SP0905, 2006-005048-97

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

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day lacosamide in subjects with osteoarthritis of the knee

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Title of trial: A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day lacosamide in subjects with osteoarthritis of the knee

Investigators: This was multicenter trial

Trial site(s): 22 sites screened/enrolled subjects; 21 sites randomized subjects

Publication (reference): None

Studied period (years): **First subject enrolled**: 29 Mar 2007 **Last subject completed**: 20 Nov 2007	**Phase of development**: Phase 2a (proof of concept)

Objectives: The primary objective of the trial was to assess efficacy of LCM 400mg/day compared with placebo in reducing pain in subjects with osteoarthritis of the knee. Secondary objectives were to investigate the effect of LCM on physical functioning and stiffness, patient's global impression of change, sleep interference, and mood as well as the safety and tolerability of LCM.

Methodology: SP905 was a multi-center, randomized, double-blind, placebo-controlled proof-of-concept trial to assess the efficacy and safety of LCM 400mg/day in treating signs and symptoms of osteoarthritis of the knee.

Subjects who developed a pain score ≥40mm on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) pain subscale and a worsening of arthritis condition in their index knee following withdrawal of analgesic and anti inflammatory medications during a 2- to 14- day Baseline Period were eligible for 1:1 randomization into a double blind trial of LCM 400mg/day or placebo (Visit 2).

Randomized subjects had their dose titrated in weekly 100mg increments to the target dose of LCM 400mg/day. One back-titration step to 300mg/day was allowed at the end of the Titration Period in case of intolerable adverse events (AEs). All subjects completing the 4-week Titration Period entered an 8-week Maintenance Period. No dose adjustment was allowed during the Maintenance Period.

At the end of the Maintenance Period, all subjects were scheduled to enter a 1-week Taper Period. Subjects then stopped the intake of trial medication and entered a 2-week

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

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Safety Follow-Up Period. Subjects who discontinued the trial at or prior to Visit 3 did not enter the Taper Period. Subjects had efficacy and safety variables periodically assessed during the trial.

Number of subjects (planned and analyzed):

As the expected treatment effect of LCM in Osteoarthritis of the knee and its variability was not known, this poof of concept trial had an adaptive 3-stage group sequential test design with 2 planned interim analyses.

The planned enrollment for the 3 test stages consisted of 48 subjects in the first stage, 94 subjects in the second stage, and if sample size would not have been adjusted after the second interim analysis 48 subjects in the third stage, to yield a total of 190 subjects (95 subjects per treatment group). It was expected that enrolment of up to 266 subjects would be required in order to randomize 190 subjects. Since the DMC's recommendation following the first interim analysis was to stop recruiting for the trial, analysis of the trial after the first interim analysis was no longer done according to the 3-stage adaptive design. Instead, data were analyzed as a whole, ie, not separating between data of subjects randomized for the first stage and those randomized afterwards.

Of the 193 enrolled subjects, 27 subjects were screen failures and 17 subjects were Baseline failures. In all, 149 subjects were randomized (73 subjects to LCM 400mg/day and 76 subjects to placebo), and comprised the Randomized Set (RS). Of the 149 randomized subjects, 148 (99.3%) subjects received trial medication. All subjects who were randomized, received at least 1 dose of trial medication, and had at least 1 post-Baseline primary efficacy assessment were included in the Full Analysis Set (FAS) (N=145). Subjects from the FAS, who started the Maintenance Period and who did not have a major protocol deviation were included in the Per Protocol Set (PPS) (N=111). Those subjects from the PPS who completed the Maintenance Period were included in the Completer Set (CS) (N=105).

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Diagnosis and main criteria for inclusion:

Main inclusion criteria:

- Subject was male or female and between 40 and 75 years of age.
- Subject had symptomatic osteoarthritis of the knee diagnosed using clinical and radiographic evidence as well as ACR criteria with symptom duration of at least 6 months.
- Subject required therapeutic dose of an NSAID, COX-2 NSAID, and/or paracetamol/acetaminophen for osteoarthritis pain of the index knee and had taken that medication at least 5 days per week for the last 4 weeks prior to the screening visit (Visit 1).

Randomization criteria:

Between 2 and 14 days after Visit 1, after withdrawal of prior analgesic medication for osteoarthritis pain, subjects had to fulfill all of the following criteria to be eligible for randomization:

- Pain score of ≥40mm on the 0 to 100mm WOMAC VAS pain subscale at Visit 2
- Pain score of at least 10mm greater than at Visit 1 on the WOMAC VAS pain subscale
- Investigator assessment of the disease status at least 1 level worse than at Visit 1

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

Subjects took 50mg and 100mg lacosamide tablets. Lacosamide was manufactured by SCHWARZ PHARMA AG, Germany. 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 participation in the trial was 17 weeks. The maximum duration of trial medication administration was 13 weeks.

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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]

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the within-subject change in the WOMAC pain subscale score from Baseline to the end of the Maintenance Period using the Visual Analogue Scale (VAS) version of the questionnaire.

Secondary efficacy variables were the following:

- Within-subject change from Baseline to end of Maintenance Period in WOMAC physical function subscale score
- Within-subject change from Baseline to end of Maintenance Period in WOMAC stiffness subscale score
- Within-subject change from Baseline to end of Maintenance Period in total WOMAC score
- Response at the end of Maintenance Period based on the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) criteria
- Within-subject change from Baseline to end of Maintenance Period in perception of pain interference with subject's sleep

Health Outcomes variables were the following:

- Patient's global impression of change (PGIC) (in osteoarthritis symptoms)
- Amount of rescue medication use during the Maintenance Period
- Within-subject change from Baseline to end of Maintenance Period in the Profile of Mood States (POMS)

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Safety:

The safety and tolerability of LCM were evaluated using the following variables:

- Adverse events 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 examination findings
- Changes in 12-lead electrocardiograms (ECGs)
- Subject withdrawals due to adverse events (AEs)
- Body weight

Statistical methods: The primary efficacy variable was the change in the WOMAC pain subscale score from Baseline (Visit 2) to the end of the Maintenance Period using the visual analogue scale (VAS) version of the WOMAC questionnaire.

The WOMAC pain subscale consisted of 5 questions on pain: when walking on a flat surface, going up or down stairs, at night while in bed, sitting or lying, and standing upright. The subscale score was calculated by simple summation of the assigned values scored on pain items. For convenience, the score was normalized and expressed on a 0 to 100mm scale, ie, the average of the 5 pain items was built. This rule followed the WOMAC osteoarthritis index user guide VII.

The comparison of LCM to placebo will be performed by an analysis of covariance (ANCOVA) model with terms for treatment group and pooled sites using the Baseline WOMAC pain subscale score as a covariate.

Because enrollment into the trial was stopped based on the results of the first interim analysis, results of statistical analyses presented in this report should be interpreted in a purely descriptive manner. Data of all randomized subjects were analyzed as a whole.

Summary and conclusions:

Efficacy:

The primary variable for this proof-of-concept trial was the reduction in WOMAC pain subscale score from Baseline to End of Maintenance Period. Based on the primary analysis, the results of this trial show no notable efficacy in the LCM treatment group over placebo from Baseline to End of Maintenance Period (Visit 6/early termination [ET]).

In the ANCOVA analysis of the primary variable for the FAS, the LSMeans in change from

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Baseline in WOMAC pain subscale score were similar between placebo and LCM 400mg/day treatment groups. The LSMean reductions in WOMAC pain subscale scores (-27.94 for the placebo group and -25.58 for the LCM treatment group) represented less improvement in WOMAC pain for LCM 400mg/day than for placebo at Visit 6/ET.

The results were similar using the alternative imputation methods for missing data and rescue medication use within the last 24 hours prior to visit (imputation method 2 and imputation method 3) to the imputation method 1 results, and for the PPS and CS populations. In all populations (FAS, PPS, CS), the Screening value for the primary variable was higher in the placebo group than in the LCM treatment group.

Additional analyses of the primary variable, using additional explanatory variables, gave similar results.

Applying imputation 1 on subjects with rescue medication intake ≥3/7 days prior to Visit 6/ET to correct for use of paracetamol as co-medication (rather than rescue medication), suggested an affect of paracetamol co-medication use such that change from Baseline in WOMAC pain subscale score was higher in placebo. Correcting for co-medication use shows changes from Baseline in WOMAC pain for the 2 treatment groups to be equivalent.

Use of non-parametric analysis, as recommended by the WOMAC manual also indicated no notable improvement in WOMAC pain subscale scores in the LCM treatment group over placebo.

By visit analysis of changes in WOMAC pain subscale scores showed treatment difference (LSMean) in change from Baseline in WOMAC pain subscale score was notably greater at Visit 4 (5.11) than at Visit 5 (0.55), or at Visit 6 (-2.36).

Overall, there was no notable improvement in percent reduction in WOMAC pain subscale scores for the LCM treatment group vs placebo. However, the proportions of subjects achieving high percent reductions WOMAC pain subscale (≥50% or ≥60%) were slightly higher in the LCM treatment group (45.1% and 36.6%, respectively) than in with the placebo group (40.5% and 33.8%, respectively).

Analysis of other secondary efficacy variables were generally consistent with the results of the primary variable. No notable improvements over placebo were observed for by visit observation of WOMAC stiffness subscale, WOMAC physical function subscale, WOMAC total, and modified OMERACT-OARSI scores.

As for the primary variable, Screening values and Baseline values of secondary variables

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were higher in the placebo group than in the LCM group.

Health Outcomes:

In general, results of Health Outcomes analyses suggested some improvements in the LCM treatment group compared with the placebo group.

Comparison of PGIC results showed notably more subjects reported a strong impression of improvement in osteoarthritis (much + very much improved) in the LCM treatment group (33.8%) than in the placebo group (22.2%). Similar proportions of subjects from each treatment group reported impression of worsening in osteoarthritis at Visit 6.

On average, rescue medication was used less frequently and at a lower dose in the LCM treatment group than in the placebo group. Median rescue medication use during the Maintenance Period was reduced by approximately one third in the LCM group vs placebo.

Comparison of POMS results indicated a lesser improvement on average in the LCM treatment group, than in the placebo group.

Safety results:

Overall, 72 subjects with osteoarthritis received at least 1 dose of LCM. The mean total duration of exposure was 75.5 days, with a maximum exposure of 89 days. Of the 72 LCM treated subjects, a total of 38 (52.8%) experienced at least 1 treatment-emergent adverse event (TEAE), compared with 40 (52.6%) of the 76 subjects in the placebo group.

In all, 6 (4.1%) subjects experienced treatment-emergent SAEs (2 subjects in the placebo group, 4 subjects in the LCM treatment group). Of these, only 1 subject experienced more than 1 SAE. No SAE was experienced by more than 1 subject.

In total, 13 (8.8%) subjects experienced AEs leading to discontinuation. By system organ class (SOC), AEs leading to discontinuation were most common in ear and labyrinth disorders. No subject died during the trial.

In the LCM 400mg/day treatment group, the most common TEAEs were vertigo (11.1% in LCM 400mg/day vs 1.3% in placebo), fatigue (5.6% in LCM 400mg/day vs 2.6% in placebo) and arthralgia (5.6% in LCM 400mg/day vs 5.3% in placebo). With the exception of vertigo and fatigue, the incidence of TEAEs was similar between the LCM 400mg/day and placebo groups.

Treatment-emergent AEs were most common in the SOCs musculoskeletal and connective

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tissue disorders (14.5% [11/76] of placebo subjects, 9.7% [7/72] of LCM treated subjects) and gastrointestinal disorders (11.8% [9/76] of placebo subjects, 12.5% [9/72] of LCM treated subjects).

For most subjects reporting TEAEs, these were of mild or moderate maximum intensity (93.6% of subjects) and were considered by the investigator as not related to trial medication (72.5% of subjects for placebo vs 63.2% for LCM 400mg/day).

Overall, the incidence of TEAEs in the SOC cardiac disorders was low and was similar between groups (3.9% in placebo vs 5.6% in LCM treatment groups, respectively).

Lacosamide had no effect upon heart rate or QRS duration and did not prolong QT/QTc interval. There was a small mean increase in PR interval observed in the LCM treatment group as compared with placebo. The mean maximum increase (anytime in the study) for PR interval was 6.4ms for placebo and 16.2ms for LCM.

Comprehensive laboratory evaluation did not reveal any issues of clinical concern. For liver function tests in particular, there were no reports of markedly abnormal alanine aminotransferase, aspartate aminotransferase or bilirubin.

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

Conclusions:

- Lacosamide was no more effective than placebo in relieving the signs and symptoms of osteoarthritis in this proof-of-concept trial.
- The primary result was confirmed by a variety of secondary endpoints.
- The safety profile of LCM indicated good tolerability of LCM in the osteoarthritis population. No new safety concerns were identified.

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