

CLINICAL STUDY REPORT SYNOPSIS: SP904

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: Vimpat®	Volume: Not applicable	
Name of active ingredient: Lacosamide	Page: Not applicable	
Title of study: A Multicenter, Open-label Extension Trial to Assess the Long-term Use of Lacosamide Monotherapy and Safety of Lacosamide Monotherapy and Adjunctive Therapy in Subjects with Partial-onset Seizures		
Investigators: A total of 124 investigators enrolled subjects.		
Study sites: A total of 108 sites in USA, Canada, Europe, and Australia participated (ie, enrolled subjects) in the study.		
Publication(s) (reference[s]): none		
Study period: The study period was approximately 6 years 10 months.		Phase of development: Phase 3
First subject enrolled: 20 Feb 2008		
Last subject completed: 10 Dec 2014		
Objectives: The objectives of this study were to: <ul style="list-style-type: none"> • Obtain information about the percentage of subjects who remained on lacosamide (LCM) monotherapy and the duration of LCM monotherapy treatment • Obtain information about the long-term safety of LCM when used as monotherapy or adjunctive therapy in subjects with partial-onset seizures 		
Methodology: SP904 was a multicenter, open-label extension study to assess the long-term use of LCM monotherapy and safety of LCM monotherapy and adjunctive therapy in subjects with partial-onset seizures (with and without secondary generalization) who were previously enrolled in the conversion to monotherapy study (SP902). Subjects who entered the Maintenance Phase of SP902 and either completed SP902 or met an exit criterion in SP902 (with the exception of subjects enrolled at sites in Germany) were eligible to enroll in this open-label extension. Subjects enrolled in SP902 at sites in Germany who entered the Maintenance Phase, but were withdrawn due to meeting an exit criterion, were not eligible to participate in SP904. At the termination of the previous study, SP902, subjects received a dose of LCM 300mg/day or LCM 400mg/day. At the beginning of this extension study, the investigator may have adjusted or maintained the LCM dose so that a subject began SP904 at a dose of LCM 200, 300, or 400mg/day for subjects who were receiving LCM 300mg/day at the end of SP902, or LCM 300,		

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<p>400, or 500mg/day for subjects who were receiving LCM 400mg/day at the end of SP902. The investigator was to increase the dose no faster than LCM 100mg/day per week up to LCM 800mg/day.</p> <p>Subjects may have had their LCM dose increased to the next level (ie, LCM 100mg/day increase) during an Unscheduled Visit (limited to 1 such increase per week). The investigator may have also chosen to bring subjects in for an Unscheduled Visit in order to add and/or adjust their concomitant antiepileptic drugs (AEDs). Concomitant AEDs may have been introduced as treatment if the medication had been approved for partial-onset seizures in the country where the subject resided.</p> <p>During the study, investigators were allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. A clinic visit (scheduled or unscheduled) was required for all LCM dose increases. For subjects receiving LCM monotherapy at the time of study entry, the addition of up to 2 concomitant AEDs was allowed to optimize tolerability and seizure reduction. Concomitant AEDs should have been added only when the subject had not optimally or adequately responded to a maximum tolerated dose of LCM monotherapy.</p> <p>For subjects who entered the study on both LCM and other concomitant AED therapy, concomitant AED(s) may have been carefully tapered and discontinued to achieve LCM monotherapy.</p> <p>Visits 1 through 3 occurred at 4-week intervals; Visits 4 through 6 occurred at 8-week intervals. Beginning at Visit 7, visits were performed at 12-week intervals (Visit 7 through the Termination Visit), with telephone contacts required at 4-week intervals to obtain information regarding concomitant medication use, adverse events (AEs), diary completion, and compliance with study medication schedule.</p> <p>At the end of treatment, or if subjects discontinued the study prematurely, a Termination Visit was performed. Subjects receiving LCM \geq300mg/day should have been tapered off gradually at a recommended decrease rate of LCM 200mg/day per week. Clinic visits were not required for LCM dose adjustments during the Taper Phase. Subjects receiving LCM 100mg/day or 200mg/day did not require a taper. A Final Visit was performed 2 weeks after the final dose of study medication.</p> <p>Taper of LCM was not required for subjects who completed or withdrew from the study and who, in consultation with the investigator, chose to initiate treatment with commercial LCM. The last scheduled study visit for subjects continuing on commercial LCM should have been the Termination Visit.</p> <p>The maximum duration of treatment was 2 years after Visit 1 in SP904, with a possible Taper</p>		

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<p>and Safety Follow-Up Phase of up to 5 weeks. If LCM was not available (eg, commercially) in a subject's country 2 years after Visit 1 in SP904, access to LCM was ensured according to local laws.</p>		
<p>Number of subjects (planned and analyzed): Of the 426 unique subjects randomized in the SP902 study, approximately 294 of these subjects were expected to enroll in the open-label extension study SP904. Approximately 120 sites in the USA, Canada, Europe, and Australia were expected to enroll subjects in SP902; therefore, up to 120 sites were expected to participate in SP904. There was no limit to the number of subjects that any site could have enrolled into this study, as long as the subject participated in the SP902 study. A total of 322 subjects were included in the Safety Set (SS), which was defined as all subjects who received at least 1 dose of study medication.</p>		
<p>Diagnosis and main criteria for inclusion: This study enrolled subjects who had entered the Maintenance Phase of the double-blind study, SP902 (ie, had taken at least 1 dose of SP902 Maintenance Phase study medication), and either completed SP902 or met an exit criterion in SP902, and were expected to benefit from participation in an open-label extension study with LCM, in the opinion of the investigator. Subjects enrolled in SP902 at sites in Germany who entered the Maintenance Phase, but were withdrawn due to meeting an exit criterion were not eligible to participate in SP904. 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 were excluded from participating in the study.</p>		
<p>Test product, doses and mode of administration, batch numbers: Lacosamide was supplied as white, oval, immediate-release, film-coated tablets in strengths of 50mg and 100mg. The manufacturer of the LCM tablets was Aesica Pharmaceuticals GmbH, Zwickau, Germany. 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. Doses ranging from LCM 100 to 800mg/day were used in this study. During the study, investigators were allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject.</p>		
<p>Duration of treatment: The maximum duration of a subject's study participation was 2 years after Visit 1 in SP904. The maximum duration of treatment was 2 years after Visit 1 in SP904, with a possible Taper and Safety Follow-Up Phase of up to 5 weeks.</p>		

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<p>Reference therapy, dose(s) and mode of administration, batch number(s): This was an open-label study and all subjects received LCM. The investigator was allowed to adjust a subject's LCM dose as needed to optimize tolerability and seizure reduction for each subject throughout the study. The batch numbers were as follows.</p> <p>090407070001, 090407070002, 090407070003, 090408100001, 090408100002, 090409030001, 090409030002, BX1003438, BX1003439, BX1004252, BX1004253, BX1005018, BX10051019, BX1005146, BX1005801, BX1005802, BX1005803, BX1005804, BX1005809, BX1007257, BX1007258, BX1009395</p>		
<p>Criteria for evaluation:</p> <p>As this was primarily a safety study, seizure frequency and seizure freedom were not analyzed. Long-term use of LCM monotherapy was assessed using the following primary variables:</p> <ul style="list-style-type: none"> • Percentage of subjects on LCM monotherapy • Duration of LCM monotherapy treatment <p>Long-term safety of LCM monotherapy or adjunctive therapy was assessed using the following secondary variables:</p> <ul style="list-style-type: none"> • Adverse events reported spontaneously by the subject and/or caregiver or observed by the investigator • Subject withdrawal due to AEs <p>Other safety variables included the following:</p> <ul style="list-style-type: none"> • Changes in hematology, blood chemistry, and urinalysis parameters • Changes in 12-lead electrocardiograms (ECGs) • Changes in vital sign measurements (eg, blood pressure, pulse) • Changes in physical or neurological examination findings • Changes in body weight 		

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Statistical methods: Descriptive statistics were displayed to provide an overview of the safety results. 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. Unless otherwise noted, all percentages were displayed to 1 decimal place. For continuous parameters, descriptive statistics included n, mean, standard deviation (SD), median, minimum, and maximum.

Subjects who prematurely discontinued the study were evaluated based on the data collected at each visit attended or phase entered unless otherwise specified. By-visit summaries do not include data from unscheduled clinic visits unless otherwise stated. Data provided at these visits were included in subject data listings.

The protocol-defined Treatment Phase was the time period, up to 2 years, that a subject took LCM. The Taper Phase could have been up to 3 weeks starting with the Termination Visit, and the Safety Follow-Up Phase is the 2 weeks following last dose of LCM.

For analysis purposes, the Treatment Phase was defined as the period of time from the first dose of study medication during the SP904 study to the date of final dose of study medication or the date of Termination Visit, whichever occurred later. The Treatment Phase included the protocol-defined Taper Phase if the subject completed it.

The Post-Treatment Analysis Phase was defined as the treatment-free observational phase after the Treatment Phase. It started 1 day after the end date of the Treatment Phase and ended on the latter of the date of the Final Visit or last contact with the subject.

Baseline values for all parameters were based on the Baseline value from the SP902 study. For laboratory and vital sign data, this was the last nonmissing evaluation prior to the first intake of LCM from SP902. For ECG data, Baseline was defined as the average of the 3 ECG assessments obtained at Visit 3 of SP902 and prior to the first intake of LCM.

The analysis set for the disposition was based on the Enrolled Set (ES), which was defined as all subjects who signed an Informed Consent form for SP904. The analysis set for all other variables was the SS.

For the primary safety analyses, the number and percentage of subjects on LCM monotherapy for >0 months, ≥3 months, ≥6 months, ≥12 months, ≥18 months, and ≥24 months during the Treatment Phase were summarized overall and by specific subgroups (monotherapy status at SP904 entry and exit status in the SP902 study). Summary statistics for the duration of the longest LCM monotherapy period and total LCM monotherapy were presented for the SS overall and by specific subgroups (monotherapy status at SP904 entry and exit status in the SP902 study); total subject-years of longest monotherapy period and total LCM monotherapy were

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given; for the monotherapy at SP904 entry subgroup, summary statistics were presented for the first period of continuous monotherapy. The first continuous period of LCM monotherapy was the time from first dose in SP904 until the LCM monotherapy was interrupted, discontinued or completed. Continuous monotherapy applied to those SP902 subjects entering SP904 on LCM monotherapy. Summary statistics of the modal and maximum doses were presented for subjects on LCM monotherapy for ≥ 6 months, ≥ 12 months, ≥ 18 months, and ≥ 24 months. Summary statistics (including Q1 and Q3) of longest period of LCM monotherapy treatment, defined as the longest single period of continuous LCM monotherapy for each subject (which could have occurred at any time in SP904), and total LCM monotherapy were presented by modal dose and at any dose. Summary statistics of the treatment duration (days), maximum daily dose (mg/day), and modal dose (mg/day) for the longest period of LCM monotherapy and total LCM monotherapy were presented. The number and percentage of subjects during their longest period of LCM monotherapy and total period of LCM monotherapy within each LCM treatment duration category by modal dose were presented where the LCM treatment duration categories (days) were as follows: 1 to 14; 15 to 28; 29 to 56; 57 to 84; 85 to 168; 169 to 336; 337 to 504; 505 to 672; >672; any duration (total of durations).

The number and percentage of subjects on entire study LCM monotherapy for >0 months, ≥ 3 months, ≥ 6 months, ≥ 12 months, ≥ 18 months, and ≥ 24 months during the Treatment Phase were summarized.

Summary statistics for the duration of the entire study LCM monotherapy were presented; total subject-years were given. Summary statistics (including Q1 and Q3) of LCM monotherapy were presented by modal dose and at any dose. Summary statistics of the treatment duration (days), maximum daily dose (mg/day), and modal dose (mg/day) were presented. The number and percentage of subjects during the entire study LCM monotherapy within each LCM treatment duration category by modal dose were presented where the LCM treatment duration categories (days) were as follows: 1 to 14; 15 to 28; 29 to 56; 57 to 84; 85 to 168; 169 to 336; 337 to 504; 505 to 672; >672; any duration (total of durations).

Following recommendation from the US Food and Drug Administration (FDA) on 23 Jan 2013, specific analyses were to be added. Therefore, all treatment-emergent adverse event (TEAE) summaries were presented by LCM monotherapy and not LCM monotherapy, as well as overall with the exception of 1 analysis that summarized TEAEs by LCM monotherapy status at SP904 entry. A TEAE was classified as occurring while on LCM monotherapy if the onset of the TEAE occurred while the subject was being treated with LCM as the only AED. If the subject was being treated with LCM and other AEDs or no AEDs at the onset of the TEAE, then the TEAE was classified as occurring while not on LCM monotherapy. For subjects with periods of both LCM monotherapy and not LCM monotherapy, TEAEs were classified according to which

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treatment the subject was on at the onset of the TEAE; therefore, a subject with multiple TEAEs could have been counted as having a TEAE in both the LCM monotherapy period and not LCM monotherapy period, depending on what period the TEAE started.

Another US FDA request was to include an analysis of TEAEs of the subjects entering SP904 on LCM monotherapy. Treatment-emergent AEs that occurred while on LCM monotherapy from Day 1 of SP904 to the end of that period of LCM monotherapy were summarized in the continuous monotherapy period column. All other TEAEs, whether they occurred during no AED therapy, polytherapy or later monotherapy periods, were summarized in the other column. The goal of this analysis was to see what types of TEAEs subjects experienced as they continued their LCM monotherapy from SP902 through SP904.

For the overall TEAEs, the rates were calculated using the total number of TEAEs (unique and non-unique) divided by the sum of the duration of the Treatment Phase, in months (sum of person-months), experienced by each subject, multiplied by 100. For the LCM monotherapy TEAEs, the rates were calculated using the total number of TEAEs (unique and non-unique) occurring during LCM monotherapy divided by the sum of the time on LCM monotherapy during the Treatment Phase, in months (sum of person-months) experienced by each subject, multiplied by 100. For the TEAEs not occurring on LCM monotherapy, the rates were calculated using the total number of TEAEs (unique and non-unique) occurring at any other time divided by the sum of the time not on LCM monotherapy during the Treatment Phase, in months (sum of person-months) experienced by each subject, multiplied by 100.

Summary and conclusions:

Subject disposition: Enrollment in SP904 included subjects who either completed SP902 (n=252, including 3 with investigator-reported exits reported after the subject completed) or early terminated SP902 (n=70, including 64 with investigator-reported exits, 1 with other reasons, and 5 with protocol deviations). Of the 70 early terminations from SP902, 64 subjects discontinued from the Maintenance Phase, 1 subject each discontinued from the Titration Phase and Transition Phase, respectively, and 4 subjects entered SP904 upon immediate completion of the Maintenance Phase of SP902.

A total of 323 subjects were enrolled in SP904, of which 322 subjects (99.7%) were treated with LCM. Subject [REDACTED] was a screen failure and did not receive LCM treatment. The subject signed the Informed Consent form for SP904 at the SP902 Termination Visit; however, upon returning for the Final Clinic Visit of SP902 (which would have been Visit 1 of SP904) the subject indicated that he decided not to participate in SP904.

A total of 210 subjects (65.2%) completed the study and 112 subjects (34.8%) discontinued. The

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most common reasons for discontinuation were consent withdrawn (9.3%), AE (6.8%), and lack of efficacy (6.2%).

Seventeen subjects (5.3%) were discontinued for other reasons. Ten subjects were discontinued due to site closure: site ■■■ was closed due to site noncompliance (8 subjects), investigator ■■■ no longer wished to participate in SP904 (1 subject), and investigator ■■■ was relocating (1 subject). Two subjects were discontinued due to pregnancy. Two subjects discontinued due to admission to the hospital (1 to a telemetry unit and 1 for a presurgical study). One subject was jailed. One subject discontinued due to a diagnosis of psychogenic nonepileptic seizures and 1 subject chose to no longer go for follow up at investigator site, but rather at a general clinic.

The percentage of subjects who discontinued was similar by region, 35.4% in North America and 32.2% in all other regions, although the specific reasons for discontinuation varied between regions. The most common reasons for discontinuation in North America were consent withdrawn (9.9% vs 6.8% in all other regions) and AE (7.6% vs 3.4% in all other regions). The most common reason for discontinuation in all other regions was lack of efficacy (13.6% vs 4.6% in North America).

The percentage of subjects who discontinued was greater in subjects who exited from SP902 compared with those not exited from SP902 (43.7% vs 31.5%). The most common reasons for discontinuation occurred in a greater percentage of subjects who exited from SP902 compared with those who did not exit from SP902 (lack of efficacy [13.8% vs 3.4%], consent withdrawn [11.5% vs 8.5%], and AE [10.3% vs 5.5%]).

The percentage of subjects who discontinued was greater in non-monotherapy subjects at SP904 entry compared with those on monotherapy at SP904 entry (50.0% vs 32.6%). The most common reason for discontinuation occurred in a greater percentage of subjects on non-monotherapy at SP904 entry compared with those on monotherapy at SP904 entry (lack of efficacy [15.0% vs 5.0%]) followed by AE (10.0% vs 6.4%). Other common reasons for discontinuation were similar in non-monotherapy at SP904 entry compared with monotherapy at SP904 entry subjects.

Of the 151 subjects that spent their entire time in SP904 on LCM monotherapy, 104 subjects (68.9%) completed the study. A smaller number of subjects on entire study LCM monotherapy discontinued the study compared with all other subjects (31.1% vs 38.0%). The most common reason for discontinuation for subjects on entire study LCM monotherapy was consent withdrawn (9.9%). The most common reason for discontinuation in all other subjects was lack of efficacy (11.1%). In addition, fewer subjects on entire study monotherapy discontinued the study due to AE and lack of efficacy compared with all other subjects (2.6% vs 10.5% and 0.7% vs 11.1%, respectively).

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Safety results: Long-term treatment with LCM in this open-label extension study was generally well tolerated in subjects with partial-onset seizures at doses of 100 to 800mg/day when used as monotherapy or adjunctive therapy.

With regard to TEAEs coded to convulsions, investigators were instructed to report any change (including improvement) in seizure type, severity, frequency, or duration as an AE. A change to a less severe seizure type would have been an improvement in the subject's condition; however, because the preferred term (PT) of convulsions captures both improvements and worsening of seizure conditions, the incidence of convulsion may have been an overestimate of the number of subjects with worsening seizures.

- Of the 322 enrolled subjects, 258 subjects (80.1%) had at least 1 year of exposure to LCM, and 216 subjects (67.1%) had at least 2 years of exposure to LCM. The total subject-years of exposure to LCM was 525.5 years (based on 322 subjects). For all subjects, the mean treatment duration was 596.1 days, and the median modal dose was 500mg/day.
- The majority of all subjects were on LCM monotherapy at SP904 entry (282 of 322 subjects, 87.6%). Of the subjects who were on LCM monotherapy at SP904 entry (and were exposed for ≥ 12 months and ≥ 24 months, respectively), 77.0% (177 of 230 subjects) had a period of LCM monotherapy of ≥ 12 months and 64.3% (126 of 196 subjects) had a period of LCM monotherapy of ≥ 24 months. A small percentage of subjects (14.7%, 5 of 34 subjects) who entered SP904 not on LCM monotherapy were able to achieve and sustain a LCM monotherapy period for ≥ 6 months.
- For subjects on LCM monotherapy at SP904 entry, the mean longest period of LCM monotherapy was 475.6 days and total LCM monotherapy was 488.3 days. By comparison, the mean first continuous period of LCM monotherapy (defined as the time on LCM monotherapy from the first dose in SP904 to the end of that period of LCM monotherapy for the subjects continuing LCM monotherapy from SP902) was 469.2 days, indicating that most LCM monotherapy periods were from the start of SP904.
- The percentage of subjects on LCM monotherapy, regardless of duration, was consistently higher for subjects who were not exited from SP902 compared with subjects who exited from SP902; however, of the subjects who exited from SP902 and were exposed to LCM for ≥ 12 months, 43.1% (28 of 65 subjects) had a LCM monotherapy period of ≥ 12 months.
- Of the 151 subjects that spent their entire time in SP904 on LCM monotherapy, 107 subjects were on LCM monotherapy ≥ 24 months, compared with 19 of 109 subjects that did not spend their entire time on LCM monotherapy.

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- The mean longest period of LCM monotherapy and total LCM monotherapy was longer for subjects who were not exited from SP902 compared with subjects who exited from SP902 (491.0 vs 369.0 days and 505.0 vs 374.9 days, respectively). Subjects on entire study LCM monotherapy had a mean and median duration of LCM monotherapy of 602.9 days and 728.0 days, respectively, and total subject-years of exposure was 249.2.
- The mean modal dose was similar during each of the longest period of LCM monotherapy categories (range: 493.7 to 502.1mg/day). The LCM maximum dose during the longest period of LCM monotherapy was similar during each of the longest period categories (range: 531.0 to 550.0mg/day). The median modal dose and median maximum dose during all LCM monotherapy periods was 500.0mg/day.
- The mean treatment duration was higher for entire study LCM monotherapy (602.9 days) compared with the longest period of LCM monotherapy and total LCM monotherapy (466.7 days and 479.1 days, respectively). Maximum daily dose was slightly higher for longest period of LCM monotherapy and total monotherapy (539.0mg/day and 542.1mg/day, respectively) compared with entire study LCM monotherapy (501.7mg/day). However, the median maximum daily dose was the same (500.0mg/day) for longest period of LCM monotherapy, total LCM monotherapy, and entire study LCM monotherapy.
- Overall, the longest period of LCM monotherapy for 126 subjects (43.2%) was >672 days at any dose and the greatest number of subjects at any dose had a duration of total (134 subjects, 45.9%) and entire study (107 subjects, 70.9%) LCM monotherapy >672 days. In general, the greatest number of subjects during the longest period (100 subjects, 34.2%), total (98 subjects, 33.6%), and entire study (65 subjects, 43.0%) LCM monotherapy had a LCM modal dose of >300 to 400mg/day.
- In general, subjects during the longest period, total, and entire study LCM monotherapy spent the greatest amount of time on LCM modal doses >400mg/day. The greatest number of subjects (100 subjects) during the longest period of LCM monotherapy, total LCM monotherapy (98 subjects), and entire study LCM monotherapy (65 subjects) were on a LCM modal dose >300 to 400mg/day for means of 466.2 days, 476.9 days, and 558.2 days, respectively.
- Time on LCM monotherapy (in 100 person months) was approximately 2.7-fold longer than time spent not on LCM monotherapy (4997 vs 1858 per 100 person months). When adjusted for exposure duration, the incidences of TEAEs overall and most of the common TEAEs were lower while on LCM monotherapy compared with while not on LCM monotherapy. The rate of any TEAE occurring while on LCM monotherapy was notably lower than while

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not on LCM monotherapy (33.36 vs 48.92 per 100 person-months). The rates for the most common TEAEs (by PT) were also lower or similar while on LCM monotherapy compared with while not on LCM monotherapy.

- A total of 91.0% of subjects reported 2576 TEAEs during the Treatment Phase. Treatment emergent AEs were most commonly reported in the system organ classes (SOC) of Nervous system disorders (61.5%) and Infections and infestations (49.4%). The TEAEs (by PT) reported at the highest incidence in all subjects ($\geq 10\%$) were dizziness (27.3%), headache (17.1%), nausea (14.3%), upper respiratory tract infection (13.7%), TEAEs coded to convulsion (13.4%), fatigue (12.4%), and nasopharyngitis (11.8%).
- More subjects reported TEAEs with a maximum severity of mild (90 subjects [28.0%]) or moderate (149 subjects [46.3%]), compared with 54 subjects (16.8%) that reported TEAEs with a maximum severity of severe. Severe TEAEs were most frequently reported in the SOC of Nervous system disorders (22 subjects [6.8%]) and the most frequently reported severe TEAE was convulsion (9 subjects [2.8%]).
- A total of 189 subjects (58.7%) reported TEAEs considered related to LCM per the investigator during the Treatment Phase; similar percentages of subjects on LCM monotherapy reported TEAEs considered related to LCM (46.6%) compared with those subjects not on LCM monotherapy (44.4%). Overall, dizziness was the most commonly reported TEAE considered related to LCM per the investigator (21.1%), followed by fatigue (8.4%), nausea (6.5%), headache (5.9%), and convulsion (5.3%).
- Overall, the percentage of subjects reporting the most commonly reported TEAEs by dose at onset was highest at doses $>600\text{mg/day}$ (81.1%) compared with all other doses. The incidence of TEAEs during the Treatment Phase by dose at onset were generally similar for subjects on monotherapy and not on monotherapy compared with all subjects.
- For subjects on LCM monotherapy at SP904 entry, the incidence of TEAEs was 85.1% in subjects while on continuous LCM monotherapy and 72.5% in subjects after the continuous LCM monotherapy period ended; these data were not adjusted for duration of exposure. The majority of subjects (282 of 322 subjects) entered SP904 on LCM monotherapy and the mean first continuous period of LCM monotherapy was 475.6 days, indicating that on average these subjects spent more than half of their time in the study on LCM monotherapy. Therefore, it would be expected that more TEAEs would be reported while on continuous LCM monotherapy.
- Three subjects died during the study (1 due to cardiac arrest, 1 due to metastatic squamous cell carcinoma, and 1 due to sudden unexplained death in epilepsy [SUDEP]). The event of

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cardiac arrest was considered by the investigator to be unlikely related, the events of metastatic squamous cell carcinoma and SUDEP were considered to be not related to study medication.

- A total of 54 subjects (16.8%) reported 97 treatment emergent SAEs during the Treatment Phase. The most commonly reported SAEs were coded to convulsion (5.3%), syncope (0.9%), status epilepticus (0.9%), and postictal state (0.6%). The incidence of SAEs was 12.0% in subjects while on LCM monotherapy and 14.6% in subjects while not on LCM monotherapy. The incidence of SAEs coded to convulsion was notably higher while not on LCM monotherapy compared with LCM monotherapy (6.4% vs 2.7%), which may suggest that these subjects had more severe disease and, thus, were required to be on polytherapy.
- A total of 23 subjects (7.1%) reported TEAEs leading to discontinuation. Treatment emergent AEs coded to convulsion were the most common TEAEs leading to discontinuation (2.2%), followed by postictal state and suicidal ideation (0.6%, each). There were no apparent differences between events reported while on LCM monotherapy and not on LCM monotherapy.
- No events of hepatotoxicity were reported during the study. There were no cases that met Hy's Law criteria for drug-induced liver injury or for multiorgan hypersensitivity.
- Seven cardiac-related TEAEs were reported during the Treatment Phase, including bradycardia (4 subjects, 1.2%), sinus bradycardia (1 subject, 0.3%), and heart rate (HR) decreased (2 subjects, 0.6%). Each subject reported a single event. Six events were reported while on LCM monotherapy, and 1 event was reported while not on LCM monotherapy. Two of the 7 cardiac-related TEAEs were SAEs (bradycardia and HR decreased) that were severe and unlikely related to study medication. No events led to study medication discontinuation, and all events resolved.
- Overall review of the ECG data showed that chronic LCM treatment was not associated with changes in HR. There was no tendency for LCM to prolong the QT interval. There was a small increase in mean PR interval associated with LCM administration, as well as a slight increase in QRS duration. The magnitude of these changes, generally, did not change with increasing duration of exposure to LCM.
- There were no reports of suicidal behavior or suicide attempt during the study. Ten subjects reported suicidal ideation; 7 subjects were on LCM monotherapy, and 3 subjects were not on LCM monotherapy.

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: Vimpat®	Volume: Not applicable	
Name of active ingredient: Lacosamide	Page: Not applicable	
<ul style="list-style-type: none"> • Six subjects (1.9%) reported 6 events of syncope during the Treatment Phase; 3 subjects (1.0%) were on LCM monotherapy and 3 subjects (1.8%) were not on LCM monotherapy. Three events were serious, all of which were considered to be unlikely related to study medication. No events of syncope led to study medication discontinuation. • Two subjects (0.6%) reported a mild TEAE of loss of consciousness during the Treatment Phase. Both of the events resolved. Neither event led to study medication discontinuation. • The most frequently reported seizure-related TEAE was coded to convulsion (43 subjects, 13.4%); the event was considered serious in 17 subjects (5.3%) and led to discontinuation in 7 subjects (2.2%). Serious AEs were reported for status epilepticus (3 subjects, 0.9%) and grand mal convulsion (1 subject, 0.3%). One subject discontinued due to a seizure related TEAE (status epilepticus [1 subject, 0.3%]). • Twelve subjects (3.7%) reported memory impairment, 8 subjects (2.5%) reported amnesia, and 6 subjects (1.9%) reported cognitive disorder. None of these events were serious or led to study medication discontinuation. • Twelve subjects (3.7%) reported weight increased, and 9 subjects (2.8%) reported weight decreased. None of these events were serious or led to study medication discontinuation. • There was no evidence for any clinically relevant effect of LCM treatment on laboratory parameters or vital signs. 		
<p>Conclusions: In this open-label extension study for subjects who were previously enrolled in the conversion to monotherapy study (SP902), the majority of subjects who were on LCM monotherapy at SP904 entry had LCM monotherapy periods of ≥ 24 months in this study. On average, subjects maintained LCM monotherapy for approximately 17 months.</p> <p>Long-term treatment with LCM at doses of 100 to 800mg/day when used as monotherapy or adjunctive therapy in subjects with partial-onset seizures in this open-label extension study was generally well tolerated. The overall safety profile was similar to that reported for LCM administered as adjunctive therapy in other long-term, open-label studies and was consistent with that observed in the double-blind monotherapy study, SP902. No new safety concerns were identified. The results of this study support the use of LCM as monotherapy treatment for adult patients with partial-onset seizures.</p>		
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