence of prolonged PR intervals that was similar across treatment groups.

**Conclusions:** In this ongoing extension study for subjects who completed SP0993 or subjects who experienced a seizure at the first or second target doses in the Maintenance Phase of SP0993, subjects were treated for a mean duration in SP0994 of approximately 1 year as of the clinical cutoff date of 22 May 2015.

There were no notable differences between treatment groups in the overall incidences of TEAEs. Long-term exposure to LCM was safe and generally well tolerated at all dose levels, including doses up to 600mg/day, when used as monotherapy in subjects newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or generalized tonic-clonic seizures. The overall safety profile of LCM observed is consistent with the currently-known safety profile of LCM and no new safety signals were identified.

**Report date:** 17 Nov 2015