SP0746, 2004-000551-42

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB BIOSCIENCES GmbH

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Official study title:

A multi-center, open-label, follow-on trial to assess the long-term safety and efficacy of lacosamide in subjects with painful distal diabetic neuropathy including a double-blind, randomized time point withdrawal subtrial

CLINICAL STUDY REPORT SYNOPSIS: SP746

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: Lacosamide	**Page:** Not applicable	

Title of study: A multi-center, open-label, follow-on trial to assess the long-term safety and efficacy of lacosamide in subjects with painful distal diabetic neuropathy including a double-blind, randomized time point withdrawal subtrial

Investigator(s): One hundred and eight investigators enrolled subjects in this study.

Study site(s): This was a multicenter study; 101 sites participated in the study.

Publication(s) (reference[s]): No publications are based on this study.

Studied period: Up to 6.7 years **First subject enrolled:** 13 May 2004 **Last subject completed:** 05 Jan 2011	**Phase of development:** Phase 3

Objectives: The primary objective of the study was to assess the tolerability and safety of long-term lacosamide (LCM) administration in subjects with painful distal diabetic neuropathy.

The secondary objective was to evaluate the efficacy of long-term use of LCM in this indication.

Methodology: SP746 was an open-label, follow-on study to the double-blind studies SP743 and SP874 to assess safety and tolerability of long-term exposure of LCM in subjects with painful distal diabetic neuropathy.

Subjects completed a blinded Transition Period at the end of the preceding double-blind study (SP743 or SP874) to adjust the dose to LCM 200mg/day. At Visit 1.0 of SP746, all subjects who had completed SP743 or SP874 were on a dose of LCM 200mg/day.

Alternatively, subjects who had prematurely discontinued the double-blind study (SP743 or SP874) due to lack of efficacy or due to intolerability to study medication, and who were eligible to participate in SP746 following discussion with the medical monitor, started the Titration Period (Visit 1.0 of SP746) on LCM 100mg/day.

At Visit 1.0, subjects entered a Titration Period during which the total daily dose was increased in 100mg weekly increments to the dose providing optimal efficacy and tolerability up to LCM 600mg/day. Following implementation of Protocol Amendment 4 (dated 16 Feb 2006), the maximum allowed dose of LCM was reduced from 600mg/day to 400mg/day in accordance with recommendation of the Independent Data Monitoring Committee (IDMC), which met on a regular basis to review the available safety data from

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all ongoing LCM studies. On 10 Nov 2006, following a review of safety data accumulated over the previous 12 months, the IDMC members concluded that daily doses of LCM of up to 600mg/day could be allowed in studies of subjects with diabetic neuropathic pain, and doses of up to 600mg/day were re-introduced with Protocol Amendment 7 (dated 10 Feb 2007). If subjects achieved adequate pain relief at a lower dose than LCM 600mg/day, they did not complete all Titration Period visits (Visits 1.x), but entered the Maintenance Period at the next scheduled visit. Titration and tapering of LCM was allowed throughout the study, up to a maximum dose of LCM 600mg/day.

During the Maintenance Period, subjects returned for clinic visits every 4 weeks for 6 months (Visits 2 to 7). Subsequent visits (Visits 8.0 to 8.x) were performed at 12-week intervals. Following Protocol Amendment 8, additional visits (Visits 9.0 to 9.x) were performed at 6-month intervals.

During the Maintenance Period, subjects from SP743 were offered the option of enrolling in a double-blind subtrial lasting a maximum of 112 days. Subjects who participated in the subtrial and wanted to continue treatment with LCM could re-enter SP746.

At the end of the Maintenance Period, or if subjects discontinued the study prematurely, a Termination Visit was performed. Depending on the maintenance dose of study medication, the dose could be tapered for 1 week. A Follow-Up Visit was performed 2 weeks after the final dose of study medication.

Number of subjects (planned and analyzed): No formal sample size determination was performed for this open-label, follow-on study. It was anticipated that approximately 320 subjects from SP743 and 519 subjects from SP874 would be enrolled in SP746.

The number of subjects enrolled from SP743 was 217; 214 of these were treated in SP746. The number of subjects enrolled from SP874 was 420; 407 of these were treated in SP746. In total, 621 subjects were treated in SP746.

Diagnosis and main criteria for inclusion: Subjects who had completed the preceding double-blind studies with LCM (SP743 or SP874) and who, in the investigator's opinion, might have benefited from long-term treatment were eligible for SP746. In addition, subjects who prematurely discontinued SP743 or SP874 due to lack of efficacy or due to intolerability to study medication could be enrolled in SP746 after consultation with the medical monitor.

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Test product, dose(s) and mode of administration, batch number(s): Lacosamide was provided as white, film-coated, immediate-release tablets in strengths of 50mg and 100mg. Lacosamide was administered orally twice daily up to a maximum dose of 600mg/day.

The following batches were used in this study: [redacted], [redacted] (100mg tablets)

Duration of treatment: Subjects completed a Titration Phase of up to 6 weeks, followed by a Maintenance Phase until LCM became commercially available for diabetic neuropathic pain. A Safety Follow-Up Visit was performed 2 weeks after the final dose of study drug.

As per the original protocol, the maximum allowed duration of study participation for subjects enrolling from SP743 was 24 months. For those subjects who elected to participate in the double-blind substudy (subjects from SP743 only), this duration was extended to allow participation until LCM became commercially available for diabetic neuropathic pain. As per Protocol Amendment 5, the maximum allowed duration of study participation for subjects enrolling from SP874 was 12 months.

The actual maximum duration of exposure to study drug in SP746 was 2401 days.

Reference therapy, dose(s) and mode of administration, batch number(s): None

Criteria for evaluation: Safety was the primary objective of this study.

Safety: The following safety variables were assessed as primary variables:

1. Adverse events (AEs) reported spontaneously by the subject or observed by the investigator
2. Changes in hematology, clinical chemistry, and urinalysis parameters
3. Changes in vital sign measurements and physical (including neurological) examination findings
4. Changes in 12-lead electrocardiograms (ECGs)
5. Subject withdrawals due to AEs

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Efficacy: The following efficacy variables were assessed as secondary variables:

1. Average daily pain score at each visit using an 11-point Likert scale (0 to 10).
2. Average pain score at each visit as measured by a 100mm visual analog scale (VAS) (only for subjects from SP743).
3. Patient's Global Impression of Change in pain (PGIC) assessed at Visit 8.0, Visits 8.x, and the Termination Visit.
4. Within-subject change in different aspects of neuropathic pain (ie, intensity, sharpness, heat/cold, dullness, overall unpleasantness, surface vs deep pain) from Visit 2 of SP743 to Visit 8.x and the Termination Visit of SP746 using the Neuropathic Pain Scale (NPS) (only for subjects from SP743).
5. Average daily sleep and activity score at each visit using an 11-point Likert scale (0 to 10). Sleep was assessed every morning and activity was assessed every evening during the assigned diary period.
6. Within-subject change in quality of life from Visit 2 of SP743 or SP874 to Visit 8.0, Visits 8.x, and the Termination Visit of SP746 using the SF-36® Health Survey (version 1) quality of life questionnaire.

Following Protocol Amendment 8, assessments that contribute to efficacy variables were reduced and only the 100mm VAS (item 2 in the list above) was still assessed.

Pharmacokinetics and other variables: The following variables were assessed as other variables in this study:

1. Frequency of use of rescue medication during the assigned diary periods.
2. Plasma concentrations of LCM assessed at all visits except the Safety Follow-Up Visit (only for subjects from SP743 prior to approval of Protocol Amendment 7. Pharmacokinetic sampling was eliminated at all visits following Amendment 7 in 2007.)
3. Pharmacoeconomic assessment using the Work Productivity and Activity Impairment (WPAI) questionnaire at Visit 8.x and the Termination Visit (only for subjects from SP743).

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Statistical methods: The primary analysis set that was used for all analyses was the Safety Set (SS), which was defined as all subjects who received at least 1 dose of study medication.

Unless stated otherwise, descriptive summaries included n, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and number and percent for categorical variables. Subjects were grouped by dose based on the modal dose prescribed during the study. The modal dose was defined as the most frequently prescribed dose.

Baseline values for all variables were determined from Baseline values of the preceding double-blind study (SP743 or SP874).

Summary and conclusions:

Subject disposition: A total of 637 subjects who continued from the preceding double-blind studies SP743 and SP874 and signed the Informed Consent Form (ICF) for the open-label study SP746 comprised the Enrolled Set (ES). Of those, 217 subjects enrolled from SP743, and 420 subjects enrolled from SP874. A total of 621 subjects received at least 1 dose of study drug and were included in the Safety Set (SS).

In the ES, a total of 385 subjects (60.4%) completed the study. The main reasons for study discontinuation were withdrawal of consent (17.3%) and AE (11.9%).

Safety results:

This study was designed to investigate the safety of LCM in subjects with diabetic neuropathy following long-term exposure. Overall, 621 subjects with painful diabetic neuropathy were treated with LCM in SP746 at doses of up to LCM 600mg/day. In total, 584 subjects received study drug in the Maintenance Phase of which 90.8% received LCM for 6 months or more, 41.6% received LCM for 12 months or more, and 20.4% received LCM for 24 months or more. As per the protocol, subjects entering SP746 from SP874 had a maximum exposure to LCM in the Maintenance Phase of 12 months. Overall, the mean exposure to LCM per subject was 593.3 days and the maximum time exposure was 2401 days. Over the entire study, the modal dose group with the most subjects was the LCM 400mg/day group, totaling 271 subjects (43.6%).

Treatment-emergent AEs were experienced by 67.0% of subjects (416/621) overall and were most common in the infection and infestation SOC and the nervous system disorder SOC, with 28.0% of subjects (174/621) experiencing at least 1 treatment-emergent adverse event (TEAE) in each of these SOCs. Treatment-emergent TEAEs with an incidence of ≥5% (in descending order) were nasopharyngitis (7.6%), dizziness (7.2%), hypertension (6.3%), headache (5.6%), vertigo (5.2%), and back pain (5.0%).

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Three subjects died during the study; 2 from cardiac failure and 1 from ovarian cancer. None of the deaths were judged to be related to LCM by the investigator.

Treatment-emergent serious adverse events (SAEs) were experienced by 21.3% of subjects (132/621). The SAEs that were experienced by more than 1 subject were as follows: osteoarthritis in 7 subjects; angina pectoris in 6 subjects; coronary artery disease and cataract in 5 subjects each; diabetes mellitus and hypertension in 4 subjects each; benign prostatic hyperplasia and myocardial infarction in 3 subjects each; and anemia, bundle branch block right, bundle branch block left, acute myocardial infarction, myocardial ischaemia, cardiac failure, pancreatitis, pyelonephritis acute, gangrene, hyperglycaemia, spinal osteoarthritis, uterine cancer, breast cancer, loss of consciousness, presyncope, diabetic neuropathy, circulatory collapse, hypertensive crisis, carpal tunnel syndrome, ischaemic stroke, ovarian cyst, peripheral arterial occlusive disease, and intermittent claudication in 2 subjects each.

Sixteen subjects (2.6% of subjects in SS) experienced SAEs that were assessed by the investigator as related to study drug. The 20 events with a relationship to study drug of possible, probable, or highly probable were as follows (each event in 1 subject unless otherwise noted): psychosomatic disease; ischaemic stroke; electrocardiogram QT prolonged; pancreatitis; cardiac failure; presyncope (in 2 subjects); hypertensive crisis; bundle branch block left, QRS axis abnormality, and bundle branch block right (all in 1 subject; bundle branch block right also occurred in another subject, see below); chronic obstructive pulmonary disease; dizziness; vertigo and circulatory collapse (both in 1 subject); gamma-glutamyltransferase increased; bundle branch block right; accidental overdose and loss of consciousness (both in 1 subject; of note, the dose of onset for both SAEs was LCM 600mg/day); and depression.

The overall incidence of subjects with TEAEs leading to discontinuation from the study was 12.1% (75/621 subjects). The AEs leading to discontinuation from the study that were experienced by more than 1 subject were as follows: fatigue in 5 subjects; aspartate aminotransferase (AST) increased in 4 subjects; vertigo, vomiting, and tremor in 3 subjects each; atrial fibrillation, angina unstable, acute myocardial infarction, myocardial ischaemia, cardiac failure, nausea, gamma glutamyltransferase (GGT) increased, alanine aminotransferase (ALT) increased, uterine cancer, dizziness, balance disorder, and circulatory collapse in 2 subjects each.

No TEAEs considered as other significant AEs were experienced by ≥1% of the subjects. Other significant TEAEs occurring most frequently were syncope (5 subjects) and atrial fibrillation and bradycardia (3 subjects each). Three subjects discontinued from the study

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due to other significant TEAEs: 2 subjects due to atrial fibrillation, and 1 subject due to ventricular fibrillation.

Evaluation of ECG data during the long-term administration of LCM did not show any tendency for LCM to prolong the QT/QTc interval or to affect heart rate. There was a small increase in PR interval and a slight increase in QRS duration during treatment with LCM that was generally stable over the long duration of LCM exposure (up to approximately 6.5 years). Increases in PR and increases in QRS intervals were reversible. A total of 63/621 subjects (10.1%) had TEAEs that were included in the cardiac disorders SOC and most of these AEs were mild or moderate in intensity.

Comprehensive laboratory evaluations did not reveal any issues of clinical concern.

Assessment of vital sign parameters (pulse rate, blood pressure [systolic blood pressure and diastolic blood pressure], and body weight), and results from physical and neurological examinations did not reveal any issues of clinical concern.

Efficacy results:

At Baseline (as established in the previous studies, SP743 and SP874), the mean pain score for all modal dose groups combined was 6.45. There was a clinically relevant reduction in the average pain score beginning in the Titration Phase with a modest further reduction which was sustained for the duration of treatment. The overall mean reduction in pain score throughout the Treatment Phase (Titration Phase plus Maintenance Phase) was 3.31; leading to an overall mean pain score of 3.14 during the entire Treatment Phase. Furthermore, for all modal dose groups, the mean Likert pain score was higher for the Safety Follow-Up Visit than at the Termination Visit. The results indicate that LCM treatment maintains a clinically relevant reduction in Likert pain score that is sustained through the entire Treatment Phase, which for many subjects coming from SP743 exceeded 2 years.

The results for the change in the subjects' perception of pain interference with sleep and activity support the Likert pain scale data, showing that after start of treatment with LCM, pain interference with sleep and activity was reduced to a similar degree as the subjects' pain and was sustained during long-term treatment with LCM. The current pain scores using the VAS were consistent with the results obtained using the Likert pain scale. Rebound increases in pain scores following discontinuation of treatment (Safety Follow-Up Visit) further support the view that LCM provides pain relief in subjects with diabetic neuropathy.

Results from the PGIC showed that most subjects indicated they felt "better" (mildly,

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moderately, or much) since they first started taking LCM; however, this was not unexpected since subjects were free to discontinue from the study at any time if they were not benefiting from treatment. Only 15 of the 637 enrolled subjects (2.4%) discontinued because of lack of efficacy.

Results of the other secondary measurements such as the NPS, days of rescue medication use, and quality of life measures (SF-36 and WPAI) were consistent and supportive of demonstrating the long-term efficacy of LCM.

Pharmacokinetic results:

- The mean LCM plasma concentration showed dose proportionality during the Titration Phase and Maintenance Phase, and remained relatively stable during long-term treatment with LCM.
- The mean LCM plasma concentration normalized by dose remained relatively stable during long-term treatment with LCM.
- The mean LCM plasma concentration normalized by weight and dose remained relatively stable during long-term treatment with LCM.
- There appeared to be no association between LCM plasma concentration and QT interval corrected for heart rate using Bazett's correction formula (QTcB interval) or QT interval corrected for heart rate using Fridericia's correction formula (QTcF interval) or QRS duration. There appeared to be a small prolongation of the PR interval with increasing LCM plasma concentration.

Conclusions:

- The safety of long-term treatment with LCM has been established in patients with diabetic neuropathy. The frequency, intensity, and pattern of AEs experienced were consistent with the known safety profile of LCM in a subject population with diabetes.
- Consistent with previous data, LCM has a generally acceptable cardiac safety profile, but is associated with small, reversible increases in PR and QRS intervals on the ECG.
- Treatment of LCM resulted in clinically relevant reductions in pain, consistent across a variety of measures. These reductions were sustained beyond 2 years with no indication of the development of tolerance.

Report date: 29 Nov 2011