Approved by UCB 27-Oct-2008

Clinical Study Summary

CT Registry ID#: NCT00220337
Study No.: SP830

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Vimpat™ (proposed)	Lacosamide	Diabetic neuropathic pain

Name of Sponsor/Company: UCB Pharma SA

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

Investigator(s) (number only): 60 (3 sites had 2 investigators over the course of the trial)

Study Center(s) (number only): 57

Length of Study:
Date first patient enrolled: 21 Dec 2004
Date last patient completed: 31 Oct 2007

Phase of Development: 3

Abstract:
SP830 was a long-term, open-label trial in which subjects with painful diabetic neuropathy received lacosamide (LCM) treatment at their optimal dose. The trial was conducted in Europe and South Africa. 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.

The primary objective of the trial was to assess the safety and tolerability of long-term LCM administration in subjects with painful diabetic neuropathy. Other objectives were to investigate the following: effect of long-term use of LCM on subjects' perception of pain, effect of LCM on the interference of pain on subjects' sleep and activity, effect of long-term use of LCM on quality of life, work productivity and activity, and sleepiness. Additional variables were the effect of add-on therapy on the safety, tolerability, and efficacy of LCM; 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; and correlation of plasma concentrations of LCM with cardiac safety variables.

A total of 505 subjects with painful diabetic neuropathy were enrolled; 371 subjects were treated with LCM, and 192 subjects completed the trial, ie, they did not discontinue before the sponsor-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. The median total exposure to trial medication per subject was 832.0 days (ie, 2.3 years) and the maximal time of exposure was 979.0 days (ie, 2.7 years).

Treatment-emergent adverse events (TEAEs) were experienced by 304 (81.9%) subjects overall and were most common in the nervous system disorders system organ class (SOC), with 49.3% of subjects reporting at least 1 AE in this SOC. Most TEAEs resolved while on treatment or were reversible by dose adjustments or drug withdrawal. Sixty-eight (18.3%) subjects discontinued the trial prematurely due to TEAEs. The overall incidence of treatment-emergent serious adverse events (SAEs) was 22.4% (83/371 subjects). Overall, the evaluation of the long-term safety profile of LCM showed no important long-term safety issues.

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At Baseline, the average Likert pain score for all subjects combined was 6.28. The overall average reduction in Likert pain score was 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.

Number of Patients:	
Planned, N:	**360**
Enrolled, N:	**505**
Treated, n(%):	**371 (100.0)**
Completed, n(%):	**192 (51.8)**
Number of Patients Withdrawn, n(%):	**179 (48.2)**
Withdrawn due to Adverse Events, n(%):	**70 (18.9)**
Withdrawn for Other Reasons, n(%):	**109 (29.4)**
Demography:	
Gender (Females/Males):	**181/190**
Age (years), mean(SD):	**58.6 (9.99)**
Race, n(%):	
White	**362 (97.6)**
Other	**9 (2.4)**

Safety Outcomes:
- Summary of treatment emergent adverse events, deaths, other serious adverse events and certain other significant adverse events:

Treatment Emergent AEs (TEAEs):

	Total N=371
Patients with at least one TEAE	304 (81.9)
TEAEs with incidence ≥5% overall (by Primary System Organ Class) [n considered drug-related by the Investigator]	
Ear and labyrinth disorders	
Vertigo	45 (12.1) [35]
Gastrointestinal disorders	
Nausea	49 (13.2) [43]
Vomiting	21 (5.7) [15]
General disorders and administration site conditions	
Fatigue	31 (8.4) [27]
Edema peripheral	20 (5.4) [1]
Infections and infestations	
Nasopharyngitis	43 (11.6) [1]
Influenza	21 (5.7) [0]
Musculoskeletal and connective tissue disorders	
Back pain	26 (7.0) [0]
Nervous system disorders	
Dizziness	75 (20.2) [66]
Headache	44 (1.9) [22]
Somnolence	34 (9.2) [33]
Tremor	24 (6.5) [20]
Vascular disorders	
Hypertension	27 (7.3) [4]

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Death, SAEs, and Other SAEs:	
Deaths	7 (1.9)
Patients with SAEs	83 (22.4)
Incidence of SAEs (by Primary System Organ Class)	
Blood and lymphatic system disorders	1 (0.3)
Cardiac disorders	16 (4.3)
Ear and labyrinth disorders	2 (0.5)
Endocrine disorders	1 (0.3)
Eye disorders	10 (2.7)
Gastrointestinal disorders	6 (1.6)
General disorders and administration site conditions	4 (1.1)
Hepatobiliary disorders	2 (0.5)
Infections and infestations	10 (2.7)
Injury, poisoning and procedural complications	8 (2.2)
Investigations	2 (0.5)
Metabolism and nutrition disorders	7 (1.9)
Musculoskeletal and connective tissue disorders	7 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.2)
Nervous system disorders	12 (3.2)
Psychiatric disorders	2 (0.5)
Renal and urinary disorders	1 (0.3)
Reproductive system and breast disorders	1 (0.3)
Surgical and medical procedures	2 (0.5)
Vascular disorders	10 (2.7)

Primary & Secondary Outcomes:

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. Most AEs were transient or manageable by dose reduction, drug interruption, or drug withdrawal. Overall, the evaluation of the long-term safety profile of LCM showed no important long-term safety issues.

The overall incidence of treatment-emergent SAEs was 22.4% (83/371 subjects). Sixty-eight (18.3%) subjects discontinued the trial prematurely due to TEAEs, including 7 subjects who discontinued due to adverse events 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.

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.

At Baseline, the average Likert pain score for all subjects combined was 6.28. The overall average reduction in Likert pain score was 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

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period of the trial.
Publication Reference(s) based on the study: None
Date of report: 22-Oct-2008