SP0874, 2005-005788-27

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.

Sponsor:

UCB BIOSCIENCES GmbH

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400 mg/day lacosamide in subjects with painful distal diabetic neuropathy using two different titration schemes

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual trial table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of finished product: Lacosamide*	**Volume:** Not applicable	
Name of active ingredient: SPM 927	**Page:** Not applicable	
Title of trial: A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day lacosamide in subjects with painful distal diabetic neuropathy using two different titration schemes		
Investigators: Investigators and their affiliations are listed separately.		
Trial site(s): Seventy-four sites within [redacted] randomized at least 1 subject		
Publication (reference): None		
Studied period (years): **First subject enrolled**: 30 Jun 2006 **Last subject completed**: 29 Jun 2007	**Phase of development: 3b**	
Objectives: The primary objective of the trial was to investigate the efficacy of LCM 400mg/day compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Secondary objectives were to investigate the onset of action under treatment of LCM, the effect of LCM on subjects' perception of pain, sleep, activity, and quality of life, and to further investigate the safety of LCM.		

*Approved as Vimpat® (this note was added for clarification purposes afterwards)

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Methodology: SP874 was a multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of LCM 400mg/day in subjects with diabetic neuropathic pain using two different titration schemes, specifically a fast titration scheme (FT) and a standard titration scheme (ST).

Subjects began the trial with a 2-week Screening Phase. The first week of the Screening Phase served as the Wash-Out Phase for prohibited concomitant medications; the second week of the Screening Phase served as the Baseline Phase for pain assessments. This Screening Phase could have been shortened to 1 week if a Wash-Out-Phase was not necessary.

Subjects who met eligibility criteria and completed the Screening Phase were randomized in a double blind 1:1:1 randomization scheme to placebo, LCM 400mg/day ST, or LCM 400mg/day FT, respectively. Subjects assigned to the LCM 400mg/day ST regimen had their dose titrated from LCM 100mg/day to 400mg/day at weekly interval of LCM 100mg. Subjects assigned to the LCM 400mg/day FT regimen received LCM 200mg/day LCM for the first 3 days, LCM 300mg/day for the next 4 days, and reached their target dose of LCM 400mg/day after 1 week. They underwent sham titration for the remaining 3 weeks of the Titration Phase. Subjects visited the clinic after 1, 2, and 4 weeks of treatment. All subjects completing the 4-week Titration Phase entered a 12-week Maintenance Phase. No dose adjustment was allowed during the Maintenance Phase.

At the end of the Maintenance Phase, subjects were offered the option of entering an open-label, follow-on trial (SP746), and all subjects entered either a blinded 2-week Transition Phase or a 2-week Safety-Follow-Up Phase. Subjects who elected to enroll in the open-label, follow-on trial had their dose adjusted to LCM 200mg/day LCM over this 2-week phase and entered the open-label trial on this dose at the End-of-Trial Visit. Subjects who elected not to enroll in the open-label, follow-on trial stopped the intake of trial medication at Visit 8 and entered a 2-week Safety Follow-Up Phase.

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Number of subjects (planned and analyzed): It was expected that approximately 765 subjects had to be screened to yield 537 randomized subjects, from which 519 were expected for primary analysis.

A total of 779 subjects were enrolled and comprised the ES. Of the ES, 228 (29.3%) subjects were screen failures leaving 551 randomized subjects of which 549 received at least 1 dose of trial medication and were included in the SS. A total of 542 subjects also had at least 1 post-baseline pain score recorded in their diary and were included in the FAS. Of the 542 subjects in the FAS, 468 had at least 1 diary pain score recorded during the Maintenance Phase and did not have any major protocol deviations and were included in the PPS. Of the FAS, 447 subjects completed the Maintenance Phase and were included in the CS.

Diagnosis and main criteria for inclusion: Subjects were male or female, 18 years of age or older. Subjects had symptoms of painful distal diabetic neuropathy for 6 months to 5 years and had a diagnosis of diabetes mellitus (Type I or Type II). Subjects had HbA1c levels <12% with optimized diabetic control (best effort to achieve best control) for at least 3 months prior to Visit 1 and also had at least moderate pain (average pain intensity during the 7 days prior to Visit 2 of ≥4 out of 10 on an 11-point Likert pain scale).

Test product, dose and mode of administration, batch number:

Subjects took 50mg and 100mg lacosamide tablets. Lacosamide was manufactured by SCHWARZ PHARMA AG. The following batches were used in this trial:

Lacosamide 50mg tablets: [redacted]

Lacosamide 100mg tablets: [redacted]

Duration of treatment: The maximum duration of a subject's trial participation was 20 weeks. The maximum duration of trial medication administration was 18 weeks.

Reference therapy, dose and mode of administration, batch number:

Placebo was provided in matching tablets. The following batches were used in this trial:

Placebo tablets: [redacted]

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Criteria for evaluation:

- **Efficacy**:

The primary efficacy variable was within-subject change in average daily pain score from the Baseline week to the last 4 weeks of the Maintenance Phase using an 11-point Likert scale (0 to 10).

Secondary efficacy variables were the following:

- Time to sustainable pain relief was defined as the time from Baseline to the day on which there was a ≥1-point improvement over Baseline in the Likert pain score that remained ≥30% over Baseline the last 4 weeks of the Maintenance Phase.
- Percentage of subjects with ≥30% or ≥2-point reduction of with-in subject change in average daily pain score from the Baseline week to the last 4 weeks of the Maintenance Phase using an 11-point Likert scale (0 to 10).
- Within-subject change in average daily pain score from the Baseline week to various time points using an 11-point Likert scale (0 to 10).

Health outcome variables were the following:

- Within-subject change from the Baseline week in daily perception of pain interference with subject's sleep and activity scores using an 11-point Likert scale (0 to 10)
- Percentage of days of rescue medication use during the Treatment Phase
- Within-subject change from Baseline in subject's quality of life measured using the Short Form-36 (SF-36) quality of life questionnaire
- Subject satisfaction with LCM treatment for pain due to diabetic neuropathy (Patient's Global Impression of Change [PGIC] and Subject Satisfaction Questionnaire)
- Effect of LCM on subject's quality of sleep assessed using the Medical Outcomes Study (MOS) sleep scale

Pharmacokinetics/pharmacodynamics: NA

Safety:

Safety variables were the following:

- Adverse events (AEs) reported spontaneously by the subject or observed by the investigator

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- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in vital sign measurements and physical (including neurological) examination findings
- Changes in 12-lead ECGs
- Subject withdrawal due to AE

Statistical methods:

The primary efficacy variable was the change in average daily pain score from Baseline to the last 4 weeks of the Maintenance Phase using the 11-point Likert scale (0 to 10). The last 4 weeks of the Maintenance Phase was defined as the last 28 days of the Maintenance Phase. Pain scores were recorded twice a day (AM and PM) in a diary beginning at Visit 1. The daily pain score was defined as the average of each daily AM and PM score. For a given day, if either the AM or PM pain score was missing, the pain score that was present was used as the daily pain score for that day.

The change in average daily pain score was analyzed using an analysis of covariance (ANCOVA) with terms for treatment and pooled sites using the baseline pain score as a covariate. Adjusted means (least square means [LSMeans]) were used to estimate the treatment difference. A sequential testing procedure was used such that the standard titration dose group was tested against placebo and second, the fast titration dose group was tested against placebo, if and only if the first hypothesis was rejected was the second hypothesis tested. The trial was considered positive if the LCM 400mg/day ST group was statistically significantly better than placebo.

Summary and conclusions:

Efficacy:

Based on the prespecified primary analysis, the results of this study shows that LCM 400mg/day, demonstrated efficacy when administered using the standard titration regimen.

The primary efficacy variable was the change in average daily pain score from Baseline to the last 4 weeks of the Maintenance Phase using the 11-point Likert scale (0 to 10). In the FAS, there were 1.90-, and 2.34-point reductions in the LSMean Likert pain scores from Baseline to the last 4 weeks of the trial for the placebo and LCM 400mg/day ST groups, respectively. The difference in LSMean pain score (-0.45) between the LCM 400mg/day ST group and placebo, was statistically significant (p=0.0410).

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In additional analyses of the primary variable, the standard LCM titration group gave consistently greater improvement in average daily pain than placebo. In support of the LOCF imputation, the BOCF imputation also gave a statistically significant difference between LCM 400mg/day ST and placebo.

In the ANCOVA analysis of the primary variable for PPS, change in average daily pain score for LCM 400mg/day ST was not significantly higher than placebo, though numerically better. Comparison of FAS subjects in each treatment group who were excluded from the PPS, showed markedly higher average improvements in average daily pain score to the last 28 days of Maintenance Phase for LCM-treated subjects, than for placebo subjects. This resulted in a smaller treatment effect in the PPS.

There was an apparent negative selection of FAS subjects reaching the Maintenance Phase, the subjects not entering the Maintenance Phase were predominantly positive responders for the LCM treatment groups, and negative responders for the placebo group. This resulted in a smaller treatment effect for the Maintenance Phase.

Non-parametric analysis indicated a statistically significant difference between placebo from Baseline to the last 4 weeks of Maintenance Phase, and to the entire Treatment Phase. The stronger significance in difference between LCM 400mg/day ST and placebo in the non-parametric analysis when compared to the ANCOVA, may suggest the criteria for a normal distribution were not fully met, making parametric analyses less sensitive.

While the treatment effect was distinct for the investigator type pools neurologists/anaesthesiologist (-0.99), endocrinologist (-0.43), and primary care/other (-0.56), there was no apparent treatment effect for the pool diabetologist (-0.08). The reasons for this inconsistency are unclear, but did not appear to correlate with Baseline pain, or years with DNP. It was noted that subjects seen by diabetologists were less likely to have had prior treatment with currently recognised effective treatments such as gabapentin.

Investigator type was also regionally distributed in this trial. As such, treatment effect also correlated with region, showing a weaker treatment effect in regions primarily represented by diabetologists.

Median time to sustainable pain relief (TTPR) in the FAS was markedly shorter for the LCM 400mg/day ST group (10.0 days) than for placebo (31.0 days).

The percentage of subjects with ≥30% or ≥2-point reduction in Likert pain score from Baseline to the last 4 weeks of the Maintenance Phase was higher in the LCM treatment

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groups than in the placebo group.

For the FAS, the percentage of subjects reaching various thresholds of pain reduction for the last 28 days of Maintenance Phase were consistently greater for the LCM treatment groups than for placebo. There was higher discrimination between the LCM and placebo groups, using the ≥50% pain reduction threshold rather than the ≥30% reduction threshold, may be a reflection of the strong placebo effect which may mask differences between LCM and placebo groups when using lower threshold values.

For the FAS, the mean change in average daily pain score was greater in the LCM treatment groups at every visit, from Visit 3 to the end of the trial. The average change in daily pain score for the last 28 days of Maintenance Phase was higher for subjects in the standard titration scheme (-2.4 points on the Likert scale), than for the placebo group (-1.9).

In the FAS, the within-subject change from Baseline in average daily pain interference with sleep was consistently better in the LCM treatment groups, than the placebo group as early as Visit 3 through to the end of the trial.

Health outcomes

The percentage of subjects using rescue medication in various trial phases was similar across all treatment groups. For subjects using rescue medication, the percentage of days with rescue medication use during the last 28 days of Maintenance Phase was similar across all treatments groups, but lower in the placebo group (42.8%) compared to 44.7% for the LCM standard titration group).

The results of the SF-36 were similar between the pooled LCM groups and placebo. This may be partly from the high variability noted in the data.

The greatest difference between groups in global impression of change in pain was seen for the category “much better” with 24.7% of LCM 400mg/day ST subjects compared with 12.3% of placebo subjects reporting that they felt much better. The proportion of subjects with a worsened global impression of pain from Baseline to Visit 8 (including early termination) was similar in all groups (5.4% for the standard titration group and 5.8% for the placebo group).

While a clear placebo effect was apparent in the proportion of subjects satisfied with trial medication across all groups, there was clearly a higher proportion of subjects in the LCM standard titration group who were satisfied/very satisfied with trial medication than in placebo. Notably fewer subjects in the standard titration group were dissatisfied with trial

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medication.

Improvement in sleep quantity from Baseline to Visit 5 and Visit 8 was higher in the LCM treatment groups than in placebo. The proportion of subjects reporting optimal sleep (between 7 and 8 hours each night) increased most from Baseline to Visit 8 in the LCM 400mg/day ST treatment group (from 33.3% to 49.5%) compared to placebo group (from 37.4% to 43.7%).

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Safety results:

Overall, 370 subjects with DNP were titrated to LCM 400mg/day for a total exposure period of up to 133 days. A total of 204 (55.1%) of 370 LCM treated subjects and 282 (51.4%) of 549 subjects in the SS, experienced at least 1 treatment-emergent AE. Among all subjects, TEAEs were most common in the nervous system disorders SOC, with 23.8% (88/370), 10.1 % (18/179), of subjects in the LCM 400mg/day and placebo groups, respectively, reporting at least 1 AE in this SOC.

Overall, in the lacosamide treatment groups combined, dizziness (7.8%), nausea (7.6%), and headache (6.2%) were the most frequently reported treatment-emergent AEs. No AE was reported by ≥10% of subjects in any treatment group.

The incidence of TEAEs was higher during the Titration Phase for subjects on the fast titration scheme than for subjects on the standard titration scheme.

No subjects died during the trial, and there were no pregnancies. No individual SAE occurred in more than 1 subject in any treatment group. The overall incidence of SAEs was 7.8%, 6.3%, and 8.8% in the placebo, LCM 400mg/day FT, and LCM 400mg/day ST treatment groups, respectively. Most of the SAEs were unlikely related or not related. Those possibly, probably, or highly probably related resolved or resolved with sequelae.

The rates of discontinuation due to AE were higher in the LCM 400mg/day FT groups (15.9%) than in the LCM 400mg/day ST group (8.8%). Discontinuation due to AE was slightly and higher in the LCM 400mg/day ST group (8.8%) than in placebo (6.7%). A total of 58 (10.6%) subjects withdrew from the trial as the result of experiencing an AE. The most common AE leading to discontinuation was dizziness (3.7% and 0.6% of subjects in the LCM 400mg/day FT and LCM 400mg/day ST groups, respectively, compared to 0% of subjects in the placebo group).

Most AEs that were reported with a maximum intensity of either mild or moderate intensity, 93.1% and 92.3%, of AEs reported by subjects in the LCM and placebo groups, respectively were of either mild or moderate intensity. The incidence of AEs with maximum intensity severe was also similar in the placebo and lacosamide treatment groups (3.4% of subjects in the placebo group, 3.8% of subjects in the LCM treatment groups, respectively).

Overall, the percentage of subjects with TEAEs considered by the investigator to be related (possibly, probably or highly probably) to trial medication was lower for the placebo treatment group than for the LCM treatment groups (16.2% for placebo and 28.1% for the LCM treatment groups). Treatment emergent AEs considered to be related to trial medication were most common in the nervous system with 23.8%, of LCM subjects and 10.1% of placebo subjects reporting at least 1 AE in this SOC considered to be treatment related.

The incidence of drug-associated TEAEs did not appear to correlate to dose at onset. The AEs of dizziness, tremor, somnolence, and vertigo had a higher incidence at the LCM 400mg/day dose than

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either at lower LCM doses or placebo.

Despite the shorter period for titration to target dose, the incidence of all drug-associated AEs except for headache was higher in the LCM 400mg/day FT group than in the LCM 400mg/day ST group. As expected, incidence of drug-associated AEs during titration to target dose was higher in each LCM group than in the placebo group during the equivalent period.

No cardiac-related TEAEs occured in ≥5% of subjects in any treatment group.

Comprehensive laboratory evaluation did not reveal any issues of clinical concern. In particular, assessment of liver tests did not show any relationship between treatment with lacosamide and clinically significant changes in liver function parameters. For those subjects who had abnormal elevations in liver enzymes, often these were either present at Baseline or returned to within the normal range by the end of the trial.

Vital signs and physical examinations showed no changes of clinical concern.

Across all treatment groups, the mean change from Baseline data did not show a QT/QTc prolonging effect of lacosamide or an effect on heart rate. There was no clinically relevant effect on QRS duration.

There was a small increase in PR interval observed in the lacosamide treatment groups as compared with placebo. The placebo-subtracted mean maximum increase in PR interval was ~7ms for the lacosamide. This small increase in mean PR interval was associated with an small increase in the frequency of first degree AV block (PR >209ms) in the lacosamide group (6.7%) compared to the placebo group (3.0%). Although ECGs were frequently acquired there were no ECG reports of second degree AV block.

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Conclusions:

- This trial confirms LCM 400mg/day ST was significantly better than placebo in treatment of DNP.
- Onset of effect was faster under LCM 400mg/day than under placebo.
- The safety profile of the LCM 400mg/day ST group was similar to the placebo group and was slightly better than observed in previous trials and the tolerability of LCM was slighty better than seen in previous trials.
- There did not appear to be a clear added benefit from the fast titration scheme over the standard titration scheme.
- Health Outcomes responses gave a trend towards greater improvement and satisfaction under LCM.

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