SP0755, 2004-000290-58

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.

Sponsor:

UCB BIOSCIENCES GmbH
(formerly SCHWARZ BIOSCIENCES GmbH)
Alfred-Nobel-Str. 10
40789 Monheim
Germany

Official study title:

A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual trial table referring to part of the dossier** NA	*(For National Authority Use Only)*
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Name of active ingredient: Lacosamide	**Page:** Not applicable	

Title of trial: A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization

Investigators: Multicenter trial

Trial site(s): Seventy-seven sites were activated in 12 countries in [redacted] and 75 sites screened, enrolled, and randomized at least 1 subject.

Publication (reference): None

Studied period (years): 1.5 years First subject enrolled: 07 Jun 2004 Last subject completed: 24 Jan 2006	**Phase of development: 3**

Objectives: The primary objective of this trial was to evaluate the efficacy of lacosamide (LCM; also referred to as SPM 927) administered concomitantly with 1, 2, or 3 antiepileptic drugs (AEDs) in subjects with or without additional vagus nerve stimulation (VNS) who currently have uncontrolled partial seizures with or without secondary generalization.

The secondary objectives were to evaluate the safety of LCM, the dose-response relationship of LCM with regards to efficacy and safety, and to examine steady-state plasma concentrations of LCM and concomitant AEDs during oral administration of LCM.

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

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Methodology: A Screening Visit was conducted to evaluate subject suitability for enrollment. This visit could have been conducted on more than 1 day, although it should not have taken place over longer than a week. The subjects were enrolled into an 8-week Baseline Phase. At the end of the Baseline Phase, subjects were randomized (1:1:1) in a double-blind fashion to 1 of the 3 treatment arms: placebo or LCM (200mg/day or 400mg/day). The duration of the trial was 26 weeks including an 8-week Baseline Phase and 18-week Treatment Phase. The Treatment Phase was comprised of the following: 4 weeks forced titration up to the respective randomized dose of LCM or placebo (a 1-step back-titration of 100mg/day LCM or placebo was allowed at the end of the Titration Phase), 12 weeks maintenance on the achieved randomized (or once back-titrated) dose, and 2 weeks transition or taper. The Transition Phase (bringing subjects to a dose of 200mg/day LCM) was required for subjects who completed the Maintenance Phase and who chose to enroll in an open-label extension trial of LCM. The Taper Phase was required for subjects who chose not to enroll in the open-label extension trial of LCM or who discontinued prior to the end of the Maintenance Phase.

Number of subjects (planned and analyzed): It was planned to enroll 577 subjects to ensure that 462 subjects (154 per treatment group) were randomized. A total of 584 subjects were screened for this trial. A total of 546 subjects were enrolled in the trial and comprised the Enrolled Set; 32 subjects were screen failures and 6 subjects denoted as Baseline failures did not meet all Screening criteria and were excluded from the count of enrolled subjects. Of the 546 enrolled subjects, 485 were randomized. All of the 485 randomized subjects received at least 1 dose of trial medication and comprise the Safety Set. A total of 477 subjects also had at least 1 post-Baseline efficacy assessment and are considered part of the Full Analysis Set (FAS). Among the 477 subjects of the FAS, 399 subjects had at least 1 seizure frequency assessment collected during the Maintenance Phase and did not have any major protocol deviations and thus comprise the Per-Protocol Set.

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Diagnosis and main criteria for inclusion: Diagnosis of partial seizures was based on the 1981 published criteria of the International League Against Epilepsy for international classification of epileptic seizures. Subjects having any of the following 3 partial seizures subtypes were eligible for inclusion in this trial:

- Simple partial seizures with motor signs (consciousness unimpaired)
- Complex partial seizures (consciousness impaired)
- Partial seizures evolving into secondary generalized seizures

Subjects were observed to have partial onset seizures for at least the last 2 years despite prior therapy with at least 2 AEDs (concurrently or sequentially) and were observed to have on the average at least 4 partial onset seizures per 28 days with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the Baseline Phase. Subjects were on a stable dosage regimen of at least 1 but no more than 3 AEDs, with or without additional concurrent stable VNS. The VNS must have been in place for at least 6 months prior to trial entry. The dosage of concomitant AED therapy and the settings of VNS must have been kept constant for a period of at least 4 weeks prior to entry into the Baseline Phase.

Test product, dose and mode of administration, batch number: Lacosamide was supplied as white, film-coated tablets available in strengths of 50mg and 100mg. Lacosamide was administered orally twice daily. Batch numbers: 50mg: [redacted] 100mg: [redacted]

Duration of treatment: The maximum duration of treatment was 18 weeks.

Reference therapy, dose and mode of administration, batch number: Placebo was supplied as white, film-coated tablets matching in size and color to LCM. Placebo was administered orally twice daily. Batch numbers: [redacted]

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Criteria for evaluation:

Efficacy: The assessment of efficacy was based on partial seizure frequency. Seizure counts were analyzed in 2 ways:

1. Efficacy was determined by the change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase.
2. Efficacy was determined by the proportion of responders where a responder is a subject experiencing a 50% or greater reduction in partial seizure frequency from the Baseline Phase to the Maintenance Phase.

For the Food and Drug Administration (FDA), change in seizure frequency (variable 1) was the primary efficacy variable and the responder rate (variable 2) was the secondary efficacy variable. For Europe, the responder rate (variable 2) was the primary efficacy variable and the change in seizure frequency (variable 1) was the secondary efficacy variable. Secondary efficacy variables for both regions included:

- Change in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase
- Proportion of subjects experiencing a ≥50% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase
- Proportion of subjects experiencing a ≥25% to <50%, 50% to <75%, or ≥75% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase
- Proportion of subjects experiencing a ≥25% to <50%, 50% to <75%, or ≥75% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase
- Proportion of subjects experiencing no change in partial seizure frequency per 28 days (ie, between <25% reduction and <25% increase in partial seizure frequency) and the proportion of subjects experiencing ≥25% increase in partial seizure frequency from the Baseline Phase to the Maintenance Phase
- Proportion of subjects experiencing no change in partial seizure frequency per 28 days (ie, between <25% reduction and <25% increase in partial seizure frequency) and the proportion of subjects experiencing ≥25% increase in partial seizure frequency from the Baseline Phase to the Treatment Phase
- Percent change in partial seizure frequency per 28 days from the Baseline Phase to the

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Maintenance Phase

- Percent change in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase
- Proportion of subjects experiencing rebound seizures defined as an increase in partial seizure frequency per 28 days ≥100% from the Baseline Phase to the Taper Phase
- Change in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase differentiated by Baseline seizure type (ie, simple partial seizures, complex partial seizures, partial seizures with secondary generalization)
- Change in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase differentiated by Baseline seizure type (ie, simple partial seizures, complex partial seizures, partial seizures with secondary generalization)
- Proportion of subjects experiencing a ≥50% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Maintenance Phase differentiated by Baseline seizure type (ie, simple partial seizures, complex partial seizures, partial seizures with secondary generalization)
- Proportion of subjects experiencing a ≥50% reduction in partial seizure frequency per 28 days from the Baseline Phase to the Treatment Phase differentiated by Baseline seizure type (ie, simple partial seizures, complex partial seizures, partial seizures with secondary generalization)
- Proportion of seizure-free days during the Maintenance Phase for subjects who entered the Maintenance Phase
- Proportion of subjects who achieved "seizure-free status" (yes/no) during the Maintenance Phase for subjects who completed the Maintenance Phase
- Clinical Global Impression of Change (CGIC) at the end of the Maintenance Phase
- Patient's Global Impression of Change (PGIC) at the end of the Maintenance Phase

Note: Treatment Phase = Titration + Maintenance Phases

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Health outcomes variables: Health outcomes variables included:

- Change in mean daily time lost and mean daily caregiver time from the Baseline Phase to the end of the Maintenance Phase
- Change in Quality of Life in Epilepsy-31 (QOLIE-31) assessment from the Baseline Phase to the end of the Maintenance Phase
- Change in Seizure Severity Scale ratings from the Baseline Phase to the end of the Maintenance Phase
- Investigator's assessment of the subject's candidacy for epilepsy surgery or VNS

Pharmacokinetics/pharmacodynamics:

Plasma concentrations of LCM and concomitant AEDs were obtained in order to investigate 1) the plasma concentration of LCM, 2) whether LCM had any effect on the steady-state plasma concentration of concomitant AEDs, and 3) the correlation between LCM plasma concentrations and efficacy. Additionally, a population pharmacokinetic analysis of LCM plasma concentration data from this trial was performed and is described in a separate report.

Safety: Safety variables included:

- 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 (including body weight) and physical (including neurological) examination findings
- Changes in 12-lead electrocardiograms
- Subject withdrawals due to AEs

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Statistical methods: To achieve a power of 90% in this trial, a sample size of 462 subjects were needed for the primary analysis. It was estimated that 577 enrolled subjects would yield 462 subjects valid for the primary analysis of efficacy.

Seizure frequency per 28 days was calculated for the Baseline and Maintenance Phase. The inferential statistical analysis, based on analysis of covariance (ANCOVA) with terms for treatment and pooled site, was performed on log-transformed seizure frequency. Log-transformed average seizure frequency during the Baseline Phase was used as the covariate. The seizure frequency between treatment and placebo was compared using least squares (LS) means.

Response to treatment of at least 50% from Baseline to Maintenance Phase was evaluated in a dichotomous manner. The responder rate between each LCM treatment and placebo was analyzed using a logistic regression model with effects for treatment and pooled site.

For FDA submissions, the reduction in partial seizure frequency was considered primary; for submissions to European regulatory agencies, the response to treatment (responder rate) was considered primary.

Both variables were tested in a hierarchical order, starting with the highest dose versus placebo. The trial was considered positive as long as the highest dose was statistically significant.

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Summary and conclusions:

Efficacy results:

Efficacy summary:

This double-blind, placebo-controlled Phase 3 trial supports that LCM at doses of 200mg/day and 400mg/day (100 and 200mg bid, respectively) is an effective treatment for partial seizures when added to 1 to 3 approved concomitant AEDs in subjects experiencing difficult to control partial seizures with or without secondary generalization.

The LCM 200mg/day and 400mg/day treatment groups were statistically superior to the placebo group in the reduction of seizure frequency per 28 days for the Maintenance Phase (200mg/day p-value=0.0223; 400mg/day p-value=0.0325). The percent reduction in seizure frequency over placebo was 14.4% (95% CI: 2.2, 25.1) and 15.0% (95% CI: 1.4, 26.8) for LCM 200mg/day and 400mg/day, respectively. Similar positive findings were observed in the statistical analysis of responders, which is defined as subjects with at least 50% seizure reduction for the Maintenance Phase. The 50% responder rates for placebo, 200mg/day, and 400mg/day were 25.8%, 35.0% and 40.5%, respectively. The p-value for LCM 400mg/day when compared with placebo was 0.0063, which indicates this LCM dose group is more likely than the placebo group to have 50% responders. Although not statistically significant, LCM 200mg/day showed a numerically improved treatment difference over placebo.

Eleven subjects were seizure-free throughout the 12-week Maintenance Phase; 8 (3.1%) subjects were taking LCM and 3 (2.1%) subjects were taking placebo. Results were similar across multiple efficacy assessments.

In both the LCM 200mg/day and 400mg/day treatment groups, the reduction in seizure frequency was greater than placebo starting by the end of the second week of active treatment. Clinically relevant improvement was consistent over time in these treatment groups during the Maintenance Phase.

Overall in both the CGIC and PGIC, a greater percentage of subjects in the LCM 400mg/day treatment group were considered improved compared to placebo; however, this difference was not statistically significant. The percentage of subjects considered improved in the LCM 200mg/day treatment group was not different than the percentage of improved subjects in the placebo treatment group.

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Efficacy conclusions:

The LCM 400mg/day treatment group showed efficacy across both primary variables for the European Union (EU) and the United States (US). The LCM 200mg/day treatment group was significant only for the US variable although the responder rate analysis showed improvement with the LCM 200mg/day dose. Results from the analysis of secondary variables were consistent with results from the primary analysis for the LCM 200mg/day and 400mg/day groups.

Data from this trial demonstrate that LCM 200mg/day and 400mg/day consistently reduce seizures and support that these doses provide effective adjunctive treatment for partial seizures in patients with epilepsy.

Health outcomes results:

For all health outcome assessments, the mean differences between Baseline and post-Baseline measurements were very small and similar across treatment groups. The current analysis used all subjects regardless of time in the trial; an analysis that only includes subjects who complete the Maintenance Phase will be considered as a possible analysis in future trials. There may not have been sufficient time in the trial for seizure reduction to affect quality of life; longer term extension trials are also evaluating these health outcome assessments.

Pharmacokinetic/pharmacodynamic results:

The plasma concentrations of LCM were proportional to the actual dose given.

Mean plasma concentrations of LCM after normalization to body weight and actual dose were comparable between males and females for most visits. Therefore, the observed slight differences in plasma concentrations in females compared with males (ie, slightly higher plasma concentrations in females) could be explained to a major part by the differences in body weight between the 2 groups.

Mean plasma concentrations for 9 of 10 selected concomitant AEDs were not affected by intake of LCM. The summary statistics suggest that mean oxcarbazepine monohydroxy levels may have been reduced in the LCM 400mg/day treatment group but not in the LCM 200mg/day treatment group.

Increasing plasma concentrations of LCM were associated with a small prolongation of the

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PR interval, but not with a prolongation of the QT interval (QT uncorrected, QTcB, QTcF, or QTcP) or QRS duration.

Safety results:

Lacosamide at doses of 200mg/day and 400mg/day was generally well tolerated compared to placebo in this controlled trial of adjunctive therapy in epilepsy. In this double-blind, placebo-controlled adjunctive trial in subjects with partial seizures 13%, 50% and 37% (Table 6.7.1) of subjects were taking 1, 2, or 3 other AEDs, respectively, when LCM was added to their treatment regimen. Across all treatment groups, treatment-emergent AEs were most common in the nervous system disorders system order class (SOC) and the gastrointestinal disorders SOC. There were 25.2%, 31.3%, and 38.4% of subjects reporting at least 1 AE in the nervous system disorders SOC for placebo, LCM 200mg/day, and 400mg/day, respectively, and 9.2%, 16.0%, and 16.4% of subjects reporting at least 1 AE in the gastrointestinal disorders SOC for placebo, LCM 200mg/day, and LCM 400mg/day, respectively. Notable events that appeared to be dose-related included dizziness, nausea, and vomiting. Most events were assessed by the investigator as mild or moderate in intensity (93.1%, 92.3%, and 92.7% of subjects experiencing any AE in the placebo, LCM 200mg/day, and LCM 400mg/day treatment groups, respectively).

The overall number of subjects with serious adverse events (SAEs) during the Treatment Phase was greater in the LCM treatment groups compared to placebo (3.7%, 8.0%, and 9.4% of subjects in the placebo, LCM 200mg/day and 400mg/day treatment groups, respectively) although most of these events were assessed by the investigator as not related to trial medication. Across all treatment groups, the most frequently reported SAEs were convulsion (1 subject in each treatment group), epilepsy (1 subject in the placebo treatment group and 2 subjects in the LCM 200mg/day treatment group), grand mal convulsion (2 subjects in the LCM 400mg/day treatment group) and psychotic disorder (2 subjects in the LCM 400mg/day treatment group). All other SAEs during the Treatment Phase were reported by 1 subject each.

For placebo and LCM 400mg/day, the overall incidence of AEs was slightly higher during the Titration Phase than during the Maintenance Phase. The overall incidence of AEs was similar between the Titration and Maintenance Phases for the LCM 200mg/day treatment group.

The number of subjects who discontinued as the result of experiencing an AE was similar

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between the placebo and LCM 200mg/day groups. The discontinuation rate was higher in the LCM 400mg/day group.

Evaluation of electrocardiogram (ECG) data from this trial did not reveal any tendency for LCM to prolong the QT/QTc interval. There was no LCM effect on the mean QRS interval and no reports of bundle branch block in any treatment group. There was a small, dose-related increase in mean PR interval change from Baseline among the LCM treatment groups. The overall mean increases at the end of the Maintenance Phase were small (4.6ms for the LCM 400mg/day group). The frequency of treatment-emergent atrioventricular block was low and similar across the LCM (1.3%-2.5%) and placebo (3.2%) treatment groups.

Comprehensive laboratory evaluations did not reveal any abnormalities that appeared to be associated with LCM administration. There were no subjects who developed an alanine aminotransferase ≥3x the upper limit of normal and a bilirubin value ≥2mg/dL concurrently.

There were few subjects with protocol-defined abnormal vital sign measurements. No abnormalities or mean changes appeared to be associated with LCM administration.

There was no effect of LCM on mean body weight. Weight increased was reported as an AE in 3 LCM-treated subjects but the mean changes in weight were similar between LCM and placebo.

Overall, safety evaluations support the further development of LCM as an AED.

Conclusions:

This adequate and well-controlled trial supports that LCM 200mg/day and LCM 400mg/day are each effective and generally well tolerated treatments for partial seizures when added to 1 to 3 approved concomitant AEDs in patients with epilepsy.

Date of the report: 08 Sep 2006