Approved by UCB 13-Nov-2008

Clinical Study Summary (CSS) Template

CT Registry ID#: *NCT00220415*
Study No.: SP755

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®	Lacosamide (SPM 927)	Epilepsy; Partial-onset seizures with or without secondary generalization

Name of Sponsor/Company: UCB

Title of Study:
A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization

Investigator(s) (number only): Multicenter trial (75)

Study Center(s) (number only): 75

Length of Study:
Date first patient enrolled: 07-Jun-2004
Date last patient completed: 24-Jan-2006

Phase of Development: 3

Abstract:

This trial was a Phase 3, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of lacosamide (LCM) as adjunctive therapy in subjects with partial-onset seizures with or without secondary generalization.

The primary objective of this trial was to evaluate the efficacy of LCM administered concomitantly with 1, 2, or 3 antiepileptic drugs (AEDs) in subjects with or without additional vagus nerve stimulation (VNS) who currently have uncontrolled partial-onset seizures with or without secondary generalization. The secondary objectives were to evaluate the safety of LCM, the dose-response relationship of LCM with regards to efficacy and safety, and to examine steady-state plasma concentrations of LCM and concomitant AEDs during oral administration of LCM.

The subjects were enrolled into an 8-week Baseline Phase. At the end of the Baseline Phase, subjects were randomized (1:1:1) in a double-blind fashion to 1 of the 3 treatment arms: placebo or LCM (200mg/day or 400mg/day). The duration of the trial was 26 weeks including an 8-week Baseline Phase and 18-week Treatment Phase. The Treatment Phase was comprised of the following: 4 weeks forced titration up to the respective randomized dose (a 1-step back-titration of 100mg/day LCM or placebo was allowed at the end of the Titration Phase), 12 weeks maintenance, and 2 weeks transition or taper.

Of the 584 subjects screened, 546 were enrolled and 485 were randomized and treated. Of the 485 treated subjects, 399 (82.3%) completed the trial. Based on the pre-specified primary analysis, LCM showed efficacy at 200mg/day and 400mg/day in this trial when added to approved concomitant AEDs in subjects experiencing difficult to control partial-onset seizures with or without secondary generalization.

Of the 485 treated subjects, 86 (17.7%) discontinued the trial prematurely and 44 (9.1%) discontinued due to adverse events (AEs). Notable events that appeared to be dose-related included dizziness, nausea, and vomiting. Most events were assessed by the investigator as mild or moderate in intensity. A total of 28 (8.7%) subjects experienced serious adverse events (SAEs).

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Number of Patients:

Planned, N:	**577**
Enrolled, N:	**546**
Randomized and treated, N (%):	**485 (100.0)**
Completed, n(%):	**399 (82.3)**
Number of Patients Withdrawn, n(%):	**86 (17.7)**
Withdrawn due to Adverse Events, n(%):	**44 (9.1)**
Withdrawn for Other Reasons, n(%):	**6 (1.2%)**

Demography:

Gender (Females/Males):	**235/250**
Age (years), mean(SD):	**37.8 (11.88)**
Race, n(%):	
White	**481 (99.2)**
Black	**1 (0.2)**
Asian	**3 (0.6)**
Other	**0**

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

Treatment Emergent AEs (TEAE):

Number of Patients with TEAEs During the Treatment Phase (by Primary System Organ Class)	**Placebo N=163**	**LCM 200mg/day N=163**	**LCM 400mg/day N=159**	**LCM Total N=322**
	n(%) [n considered drug-related by the Investigator]			
Any System Organ Class (patients who experienced at least one TEAE)	87 (53.4) [49]	104 (63.8) [60]	109 (68.6) [76]	213 (66.1) [136]
Blood and lymphatic system disorders	7 (4.3) [3]	8 (4.9) [4]	3 (1.9) [2]	11 (3.4) [6]
Cardiac disorders	1 (0.6) [1]	2 (1.2) [1]	5 (3.1) [3]	7 (2.2) [4]
Ear and labyrinth disorders	5 (3.1) [3]	12 (7.4) [9]	14 (8.8) [11]	26 (8.1) [20]
Eye disorders	7 (4.3) [5]	20 (12.3) [16]	23 (14.5) [21]	43 (13.4) [37]
Gastrointestinal disorders	15 (9.2) [8]	26 (16.0) [18]	26 (16.4) [13]	52 (16.1) [31]
General disorders and administration site conditions	12 (7.4) [8]	18 (11.0) [10]	22 (13.8) [18]	40 (12.4) [28]
Immune system disorders	0	0	1 (0.6) [0]	1 (0.3) [0]
Infections and infestations	23 (14.1) [0]	26 (16.0) [0]	26 (16.4) [1]	52 (16.1) [1]
Injury, poisoning and procedural complications	7 (4.3) [0]	9 (5.5) [0]	10 (6.3) [1]	19 (5.9) [1]
Investigations	4 (2.5) [1]	16 (9.8) [8]	9 (5.7) [1]	25 (7.8) [9]
Metabolism and nutrition disorders	5 (3.1) [3]	9 (5.5) [2]	9 (5.7) [3]	18 (5.6) [5]
Musculoskeletal and connective tissue disorders	11 (6.7) [4]	8 (4.9) [0]	8 (5.0) [0]	16 (5.0) [0]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6) [1]	2 (1.2) [0]	1 (0.6) [0]	3 (0.9) [0]
Nervous system disorders	41 (25.2) [27]	51 (31.3) [37]	61 (38.4) [53]	112 (34.8) [90]
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.6) [0]	1 (0.3) [0]
Psychiatric disorders	10 (6.1) [8]	10 (6.1) [4]	11 (6.9) [7]	21 (6.5) [11]

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Renal and urinary disorders	3 (1.8) [0]	2 (1.2) [0]	1 (0.6) [0]	3 (0.9) [0]
Reproductive system and breast disorders	2 (1.2) [0]	1 (0.6) [0]	2 (1.3) [0]	3 (0.9) [0]
Respiratory, thoracic and mediastinal disorders	7 (4.3) [1]	7 (4.3) [0]	9 (5.7) [1]	16 (5.0) [1]
Skin and subcutaneous tissue disorders	8 (4.9) [5]	8 (4.9) [4]	11 (6.9) [5]	19 (5.9) [9]
Surgical and medical procedures	2 (1.2) [0]	0	1 (0.6) [0]	1 (0.3) [0]
Vascular disorders	3 (1.8) [1]	4 (2.5) [1]	2 (1.3) [0]	6 (1.9) [1]

Death, SAEs, and Other SAEs :
Death, n (%): **0**
Patients with SAEs, n(%): **28 (8.7)**

Number of Patients with SAEs During the Treatment Phase (by Primary System Organ Class)	**Placebo N=163**	**LCM 200mg/day N=163**	**LCM 400mg/day N=159**	**LCM Total N=322**
	n(%)			
Blood and lymphatic system disorders	0	0	1 (0.6)	1 (0.3)
Cardiac disorders	0	0	1 (0.6)	1 (0.3)
Ear and labyrinth disorders	0	0	2 (1.3)	2 (0.6)
General disorders and administration site conditions	0	0	2 (1.3)	2 (0.6)
Infections and infestations	0	0	1 (0.6)	1 (0.3)
Injury, poisoning and procedural complications	0	1 (0.6)	0	1 (0.3)
Investigations	0	2 (1.2)	1 (0.6)	3 (0.9)
Metabolism and nutrition disorders	1 (0.6)	1 (0.6)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	0	1 (0.6)	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (1.2)	0	2 (0.6)
Nervous system disorders	4 (2.5)	4 (2.5)	3 (1.9)	7 (2.2)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.6)	1 (0.3)
Psychiatric disorders	0	1 (0.6)	3 (1.9)	4 (1.2)
Renal and urinary disorders	0	0	1 (0.6)	1 (0.3)
Reproductive system and breast disorders	1 (0.6)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)	0	1 (0.3)
Surgical and medical procedures	1 (0.6)	0	0	0
Vascular disorders	0	0	1 (0.6)	1 (0.3)

Primary & Secondary Efficacy Outcomes:

The LCM 200mg/day and 400mg/day treatment groups were statistically superior to the placebo group in the reduction of seizure frequency per 28 days for the Maintenance Phase (200mg/day p-value=0.0223; 400mg/day p-value=0.0325). The percent reduction in seizure frequency over placebo was 14.4% (95% CI: 2.2, 25.1) and 15.0% (95% CI: 1.4, 26.8) for LCM 200mg/day and 400mg/day, respectively. Similar positive findings were observed in the statistical analysis of responders, which is defined as subjects with at least 50% seizure reduction for the Maintenance Phase. The 50% responder rates for placebo, 200mg/day, and 400mg/day were 25.8%, 35.0% and 40.5%, respectively.

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Conclusion
This adequate and well-controlled trial supports that LCM 200mg/day and LCM 400mg/day are each effective and generally well tolerated treatments for partial-onset seizures when added to 1 to 3 approved concomitant AEDs in patients with epilepsy.

Publication Reference(s) based on the study:
None

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