SP0757, 2004-002322-22

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, Inc.

(formerly SCHWARZ BIOSCIENCES, Inc.)

8010 Arco Corporate Drive

Raleigh, NC 27617

USA

Official study title:

A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization

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Name of active ingredient: Lacosamide	**Page:** Not applicable	

Title of trial: A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization

Investigators: Multicenter trial

Trial site(s): Thirty-three sites were activated in the [redacted] and 4 countries in [redacted] Twenty-six of these sites screened and enrolled at least 1 subject.

Publication (reference): None

Studied period (years): 1.5 years First subject enrolled: 03 Feb 2005 Last subject completed: 10 May 2006	**Phase of development: 3**

Objectives: The objectives of this trial were to evaluate the safety and tolerability of lacosamide (LCM; SPM 927) when given as intravenous (iv) infusions in subjects who were receiving oral LCM in addition to up to 3 concomitant antiepileptic drugs (AEDs) for partial seizures with or without secondary generalization.

Methodology: This multicenter, open-label, inpatient trial was conducted at 26 enrolling sites in the [redacted] participating in an open-label extension trial of oral LCM (SP615, SP756, or SP774). A total of 160 subjects were enrolled into 1 of 5 possible cohorts in this trial.

This trial was designed to identify the appropriate infusion duration(s) for LCM and provide the data to support the safety of that infusion rate. Execution of this trial design resulted in the administration of LCM at progressively faster infusion durations under the direction of a Data Monitoring Committee (DMC). The subjects were maintained on the stable dose (100 to 300mg twice daily) that they had last received in the open-label extension trial. In Cohorts A2 and B2, subjects receiving 700mg/day or 800mg/day were to be allowed to enter the trial only after review of the safety data from the first 3 cohorts.

Subjects entered into a 1-day Screening Phase followed by a Treatment Phase during which

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

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subjects received iv LCM infused over 10, 15, or 30 minutes twice daily (depending on cohort assignment). For Cohort A1, the Treatment Phase was 2 days. However, in all subsequent cohorts, subjects had the option to receive inpatient iv dosing of LCM for 2 to 5 days. The dose of iv LCM was the same as the subject's current daily dose in the open-label extension trial of oral LCM. End of Trial Phase assessments were performed the day after the Treatment Phase was completed, after which subjects continued in the open-label extension trial (SP615, SP756, or SP774) where they resumed dosing with oral LCM as stipulated in that protocol.
Number of subjects (planned and analyzed): A total of 160 subjects were enrolled into 4 of 5 possible cohorts in this trial (Cohorts A1, B1, C, and B2). The trial exposed 40 subjects to an infusion duration of 30 minutes of iv LCM, 100 subjects to an infusion duration of 15 minutes of iv LCM, and 20 subjects to an infusion duration of 10 minutes of iv LCM.
Diagnosis and main criteria for inclusion: At Screening, eligible male and female subjects were currently enrolled in an open-label extension trial receiving oral LCM for the treatment of partial seizures and had been enrolled for at least 8 weeks. The subjects had, in the opinion of the investigator, adequate seizure control for participation in the trial, and were willing and able to comply with all trial requirements including hospitalization, multiple blood draws, and iv infusions. The subjects had been on a stable twice daily (bid) dosage regimen of LCM between 200mg/day and 600mg/day, inclusive, for the last 2 weeks, or the subjects had been on a stable bid dosage regimen of LCM 700mg/day or 800mg/day for the last 2 weeks (applicable only if doses above 600mg/day were allowed). The subjects had been on a stable dose of concomitant AED(s) for the last 2 weeks. The subjects had stable vagus nerve stimulation settings for the last 2 weeks, if applicable.

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Test product, dose and mode of administration, batch number: On Day -1, oral LCM tablets were administered in accordance with each subject's LCM dosage regimen in the open-label extension trial (SP615, SP756, or SP774). The tablets were taken from the open-label extension supply.

During the Treatment Phase, trial medication (iv LCM solution) was administered twice daily at 12-hour intervals, once in the morning and once in the evening. Subjects remained on the same stable dose that they had received during their previous 2 weeks in the open-label extension trial (100 to 400mg bid). Asymmetrical dosing (ie, taking a different dose morning vs evening) was not permitted. Subjects on 700mg/day or 800mg/day were allowed to enter the trial only after review of the safety data from the first 3 cohorts.

On the day after the Treatment Phase was completed, oral LCM tablet(s) were administered in the morning in accordance with each subject's LCM dosage regimen in the open-label extension trial (SP615, SP756, or SP774). Tablets were taken from the open-label extension supply.

Batch numbers: [redacted]

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Duration of treatment: The Treatment Phase was 2 to 5 days.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation:

Safety: Safety variables evaluated were adverse events (AEs) as well as the results of vital sign monitoring, electrocardiograms (ECGs), clinical laboratory tests, physical examination, neurological examination, and seizure counts.

Pharmacokinetics: Blood samples were collected for analysis of trough concentration (C_{trough}) and measured maximum concentration (end of infusion) (C_{max}) for LCM as well as the O-desmethyl-metabolite of LCM (SPM 12809). In addition, predose concentrations of concomitant AEDs were determined at Day -1.

Statistical methods: Data summaries and analyses were presented in order to assess the safety and tolerability of iv LCM. As appropriate, changes in clinical outcomes from Baseline to the end of treatment were also presented. No inferential statistical testing was carried out for any variables.

Appropriate descriptive statistics were computed and displayed for both continuous and categorical variables. For continuous variables, descriptive statistics included n (the number of subjects with non-missing data), mean, standard deviation (SD), median, minimum, and maximum values. For categorical parameters, the numbers and percentages of subjects within each category were presented. The denominator for percentages was based on the number of subjects with data appropriate for summary purposes.

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Summary and conclusions:

Safety results:

Across all infusion duration groups, 111 subjects (69%) were taking a daily dose of LCM 400mg/day to LCM 800mg/day. In the 15-minute infusion duration group, 65 subjects (65%) were taking a daily dose of LCM 400mg/day to LCM 800mg/day; 26 subjects (26%) were taking LCM 600mg/day to LCM 800mg/day. Overall, 79 subjects (49%) were exposed to 4 or 5 days of iv LCM (all at the 15- or 10-minute infusion durations).

There were relatively few treatment-emergent AEs reported during the trial. In the 30-, 15-, and 10-minute infusion duration groups, 43%, 24%, and 35% of subjects, respectively, reported at least 1 treatment-emergent AE during the Treatment Phase. The frequency of AEs did not increase with more days of exposure nor with shorter infusion durations.

Across all infusion duration groups, treatment-emergent AEs were most common in the nervous system disorders system organ class (SOC). There were 33%, 12%, and 15% of subjects reporting at least 1 AE in the nervous system disorders SOC for 30-, 15-, and 10-minute infusion duration groups, respectively. Within the nervous system disorders SOC, headache and dizziness were the most common AEs reported during the Treatment Phase.

All AEs were assessed by the investigator as mild or moderate in intensity. Overall, most subjects (80%) experienced AEs that were assessed by the investigator as not related to LCM. Intravenous LCM was locally well tolerated as evidenced by few injection site reactions.

No subject died during the trial. There was 1 serious adverse event (SAE) reported during the trial. This SAE of bradycardia occurred during a 15-minute infusion on Day 2 of iv LCM but had not occurred the preceding day with 2 identical infusions. The investigator assessed the event as probably related to LCM. The subject was discontinued from this trial and returned to the open-label extension trial. One additional subject withdrew early from the trial, per protocol, due to an AE of ECG QT correct interval prolonged.

Evaluation of ECG data from this trial did not show any tendency for iv LCM to prolong the QT/QTc interval.

No clear differences in mean PR or QRS intervals were noted among the infusion duration

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groups. A small increase in mean PR interval was observed in all infusion duration groups. These increases were noted when comparing to the Baseline of this trial as well as when comparing to the Baseline of the subject's original trial. Two subjects had a PR interval >250ms; however, both events were isolated occurrences that were transient and both subjects were asymptomatic.

Comprehensive laboratory evaluations as well as assessment of heart rate and systolic and diastolic blood pressure showed that there was generally no effect of the infusion durations on these parameters. As noted above, 1 subject had an SAE of bradycardia. The pattern of seizure frequency for the individual subjects did not appear to be different compared to the 8 weeks prior to their entry into this trial.

Overall, this comprehensive evaluation supports the safety of iv LCM as a short-term (up to 5 days) replacement for oral LCM in patients with partial-onset seizures.

Pharmacokinetics results:

The plasma concentrations (C_{max}, C_{trough}) of LCM were proportional to the actual daily dose given and similar across all infusion duration groups. After normalization for body weight and actual dose, LCM plasma concentrations were comparable across LCM doses. The plasma concentration of the main metabolite of LCM, SPM 12809, was similar across all infusion duration groups within the daily dose groups. Across all infusion durations, normalized C_{trough} plasma concentrations following iv LCM administration were comparable to the normalized C_{trough} plasma concentrations after oral LCM administration.

Conclusions:

Overall, this comprehensive evaluation supports the safety of iv LCM at doses of 200mg/day to 600mg/day (100mg to 300mg bid, respectively) at infusion durations of 30 minutes, 15 minutes, and 10 minutes as a short-term (2 to 5 days) replacement for oral LCM in patients with partial-onset seizures. Similar findings were observed at doses of LCM 700mg/day to 800mg/day at an infusion duration of 15 minutes for up to 4 days; however, there was a limited number of exposures at these doses.

Date of the report: 01 Dec 2006