Approved by UCB 10-Jun-2008

Clinical Study Summary (CSS) Template

CT Registry ID#: NCT00235469
Study No.: SP742

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

Based on Clinical Study Report document reference code:

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Vimpat™	Lacosamide	Painful diabetic neuropathy

Name of Sponsor/Company: UCB Inc.

Title of Study:
A multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to assess the efficacy and safety of 200, 400, and 600 mg/day SPM 927 in subjects with painful distal diabetic neuropathy.

Investigator(s) (number only): 53

Study Center(s) (number only): 53

Length of Study:
Date first patient enrolled: 12 April 2004
Date last patient completed: 6 June 2005

Phase of Development: 2b

Abstract:

The primary objective of the 18-week multi-center, randomized, double-blind, placebo-controlled, parallel-group trial was to investigate the efficacy of 200, 400, and 600 mg/day lacosamide compared with placebo in reducing pain in subjects with painful distal diabetic neuropathy. Secondary objectives were to investigate the effect of lacosamide on subjects' perception of pain, sleep, activity, and quality of life, as well as to investigate the pharmacokinetics and safety of lacosamide. Subjects (male or female, ≥18 years old) with symptomatic painful distal diabetic neuropathy ranging in duration from 6 months to 5 years with an average pain intensity ≥4 on an 11-point Likert scale during the 7 day period before start of treatment and type I or II diabetes mellitus (HbA1c levels <12% for the previous 3 months). The trial began with a 2-week run-in period with the second week serving to establish baseline assessment values. Eligible subjects were then randomized (1:1:1:1) to receive placebo, or lacosamide 200, 400, or 600 mg/day for a 6-week forced titration period beginning with a dose of 100 mg/day (all doses were administered in 2 equal daily doses) with weekly increments until target dose was attained. Thereafter, patients entered a 12-week maintenance period during which no dose adjustment was permitted. At the end of the maintenance phase, subjects were offered the option of entering the open-label follow-on trial (NCT00235443; SP745). Subjects who elected not to enroll in the open-label study tapered off their dose of trial medication over 1 week and entered a 2-week safety follow-up period.

An 11-point Likert scale (0-10) used to assess overall pain was provided to subjects as part of their daily diary to be completed twice daily (morning and evening). Each subject rated the pain intensity over the preceding 12 hours from 0 (no pain) to 10 (worst pain ever experienced). The daily pain score was defined as the average score of those collected in the morning and the evening. Within-patient change in average daily pain score from baseline to the average over the last 4 weeks of maintenance phase served as the primary efficacy measure. Secondary measures of efficacy included changes in Likert pain scores over the treatment period, the proportion of patients showing ≥30% or a 2-point reduction in Likert pain score, impact of pain on sleep and daily activity, and Patient's Global Impression of Change (PGIC) from baseline. Safety evaluation considered adverse event reporting and discontinuation due to adverse events, clinically relevant changes in hematology, blood chemistry, urinalysis, vital measurements, physical and neurological examinations, and 12-lead ECG

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readings.

Number of Patients:	
Planned, N:	**360**
Enrolled, N:	**496**

Randomized, N	**Placebo**	**Lacosamide**			**Total**
		200 mg/day	**400 mg/day**	**600 mg/day**	
	93	93	91	93	**370**
Completed, n (%):	67 (72.0)	69 (74.2)	56 (61.5)	42 (45.2)	**234 (63.2)**
Number of Patients Withdrawn, n (%):	26 (28.0)	24 (25.8)	35 (38.5)	51 (54.8)	**136 (36.8)**
Withdrawn due to Adverse Events, n (%):	8 (8.6)	8 (8.3)	21 (23.1)	37 (39.8)	**74 (20.0)**
Withdrawn for Other Reasons, n (%):	18 (19.4)	16 (17.2)	14 (15.4)	14 (15.1)	**62 (16.8)**

Demography:	
Gender (Females/Males):	**168/202**
Age (years), mean(SD):	**58.2 (9.6)**
Race, n (%):	
White	**300 (81.1)**
Black	**27 (7.3)**
Asian	**4 (1.1)**
Other	**39 (10.5)**

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

Treatment Emergent AEs (TEAE) (if applicable):

Patients with at least one TEAE, n (%):	**Placebo**	**Lacosamide**			**Total**
		200 mg/day	**400 mg/day**	**600 mg/day**	
	73 (78.5)	70 (75.3)	71 (78.0)	83 (89.2)	297 (80.3)

Patients with TEAEs (by Primary System Organ Class) n(%) [n considered drug-related by the Investigator]	**Placebo**	**Lacosamide**		
		200 mg/day	**400 mg/day**	**600 mg/day**
Blood and lymphatic system disorders	3 (3.2) [2]	1 (1.1) [0]	1 (1.1) [0]	3 (3.2) [2]
Cardiac disorders	8 (8.6) [2]	2 (2.2) [0]	7 (7.7) [3]	4 (4.3) [3]
Ear and labyrinth disorders	2 (2.2) [0]	3 (3.2) [1]	4 (4.4) [1]	7 (7.5) [7]
Vertigo	1 (1.1) [0]	1 (1.1) [1]	2 (2.2) [0]	6 (6.5) [6]
Eye disorders	2 (2.2) [1]	4 (4.3) [0]	0	10 (10.8) [5]
Diplopia	0	0	0	6 (6.5) [4]
Gastrointestinal disorders	19 (20.4) [7]	13 (14.0) [7]	18 (19.8) [9]	30 (32.3) [20]
Nausea	8 (8.6) [3]	8 (8.6) [3]	7 (7.7) [6]	14 (15.1) [11]
Diarrhea	4 (4.3) [2]	0	5 (5.5) [1]	3 (3.2) [1]
General disorders and administration site conditions	12 (12.9) [7]	10 (10.8) [4]	15 (16.5) [7]	21 (22.6) [14]
Fatigue	3 (3.2) [3]	3 (3.2) [2]	6 (6.6) [5]	9 (9.7) [8]
Asthenia	2 (2.2) [2]	1 (1.1) [1]	3 (3.3) [1]	5 (5.4) [3]

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Infections and Infestations	29 (31.2) [0]	28 (30.1) [0]	25 (27.5) [0]	19 (20.4) [0]
Nasopharyngitis	7 (7.5) [0]	9 (9.7) [0]	3 (3.3) [0]	3 (3.2) [0]
Upper respiratory tract infection	5 (5.4) [0	4 (4.3) [0]	5 (5.5) [0]	6 (6.5) [0]
Influenza	3 (3.2) [0]	1 (1.1) [0]	5 (5.5) [0]	0
Injury, poisoning and procedural complications	8 (8.6) [0]	10 (10.8) [0]	8 (8.8) [0]	10 (10.8) [1]
Musculoskeletal and connective tissue disorders	15 (16.1) [2]	2 (2.2) [0]	12 (13.2) [1]	15 (16.1) [4]
Back pain	2 (2.2) [0]	1 (1.1) [0]	5 (5.5) [0]	2 (2.2) [0]
Nervous system disorders	14 (15.1) [7]	20 (21.5) [10]	24 (26.4) [16]	45 (48.4) [39]
Dizziness	5 (5.4) [2]	9 (9.7) [5]	12 (13.2) [10]	27 (29.0) [24]
Headache	6 (6.5) [2]	6 (6.5) [3]	7 (7.7) [2]	9 (9.7) [5]
Tremor	0	1 (1.1) [1]	5 (5.5) [4]	9 (9.7) [8]
Balance disorder	0	0	1 (1.1) [1]	6 (6.5) [6]
Memory impairment	0	0	0	5 (5.4) [3]
Psychiatric disorders	4 (4.3) [2]	3 (3.2) [1]	4 (4.4) [1]	5 (5.4) [5]
Respiratory, thoracic and mediastinal disorders	4 (4.3) [1]	8 (8.6) [0]	9 (9.9) [1]	9 (9.7) [0]
Skin and subcutaneous tissue disorders	6 (6.5) [2]	12 (12.9) [3]	8 (8.8) [4]	11 (11.8) [7]

Death, SAEs, and Other SAEs:

Death, n (%): **1 (1.1)**
Patients with SAEs, n (%): **27 (7.3)**
Patients with SAEs (by Primary System Organ Class) *n(%) [n considered drug-related by the Investigator]*

	Placebo	**Lacosamide**		
		200 mg/day	**400 mg/day**	**600 mg/day**
Any System Organ Class	6 (6.5)	3 (3.2)	9 (9.9)	9 (9.7)
Blood and lymphatic system disorders	0	0	0	2 (2.2) [1]
Cardiac disorders	4 (4.3) [2]	0	3 (3.3) [0]	1 (1.1) [1]
Gastrointestinal disorders	0	1 (1.1) [0]	1 (1.1) [0]	0
General disorders and administration site conditions	1 (1.1) [1]	0	1 (1.1) [0]	2 (2.2) [1]
Hepatobiliary disorders	0	0	0	1 (1.1) [0]
Infections and Infestations	0	1 (1.1) [0]	3 (3.3) [0]	1 (1.1) [0]
Investigations	0	1 (1.1) [1]	0	1 (1.1) [1]
Musculoskeletal and connective tissue disorders	0	0	1 (1.1) [0]	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (1.1) [0]
Nervous system disorders	1 (1.1) [0]	0	0	2 (2.2) [2]

Primary & Secondary Outcomes:

For the primary efficacy variable of within-subject change in the average daily pain score from the baseline week to the last 4 weeks of the Maintenance Phase, the difference in LSMean pain score over placebo was 0.39 for the lacosamide 200 mg/day dose, 0.74 for the 400 mg/day, and 0.42 for the 600 mg/day dose. The primary efficacy variable was statistically significant for the comparison of the 400 mg/day lacosamide versus

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placebo (p=0.01). Reductions in Likert pain score with lacosamide 400 mg/day were higher than with placebo beginning in week 5 of the Titration Phase (p<0.04) through end of treatment. Likert pain score reductions on lacosamide 600 mg/day were better than with placebo from the sixth week of titration period (p<0.02) until week 15 of the maintenance phase. PGIC assessment showed preference for both lacosamide 400 and 600 mg/day doses compared with placebo.
Publication Reference(s) based on the study: **None**
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