SP0830, 2004-000960-28

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

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

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A multi-center, open-label trial to assess the long-term safety and efficacy of lacosamide in subjects with painful diabetic neuropathy

Name of company: SCHWARZ BIOSCIENCES GmbH	**Individual trial table referring to part of the dossier** Not applicable	*(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, open-label trial to assess the long-term safety and efficacy of lacosamide in subjects with painful diabetic neuropathy		
Investigators: Multicenter trial		
Trial site(s): The trial was conducted at 57 sites in 15 countries ([redacted]).		
Publication (reference): None		
Studied period (years): First subject enrolled: 21 Dec 2004 Last subject completed: 31 Oct 2007	**Phase of development:** 3	
Objectives: The primary objective of the trial was to assess the safety and tolerability of long-term lacosamide (LCM) administration in subjects with painful diabetic neuropathy. Additional objectives were to investigate the following: • Effect of long-term use of LCM on subjects' perception of pain as measured by various assessments • Effect of LCM on the interference of pain on subjects' sleep and activity • Effect of long-term use of LCM on subjects' quality of life • Effect of long-term use of LCM on subjects' work productivity and activity • Effect of long-term use of LCM on subjects' sleepiness • Effect of add-on therapy on the safety, tolerability, and efficacy of LCM in subjects with painful diabetic neuropathy • Effect of long-term use of LCM in subjects who had not previously responded to treatment with gabapentin • Subject satisfaction with LCM treatment for pain as a result of diabetic neuropathy compared with any prior pain medications • Correlation of plasma concentrations of LCM with cardiac safety variables		

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

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Methodology: This was a long-term, open-label trial in which subjects with painful diabetic neuropathy received LCM treatment at their optimal dose. After a 2-week Run-In Phase, subjects entered a 4- to 6-week Titration Phase to be titrated to their optimal dose level. At the optimal dose, a 12-week Maintenance Phase A with LCM monotherapy was followed by Maintenance Phase B (12 weeks and x periods of 12 weeks) in which additional medications were allowed for optimal pain control. Two weeks after the last dose of trial medication, a Safety Follow-Up Visit was done.

Number of subjects (planned and analyzed): 505 subjects with painful diabetic neuropathy were enrolled, 371 subjects were treated at their optimal dose level, and 192 subjects completed the trial, ie, they did not discontinue before the sponsor-determined termination date of the trial, ie, 31 Oct 2007.

Diagnosis and main criteria for inclusion: Male and female subjects (≥18 years of age) with symptoms of painful diabetic neuropathy for at least 6 months and a diagnosis of diabetes mellitus (Type I or Type II)

Test product, dose and mode of administration, batch number: Subjects took 50mg and 100mg LCM tablets. Lacosamide was manufactured by SCHWARZ PHARMA AG, Germany. The following batches were used: 50mg-tablets- [redacted] and 100mg-tablets [redacted].

Duration of treatment: The maximum duration of subject participation in this trial was from December 2004 to October 2007.

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

Criteria for evaluation:

Safety: Safety was the primary objective of this trial. Safety variables were:

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

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The following variables were assessed as secondary variables in this trial:

Efficacy:

- Within-subject change in average daily pain score from the Baseline week to the 7 days prior to each visit of the trial using an 11-point Likert scale (0-10)
- Within-subject change in the effect of pain on subject's sleep and activity from the Baseline week to the 7 days prior to each visit of the trial using an 11-point Likert scale (0-10)
- Within-subject change in current pain from Visit 2.0 to each subsequent visit as measured by a 100mm visual analogue scale
- Patient's Global Impression of Change in Pain (PGIC) assessed at Visit 4, Visit 6, Visit 9.x, and the Termination Visit
- Within-subject change in different symptoms of neuropathic pain from Visit 2.0 to the end of the first 4 weeks of the Maintenance Phase A (Visit 4), end of the Maintenance Phase A (Visit 6), Visit 9.x, and Termination Visit using the Neuropathic Pain Symptom Inventory (NPSI)
- Within-subject change in quality of life from Visit 2.0 to the end of the first 4 weeks of Maintenance Phase A (Visit 4), end of Maintenance Phase A (Visit 6), Visit 9.x, and the Termination Visit using the Short Form-36® (SF-36®) Health Survey (version 1) quality-of-life questionnaire

Health outcomes:

- Pharmacoeconomic assessments using the Work Productivity and Activity Impairment (WPAI) questionnaire at Visit 2.0, Visit 4, Visit 6, Visit 9.x, and the Termination Visit
- Pharmacoeconomic assessment of subject satisfaction with LCM and prior pain medications as treatment for painful diabetic neuropathy at Visit 1, Visit 6, Visit 9x, and the Termination Visit
- Frequency of use of rescue medication

Clinical pharmacology:

- Determination of plasma concentrations of LCM

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Statistical methods: Data were analyzed descriptively without statistical testing of hypotheses. Descriptive summaries include n, mean, standard deviation, median, minimum, and maximum for continuous variables, and number and percent for categorical variables. All safety parameters are presented by modal dose group and for all doses combined, unless otherwise noted.

Summary and conclusions:

Safety results: This trial showed that LCM was well tolerated by most subjects. Overall, 371 subjects with DNP were treated with LCM at doses up to 600mg/day for an average of 1.6 years. Of these, 192 subjects completed the trial, ie, they did not discontinue before the protocol-determined termination date of the trial, ie, 31 Oct 2007. Over the entire trial, the largest number of subjects (236/371 [63.6%]) was maintained at a modal dose of LCM 400mg/day.

Treatment-emergent AEs were experienced by 304 (81.9%) subjects overall and were most common in the nervous system disorders SOC, with 49.3% of subjects reporting at least 1 AE in this SOC. The most frequently reported TEAEs with incidences of ≥5% of subjects overall were dizziness (20.2% of subjects), nausea (13.2%), vertigo (12.1%), headache (11.9%), nasopharyngitis (11.6%), somnolence (9.2%), fatigue (8.4%), hypertension (7.3%), back pain (7.0%), tremor (6.5%), and vomiting (5.7%), and edema peripheral (5.4%). Most AEs were transient or manageable by dose reduction, drug interruption, or drug withdrawal.

Sixty-eight (18.3%) subjects in the SS discontinued the trial prematurely due to TEAEs, including 7 subjects who discontinued due to AEs during the Safety Follow-Up Phase. Nausea, vomiting, and dizziness (in 5 subjects [1.3%] each) were the only TEAEs resulting in discontinuation of more than 1% of subjects.

Long-term treatment with LCM did not reveal a tendency for new AEs of significance (eg, cardiac and ECG-related events, abnormal liver function-related events) to occur with any frequency of concern, and AEs of significance did not occur with increasing frequency after long-term treatment with LCM.

Seven subjects died during this long-term trial, as a result of AEs of cardiac failure, myocardial infarction, myocarditis, colon cancer and associated gastric hemorrhage and shock hemorrhagic, leukemia, bronchial carcinoma, and brain herniation. Neither of the cardiac events was considered related to the trial medication. Of the events related to cancer, only the leukemia was assessed by the investigator as possibly related to trial medication, although anemia was noted in the subject at Baseline.

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The overall incidence of treatment-emergent SAEs was 22.4% (83/371 subjects). Twenty-one individual treatment-emergent SAEs occurred in more than 1 subject. The following SAEs occurred in 3 subjects (0.8%) each: myocardial infarction, cerebrovascular accident, and hypertension; the following SAEs occurred in 2 subjects (0.5%) each: angina pectoris, myocardial ischemia, coronary artery disease, vestibular disorder, retinal detachment, diabetic retinopathy, cataract, umbilical hernia, chest pain, appendicitis, lower limb fracture, diabetes mellitus, hyperglycemia, diabetic foot, intervertebral disc protrusion, osteoarthritis, colon cancer, and carotid artery stenosis.

The evaluation of ECG data in this trial showed no indication that treatment with LCM resulted in a prolongation of the QT/QTc interval or caused associated effects on repolarization. There was a trend towards a small prolongation of the PR interval and a slight increase in the QRS duration during treatment with LCM; this is consistent with results from other LCM trials. The small PR prolongation did not increase further during long-term treatment with LCM and was reversible after discontinuation of trial medication. Single cases of several different types of cardiac-related AEs were noted.

Seventeen subjects experienced TEAEs related to abnormal liver enzymes and 3 subjects terminated the trial prematurely because of increased or abnormal liver enzymes; these 3 AEs resolved after the subjects were withdrawn from trial medication.

Hypertension and increased blood pressure were the most common AEs related to vital signs. Lacosamide had no effect on body weight.

Overall, the evaluation of the long-term safety profile of LCM showed no important long-term safety issues.

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Efficacy results: At Baseline, the average Likert pain score for all subjects combined was 6.28. The overall average reductions in Likert pain score were -3.28 during Maintenance Phase A and -3.68 during Maintenance Phase B. The results indicate that after start of treatment with LCM there was a clinically relevant reduction in the Likert pain score that was sustained throughout the whole period of the trial. In most of the subjects, treatment exceeded 2 years. Subsets of subjects in the LCM 400mg/day modal dose group who received LCM for ≥18 or ≥24 months showed similar reductions in pain as the overall population, indicating that the improvement seen over time was not due to subjects with inadequate pain relief discontinuing prematurely.

Clear improvements in pain were observed in a subset of subjects who had, by self report, not previously responded to treatment with gabapentin, however, results were derived from a small number of subjects and should be interpreted with caution.

The average current pain of subjects continued to decrease with increasing exposure to LCM, with most subjects experiencing spontaneous pain for less than 1 hour per day.

Results from the PGIC showed that most subjects reported feeling "better" (mildly, moderately, or much better) since they first started taking LCM; however, this is not unexpected in an open-label trial. Only 17 of the 371 subjects (4.6%) in the trial discontinued because of lack of efficacy.

The results for the change in the subjects' perception of pain interference with sleep and activity indicate that after start of treatment with LCM, pain interference with sleep and activity was substantially reduced to a similar degree as the subjects' pain, and this was sustained during long-term treatment with LCM.

This was supported by the MOS Sleep Scale which suggests an improvement of the subjects' sleep under long-term treatment with LCM.

Improvements in all domains of the SF-36® questionnaire indicate an overall improvement in the subjects' quality of life. The largest improvements were observed for bodily pain and role physical. Improvements were sustained throughout the duration of the trial.

The results from the efficacy analyses in this trial support the long-term efficacy of LCM in subjects with DNP.

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Health outcomes results:

- Only a small proportion of subjects reported to be employed during this trial. For these, there appeared to be some improvements in work productivity and activity during long-term treatment with LCM.
- At Screening, more than 50% of subjects reported that they were dissatisfied or neither satisfied nor dissatisfied with their prior treatment for pain. Throughout the duration of the trial, the majority of subjects (approximately 80%) reported that they were satisfied or very satisfied with their current pain treatment.
- There was a substantial decrease in rescue pain medication use (paracetamol up to 2g/day) in those subjects using rescue medication at Baseline.

Clinical pharmacology results:

- The mean LCM plasma concentration showed dose proportionality during the Titration Phase and the Maintenance Phase and remained relatively stable during long-term treatment with LCM.
- Elderly subjects (≥65 years) had a slightly higher mean LCM plasma concentration compared with younger subjects (<65 years), also after body weight normalization, which indicates a slight influence of other age-related factors like reduced total body water and reduced renal clearance.
- No difference was observed between male and female subjects for the measured mean LCM plasma concentration.
- Correlation analysis of LCM plasma concentration and cardiac safety variables showed no clear influence on QRS duration and a small prolongation of the PR interval with increasing LCM plasma concentration.

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Conclusions:

- Most subjects were managed on LCM 400mg/day as their long-term maintenance dose.
- In this long-term trial with LCM, most AEs resolved while on treatment or were reversible by dose adjustments or drug withdrawal.
- Treatment with LCM resulted in a slight increase the QRS duration and a small prolongation of the PR interval. The small prolongation of the PR interval was correlated with increasing LCM plasma concentration but was not associated with other related cardiac disorders. The PR prolongation did not increase with time and was reversible after discontinuation of LCM.
- Long-term treatment with LCM did not result in additional safety concerns.
- Efficacy results from different pain assessments (Likert pain scale, PGIC) show that after start of treatment with LCM there was a clinically relevant reduction in the Likert pain score that was sustained throughout the whole period of the trial. There was no indication of tachyphylaxis.
- The results for the change in the subjects' perception of pain interference with sleep and activity indicate that after start of treatment with LCM, pain interference with sleep and activity was substantially reduced and this was sustained during long-term treatment with LCM.
- Improvements were seen in the subjects' quality of life, work productivity and activity, and sleep during long-term treatment with LCM.
- The effect of add-on therapy during Maintenance Phase B could not be evaluated since too few subjects elected to take additional medication to achieve adequate pain relief.
- A subset of subjects who had not previously responded to treatment with gabapentin also showed a clear decrease in pain while under exposure of LCM.
- A high proportion of subjects reported being satisfied with their LCM treatment.

Date of the report: 29 May 2008