CLINICAL STUDY REPORT SYNOPSIS: SP0994

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: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

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: Approximately 4 years and 7 months. **First subject enrolled:** 16 May 2012 **Last subject completed:** 03 Jan 2017	**Phase of development:** Phase 3

Objectives: The objectives of this study were 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 was 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 occurred 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 returned to the clinic for an Escalation Visit followed by a Stabilization Visit (SV); subsequent regularly scheduled visits occurred at 13-week intervals relative to the SV.

Visit 1 for SP0994 was 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 was 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 Subjects who were withdrawn from SP0993 while at the third target dose level were not allowed to participate in SP0994 with the exception of subjects who were terminated from SP0993 due to SP0993 Protocol Amendment 6.2. In SP0994, subjects received a dose of LCM 200mg/day, 300mg/day,

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
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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) indicated 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 was a follow-up study and subjects continued into SP0994 based on their completion status of SP0993, no formal sample size determination was 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).

Overall in SP0994, 548 subjects had received at least 1 dose of study medication and were included in the Safety Set (SS) (279 in the LCM treatment group and 269 in the CBZ-CR treatment group).

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 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.

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

For LCM tablets and LCM matching placebo, the following investigational medicinal product (IMP) batch numbers were used: BX1003096, BX1004314, BX1004421, BX1004422, BX1004424, BX1004471, BX1005849, BX1006033, BX1006034, BX1006035, BX1006037, BX1006038, BX1006109, , BX1006330, BX1006331, BX1006406, BX1007271, BX1007780, BX1007782, BX1008174, BX1008178, BX1008180, BX1008181, BX1008432, BX1008919, BX1009104, BX1009105, BX1009106, BX1009107, BX1010467, BX1010986, BX1010989, BX1011762, BX1011764, BX1011768, BX1011772, , BX1011781, BX1011782, BX1011995.

Reference therapy, doses and mode of administration, batch numbers: Carbamazepine (controlled release) was 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 was supplied as yellow, opaque capsules size A with an overfill.

For CBZ-CR capsules and for CBZ-CR matching placebo, the following IMP batch numbers were used: BX1004424, BX1005841, BX1005842, BX1005844, BX1006083, BX1006105, BX1006107, BX1006111, BX1006112, BX1006113, BX1006330, BX1007493, BX1008147, BX1008234, BX1008411, BX1008142, BX1008143, BX1008144, BX1008147, BX1008234, BX1008411, BX1008430, BX1008914, BX1008919, BX1010466, BX1010989, BX1011763, BX1011765, BX1011766, BX1011767, BX1011779, BX1011780, BX1012049, BX1012087, BX1012951, BX1013343, BX1013416.

Duration of treatment: Following the database lock and unblinding of SP0993, SP0994 was unblinded and closed for all subjects when follow-up access to LCM monotherapy was established. Subjects who were receiving CBZ-CR and wished to continue treatment after the close of SP0994 may have received prescribed CBZ (ie, not supplied by UCB BIOSCIENCES). Subjects who completed SP0994 and who were treated with LCM monotherapy had 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 did not wish to continue LCM therapy after unblinding of SP0994 or subjects assigned to CBZ-CR treatment were tapered off study medication and did not participate in the follow-on program.

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

Criteria for evaluation:

Safety: The primary safety variables were 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 electrocardiograms (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

Efficacy: Efficacy evaluations were based on subject diaries where types, dates, and number of seizures were recorded.

The exploratory efficacy variables were as follows:

- Percentage of subjects seizure free
- Time to discontinuation

Health outcomes: The exploratory health outcomes variables were as follows:

- Health care resource use: Additional health care provider visits unforeseen by the protocol and hospitalizations

Pharmacokinetics: The pharmacokinetic variable was as follows:

- Plasma concentration of LCM and CBZ

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

Statistical methods: This is the final clinical study report (CSR) for the completed study. Interim data from SP0994 for 2 prior interim analyses were summarized to support a regulatory submission, regular safety signal detection monitoring, publications, and annual reports to Regulatory Agencies. The first interim CSR was based on a clinical cutoff date of 22 May 2015 and presented interim data for 452 ongoing subjects in the SS. The second CSR presents the final data for these 548 subjects and includes results for all of the statistical analysis plan defined analyses.

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

Treatment Period: the start of the Treatment Period was the date of Visit 1. The end of the Treatment Period was the date of the Termination Visit or ETV for subjects who were prematurely discontinued. For subjects who discontinued during the Treatment Period without an ETV, the end of the Treatment Period was 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 was 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 was 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

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

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, rates of TEAEs per 100 subject-months, incidence of TEAEs by maximum relationship per investigator, 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 lipid) 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] and Bazett's corrections [QTcB], PR and QRS duration, and HR values) were summarized.

Efficacy and health outcome variables in SP0994 were for exploratory purposes only. Percentages of subjects remaining seizure free for 6, 12, 18, 24, 30, and 36 months since the date of first dose in SP0994 were estimated by the Kaplan-Meier (KM) methods. Time to discontinuation was estimated by treatment group using the KM methods. The number of health care provider consultations not foreseen by the protocol, the number of hospitalizations and ER visits, duration of hospital visits, and the number of concomitant medical procedures during the Treatment Period were summarized as continuous and categorical variables.

Descriptive statistics of LCM and CBZ plasma concentrations were presented by visit and actual dose.

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

Summary and conclusions:

Subject disposition: Overall, 391 subjects (71.4%) completed the study and 157 subjects (28.6%) discontinued from the study. The most common reasons for discontinuation were consent withdrawn (12.2%), "adverse event" (6.4%), and "other" (3.8%). Overall, 451 subjects (82.3%) remained in SP0994 until SP0993 unblinding and 97 subjects (17.7%) discontinued from SP0994 prior to SP0993 unblinding. The most common reasons for discontinuation prior to SP0993 unblinding were "consent withdrawn" (7.8%) and "adverse event" (4.7%).

Safety results: 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 median duration of approximately 2 years when compared with CBZ-CR at doses up to 1200mg/day.

- The median duration of exposure and subject-years exposed were slightly longer in the LCM treatment group compared with the CBZ-CR treatment group (603.0 days [489.2 subject-years exposed] in the LCM treatment group compared with 549.0 days [437.1 subject-years exposed] in the CBZ-CR treatment).
- The median of the mean exposure to LCM per subject was 200mg/day and the median of the mean exposure to CBZ-CR per subject was 400mg/day during the Treatment Period, consistent with the observation that most subjects remained at the first dose level (>100 to 200mg/day for LCM and >200 to 400mg/day for CBZ-CR).
- Overall, during the Treatment Period, 181 subjects (64.9%) and 182 subjects (67.7%) in the LCM and CBZ-CR treatment groups, respectively, experienced at least 1 TEAE. In the LCM and CBZ-CR treatment groups, SAEs occurred in 32 subjects (11.5%) and 22 subjects (8.2%) respectively, TEAEs leading to permanent discontinuation occurred in 12 subjects (4.3%) and 21 subjects (7.8%), respectively, and drug related TEAEs occurred in 43 subjects (15.4%) and 54 subjects (20.1%), respectively.
- The overall incidences of the most commonly reported TEAEs (≥2% in either treatment group) were low in both treatment groups. There were no clinically meaningful differences in the incidences and exposure-adjusted event rates of the most commonly reported TEAEs (by PT) between the LCM and CBZ-CR treatment groups. Treatment-emergent AEs reported at ≥3.0% in the LCM treatment group were nasopharyngitis (7.2% [event rate=0.63 per 100 subject-months]), headache (6.1% [event rate=0.44 per 100 subject-months]), dizziness (4.3% [event rate=0.22 per 100 subject-months]), hypercholesterolemia (3.6% [event rate=0.16 per 100 subject-months]), back pain (3.6% [event rate=0.20 per

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

100 subject-months]), hypertension (3.2% [event rate=0.16 per 100 subject-months]), and nausea (3.2% [event rate=0.14 per 100 subject-months]). Treatment-emergent AEs reported at ≥3% in the CBZ-CR treatment group were dizziness (6.3% [event rate=0.33 per 100 subject-months]), nasopharyngitis (5.9% [event rate=0.39 per 100 subject-months]), headache (5.6% [event rate=0.44 per 100 subject-months]), hypercholesterolemia (4.8% [event rate=0.28 per 100 subject-months]), gamma glutamyl transferase (GGT) increased (4.1% [event rate=0.19 per 100 subject-months]), and upper respiratory tract infection (3.3% [event rate=0.19 per 100 subject-months]).

- Most TEAEs were mild or moderate in both treatment groups. Twenty-one subjects (7.5%) and 20 subjects (7.4%) in the LCM and CBZ-CR treatment groups, respectively, reported TEAEs with a maximum intensity of severe. The only severe TEAE reported by >1 subject in the LCM treatment group was syncope (2 subjects [0.7%]), and the only severe TEAEs reported by >1 subject in the CBZ-CR treatment group were suicidal ideation (3 subjects [1.1%]) and back pain (2 subjects [0.7%]).
- A lower percentage of subjects in the LCM treatment group reported TEAEs considered related to study medication per the investigator during the Treatment Period (43 subjects [15.4%]) compared with the CBZ-CR treatment group (54 subjects [20.1%]). The incidence of TEAEs considered related to study medication per the investigator for the LCM and CBZ-CR treatment groups were most frequently reported in the SOC of Investigations (13 subjects [4.7%] and 21 subjects [7.8%], respectively). Treatment-emergent AEs considered related to study medication per the investigator that were reported by >2% of subjects in either treatment group were GGT increased (1.4% and 2.2%, in the LCM and CBZ-CR treatment groups, respectively) and hypercholesterolemia (no subjects and 2.6%, in the LCM and CBZ-CR treatment groups, respectively).
- 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.
- The number of subjects who reported TEAEs leading to discontinuation tended to be lower in the LCM treatment group (12 subjects [4.3%]) compared with the CBZ-CR treatment group (21 subjects [7.8%]). The only TEAEs leading to discontinuation reported in ≥2 subjects in either treatment group were GGT increased (1 subject [0.4%] in the LCM treatment group and 2 subjects [0.7%] in the CBZ-CR treatment group), pregnancy on contraceptive (no subjects in the LCM treatment group and 4 subjects [1.5%] in the CBZ-CR treatment group), suicidal ideation (1 subject [0.4%] in the LCM treatment group and 2 subjects [0.7%]

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

in the CBZ-CR treatment group), and suicide attempt (no subjects in the LCM treatment group and 2 subjects [0.7%] in the CBZ-CR treatment group).

- The most frequently reported SAEs in the LCM and CBZ-CR treatment groups were gastroenteritis (no subjects and 3 subjects [1.1%], respectively) and suicidal ideation (1 subject [0.4%] and 2 subjects [0.7%], respectively).
- Eleven cardiac-related other significant TEAEs were reported by 5 subjects in the LCM treatment group and 3 cardiac-related other significant events were reported by 3 subjects in the CBZ-CR treatment group during the Treatment Period. These included sinus bradycardia (3 subjects [1.1%] and 1 subject [0.4%] in the LCM and CBZ-CR treatment groups, respectively), atrial fibrillation (2 subjects [0.7%] and 1 subject [0.4%] in the LCM and CBZ-CR treatment groups, respectively), 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).
- Four TEAEs related to suicidality were reported by 3 subjects in the LCM treatment group and 6 TEAEs were reported by 4 subjects in the CBZ-CR treatment group during the Treatment Period. These included suicidal ideation (3 subjects [1.1%] and 4 subjects [1.5%], in the LCM and CBZ-CR treatment groups, respectively), suicide attempt (2 subjects [0.7%] 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).
- Five subjects (1.8%) reported 8 TEAEs of syncope in the LCM treatment group and 2 subjects (0.7%) reported 2 TEAEs 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 grand mal convulsion (3 subjects [1.1%]), and complex partial seizures and convulsion (2 subjects [0.7%] for each). One of the events of grand mal convulsion was considered serious and did not lead to discontinuation. One event of status epilepticus was considered serious and led to discontinuation. The most frequently reported seizure related TEAE in the CBZ-CR treatment group was grand mal convulsion (2 subjects [0.7%]), neither of which were serious or led to discontinuation. One subject (0.4%) had a TEAE of convulsion that was considered serious and led to discontinuation.
  - In the LCM treatment group, memory impairment and cognitive disorder were reported

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Name of finished product: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

by 4 subjects (1.4%) and 2 subjects (0.7%), respectively. One event of cognitive disorder was considered serious and none of the events led to discontinuation. In the CBZ-CR treatment group, cognitive disorder and memory impairment were reported by 2 subjects (0.7%) and 1 subject (0.4%), respectively; 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 was 1 TEAE related to body weight change reported in the LCM treatment group (weight decreased); the event was considered nonserious and did not lead to discontinuation. In the CBZ-CR treatment group 3 subjects (1.1%) reported weight decreased and 1 subject (0.4%) reported weight increased; none of the events were considered serious and none led to discontinuation.

- One subject in the LCM treatment group died during the study 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.
- The majority of subjects in both treatment groups had normal neurological examination results at Baseline and at the End of the Treatment Period across all neurological parameters assessed (mental status, cranial nerves, reflexes, motor system, muscle strength, motor tone, and upper/lower extremities sensation).
- In general, there were no clinically relevant effects of LCM treatment observed for laboratory parameters, body weight, or vital signs. For the CBZ-CR treatment group, clinically relevant changes from Baseline in the laboratory values were related to hepatic enzymes (GGT) and thyroid hormones (thyroxine). Changes were also observed in sex hormones and lipids after CBZ-CR treatment but with less clinical significance.
- There were no notable differences observed for the safety results in SP0994 compared with the safety results observed in SP0993.

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: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

Efficacy results: The efficacy variables in SP0994 were based on subject diaries where types, dates, and number of seizures were recorded for exploratory purposes only and included the percentage of subjects seizure free and time to discontinuation.

- Seizure control was maintained for most subjects in both treatment groups from the first dose in SP0994 until the time of SP0993 unblinding. Approximately 94%, 90%, and 85% of subjects remained seizure free for 6, 12, and 24 months, respectively, in both treatment groups. In contrast to the results observed in SP0993, no meaningful differences were observed between the strata; the KM curves for time to first seizure during SP0994 until the time of SP0993 unblinding were generally similar for LCM and CBZ-CR in both strata.
- For the subjects who reported seizures from the date of the first dose of study medication in SP0994 until the time of SP0993 unblinding, a longer median duration was observed in Stratum 1 compared with Stratum 2 in both treatment groups. A longer median time to first seizure was also observed in the LCM treatment group compared with the CBZ-CR treatment group in Stratum 1.
- The majority of subjects (≥81.0%) who completed a specified duration of treatment in SP0994 remained seizure free. Among subjects who completed 24, 30, and 36 months of treatment, a higher percentage (>5%) remained seizure free in the LCM treatment group compared with the CBZ-CR treatment group.
- The retention rates during SP0994 until the time of SP0993 unblinding were high and similar in both treatment groups. The KM estimates of the retention rates at 36 months were 72.7% in the LCM treatment group and 74.8% in the CBZ-CR treatment group.

Health outcomes results:

- The majority of subjects in both treatment groups had no health care provider consultations not foreseen by the protocol, hospitalization or ER visits, or concomitant medical procedures during the Treatment Period.
- Health care resource use was comparable between the LCM and CBZ-CR treatment groups.

Pharmacokinetic results: The LCM and CBZ-CR plasma concentration data separated by actual dose per intake reflect that subjects were treated with active drug and nearly all of the resulting concentrations are within the expected ranges for LCM and CBZ-CR.

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: VIMPAT®	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide)	**Page:** Not applicable	

Conclusions: In this long-term, 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 median duration in SP0994 of approximately 2 years.

There were no notable differences between treatment groups in the overall incidences of TEAEs. Long-term exposure to LCM was [redacted] 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.

Seizure control was maintained for most subjects in both treatment groups during the study.

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