Approved by UCB 10-Jun-2008

Clinical Study Summary (CSS) Template

CT Registry ID#: *NCT00350103*
Study No.: SP874

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

Name of Sponsor/Company: UCB

Title of Study:
A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day lacosamide in subjects with painful distal diabetic neuropathy using two different titration schemes

Investigator(s) (number only): 88

Study Center(s) (number only): 78 (74 sites randomized at least 1 subject).

Length of Study:
Date first patient enrolled: 30 Jun 2006
Date last patient completed: 29 Jun 2007

Phase of Development: 3b

Abstract:
SP874 was a multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 200mg lacosamide (LCM) twice daily (400mg/day) in subjects with diabetic neuropathic pain using two different titration schemes, specifically a fast titration scheme (FT) and a standard titration scheme (ST).

The primary objective of the trial was to investigate the efficacy of 400mg/day LCM compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Two titration schemes were used; the first was a standard titration scheme such that the target dose of 400mg/day LCM was attained at Day 22, the second was a more rapid titration scheme and the target dose of 400mg/day was attained at Day 8. Each titration scheme was compared with placebo. Secondary objectives included investigation of the onset of action under treatment of LCM, the effect of LCM on the interference of pain with sleep and activity, and to further investigate the safety of LCM.

Of 779 screened subjects, 551 were randomized and 549 were treated. Of the treated subjects, 443 (80.4%) completed the trial. Based on the prespecified primary analysis, the results of this study shows that LCM 400mg/day, demonstrated efficacy when administered using the standard titration regimen. In additional analyses of the primary variable, the standard LCM titration group gave consistently greater improvement in average daily pain than placebo.

Of the 108 (19.6%) subjects who discontinued early, 58 (10.5%) did so due to adverse events (AEs) and 13 (2.4%) due to “Other Reasons”. Among all subjects, TEAEs were most common in the nervous system disorders SOC, with 23.8% (88/370), 10.1 % (18/179), of subjects in the LCM 400mg/day and placebo groups, respectively, reporting at least 1 AE in this SOC. Overall, in the lacosamide treatment groups combined, dizziness (7.8%), nausea (7.6%), and headache (6.2%) were the most frequently reported treatment-emergent AEs. No cardiac-related TEAEs occured in ≥5% of subjects in any treatment group.

Comprehensive laboratory evaluation did not reveal any issues of clinical concern. Vital signs and physical examinations showed no changes of clinical concern. Across all treatment groups, the mean change from Baseline data did not show a QT/QTc prolonging effect of lacosamide or an effect on heart rate.

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Number of Patients:	(If applicable)
Planned, N:	**765**
Enrolled, N:	**779**
Randomized, n(%)	**551 (100.0)**
Completed, n(%):	**447 (81.1)**
Number of Patients Withdrawn, n(%):	**108 (19.6)**
Withdrawn due to Adverse Events, n(%):	**58 (10.5)**
Withdrawn for Other Reasons, n(%):	**50 (9.1)**
Demography:	(If applicable)
Gender (Females/Males):	**272/279**
Age (years), mean(SD):	**57.3 (9.68)**
Race, n(%):	
White	**550 (99.8)**
Black	**1 (0.2)**

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

Treatment Emergent AEs (TEAE):
Patients with at least one TEAE, n(%): **282 (51.4)**

TEAEs with incidence ≥5% in any treatment group (by Primary System Organ Class)	**Placebo N=179**	**LCM 400mg/day FT N=189**	**LCM 400mg/day ST N=181**
	n(%)		
Ear and labyrinth disorders			
Vertigo	2 (1.1)	11 (5.8)	10 (5.5)
Gastrointestinal disorders			
Nausea	4 (2.2)	17 (9.0)	11 (6.1)
Infections and infestations			
Nasopharyngitis	11 (6.1)	8 (4.2)	12 (6.6)
Nervous system disorders			
Dizziness	3 (1.7)	16 (8.5)	13 (7.2)
Headache	6 (3.4)	10 (5.3)	13 (7.2)
Somnolence	1 (0.6)	12 (6.3)	5 (2.8)

Death, SAEs, and Other SAEs:
Death, n (%): **0**

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Patients with SAEs, n(%):	**42 (7.7%)**		
Incidence of Serious TEAEs *(by Primary System Organ Class)*	**Placebo** **N=179**	**LCM 400mg/day FT** **N=189**	**LCM 400mg/day ST** **N=181**
	n(%)		
Any	14 (7.8)c	12 (6.3)	16 (8.8)
Cardiac disorders	1 (0.6)	1 (0.5)	1 (0.6)
Eye disorders	1 (0.6)	0	0
Gastrointestinal disorders	0	0	1 (0.6)
General disorders and administration site conditions	1 (0.6)	0	1 (0.6)
Hepatobiliary disorders	0	1 (0.5)	0
Infection and infestations	2 (1.1)	1 (0.5)	2 (1.1)
Injury, poisoning and procedural complications	0	1 (0.5)	0
Investigations	1 (0.6)	0	0
Metabolism and nutrition disorders	2 (1.1)	2 (1.1)	0
Musculoskeletal and connective tissue disorders	1 (0.6)	2 (1.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.6)
Nervous system disorders	1 (0.6)	1 (0.5)	6 (3.3)
Renal and urinary disorders	1 (0.6)	0	2 (1.1)
Reproductive system and breast disorders	0	0	2 (1.1)
Surgical and medical procedures	0	1 (0.5)	0
Vascular disorders	2 (1.1)	3 (1.6)	1 (0.6)

Primary & Secondary Outcomes:
Based on the prespecified primary analysis, the results of this study shows that LCM 400mg/day, demonstrated efficacy when administered using the standard titration regimen. The primary efficacy variable was the change in average daily pain score from Baseline to the last 4 weeks of the Maintenance Phase using the 11-point Likert scale (0 to 10). In the FAS, there were 1.90-, and 2.34-point reductions in the LSMean Likert pain scores from Baseline to the last 4 weeks of the trial for the placebo and LCM 400mg/day ST groups, respectively. The difference in LSMean pain score (-0.45) between the LCM 400mg/day ST group and placebo, was statistically significant (p=0.0410). The change in LSMean pain score was higher in the LCM 400mg/day FT group than in placebo, though the difference was not statistically significant.

Analysis of the secondary variables also showed a strong placebo result for many of the variables, though the results indicated a clearly greater improvement in the LCM 400mg/day ST treatment group than in placebo. Furthermore, median time to sustainable pain relief in the FAS was markedly shorter for the LCM 400mg/day ST and FT groups (10.0 days for each) than for placebo (31.0 days). The mean change in average daily pain score was greater in the LCM treatment groups at every visit, from Visit 3 to the end of the trial and the mean within-subject change from Baseline in average daily pain interference with sleep (and also with activity) was consistently better in the LCM treatment groups than the placebo group from as early as Visit 3 through to the end of the trial.

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The ST LCM group showed significant improvement in pain over placebo and the FT group was improved but not significant compared to placebo. Both groups showed the time to onset of pain relief was notably better than placebo. Both LCM titration schemes showed good safety profiles in this trial. The overall incidence of AEs was low and similar between the LCM 400mg/day ST group and placebo, and while slightly higher in the LCM 400mg/day FT group, remained similar to that seen in previous double-blind trials of LCM

Publication Reference(s) based on the study:
NA

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