Approved by UCB 13-Nov-2008

Clinical Study Summary (CSS) Template

CT Registry ID#: *NCT00136019*
Study No.: SP754

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 (400 and 600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization

Investigator(s) (number only): Multicenter trial (72)

Study Center(s) (number only): 72

Length of Study:
Date first patient enrolled: 18-Mar-2004
Date last patient completed: 16-Aug-2006

Phase of Development: 3

Abstract:
This was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to evaluate efficacy and safety of oral 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 vagal nerve stimulation (VNS) who currently had 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.

Subjects were enrolled and entered into an 8-week Baseline Phase. At the end of the Baseline Phase, eligible subjects were randomized (1:2:1) in a double-blind fashion to 1 of 3 treatment arms (placebo, LCM 400mg/day, or LCM 600mg/day). The duration of the trial was up to 29 weeks including an 8-week Baseline Phase and up to a 21-week Treatment Phase comprised of 6 weeks forced titration 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 3 weeks taper.

Of 556 subjects screened, 489 were enrolled and 405 were randomized and treated. Of the 405 treated subjects, 316 (78.0%) completed the trial. Based on the prespecified primary analysis, lacosamide showed efficacy at 400mg/day and 600mg/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 405 treated subjects, 89 (22.0%) discontinued the trial prematurely and 67 (16.5%) discontinued due to adverse events (AEs). The most clearly dose-related treatment-emergent adverse events (TEAEs) appeared to be diplopia, vision blurred, nausea, vomiting, dizziness, tremor, coordination abnormal, and nystagmus. Most events were assessed by the investigator as mild or moderate in intensity. A total of 15 (5.0%) subjects experienced serious adverse events (SAEs).

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Number of Patients:

Planned, N:	**500**
Enrolled, N:	**489**
Randomized and treated, N (%):	**405 (100.0)**
Completed, n(%):	**316 (78.0)**
Number of Patients Withdrawn, n(%):	**89 (22.0)**
Withdrawn due to Adverse Events, n(%):	**67 (16.5)**
Withdrawn for Other Reasons, n(%):	**0**

Demography:

Gender (Females/Males):	**205/200**
Age (years), mean(SD):	**38.3 (12.13)**
Race, n(%):	
White	**330 (81.5)**
Black	**38 (9.4)**
Asian	**5 (1.2)**
Other	**32 (7.9)**

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=104**	**LCM 400mg/day N=204**	**LCM 600mg/day N=97**	**LCM Total N=301**
	n (%) [n considered drug-related by the Investigator]			
Any System Organ Class (patients who experienced at least one TEAE)	79 (76.0) [49]	191 (93.6) [154]	92 (94.8) [78]	283 (94.0) [232]
Blood and lymphatic system disorders	3 (2.9) [0]	6 (2.9) [3]	3 (3.1) [1]	9 (3.0) [4]
Cardiac disorders	2 (1.9) [1]	6 (2.9) [5]	2 (2.1) [1]	8 (2.7) [6]
Congenital, familial and genetic disorders	0	0	1 (1.0) [0]	1 (0.3) [0]
Ear and labyrinth disorders	6 (5.8) [1]	10 (4.9) [8]	3 (3.1) [1]	13 (4.3) [9]
Eye disorders	7 (6.7) [7]	51 (25.0) [44]	34 (35.1) [31]	85 (28.2) [75]
Gastrointestinal disorders	20 (19.2) [7]	66 (32.4) [44]	31 (32.0) [24]	97 (32.2) [68]
General disorders and administration site conditions	20 (19.2) [10]	47 (23.0) [29]	23 (23.7) [16]	70 (23.3.) [45]
Hepatobiliary disorders	0	1 (0.5) [0]	1 (1.0) [0]	2 (0.7) [0]
Immune system disorders	0	4 (2.0) [0]	0	4 (1.3) [0]
Infections and infestations	25 (24.0) [1]	55 (27.0) [1]	19 (19.6) [0]	74 (24.6) [1]
Injury, poisoning and procedural complications	10 (9.6) [1]	47 (23.0) [8]	15 (15.5) [3]	62 (20.6) [11]
Investigations	10 (9.6) [6]	33 (16.2) [22]	22 (22.7) [14]	55 (18.3) [36]
Metabolism and nutrition disorders	1 (1.0) [0]	9 (4.4) [4]	6 (6.2) [4]	15 (5.0) [8]
Musculoskeletal and connective tissue disorders	12 (11.5) [1]	22 (10.8) [7]	9 (9.3) [1]	31 (10.3) [8]
Nervous system disorders	43 (41.3) [31]	137 (67.2) [119]	74 (76.3) [68]	211 (70.1) [187]
Psychiatric disorders	6 (5.8) [2]	40 (19.6) [30]	14 (14.4) [12]	54 (17.9) [42]
Renal and urinary disorders	0	4 (2.0) [1]	3 (3.1) [0]	7 (2.3) [1]

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Reproductive system and breast disorders	2 (1.9) [0]	6 (2.9) [2]	1 (1.0) [0]	7 (2.3) [2]
Respiratory, thoracic and mediastinal disorders	8 (7.7) [0]	26 (12.7) [2]	13 (13.4) [1]	39 (13.0) [3]
Skin and subcutaneous tissue disorders	13 (12.5) [6]	23 (11.3) [9]	8 (8.2) [3]	31 (10.3) [12]
Social circumstances	0	1 (0.5) [0]	0	1 (0.3) [0]
Surgical and medical procedures	2 (1.9) [0]	0	0	0
Vascular disorders	1 (1.0) [0]	7 (3.4) [1]	2 (2.1) [0]	9 (3.0) [1]

Death, SAEs, and Other SAEs:
Death, n (%): **1 (subject neither randomized nor treated)**
Patients with SAEs, n(%): **15 (5.0)**

Number of Patients with SAEs During the Treatment Phase (by Primary System Organ Class)	**Placebo N=104**	**LCM 400mg/day N=204**	**LCM 600mg/day N=97**	**LCM Total N=301**
	n (%)			
Congenital, familial and genetic disorders	0	0	1 (1.0)	1 (0.3)
Gastrointestinal disorders	0	2 (1.0)	0	2 (0.7)
Hepatobiliary disorders	0	1 (0.5)	0	1 (0.3)
Infections and infestations	1 (1.0)	1 (0.5)	2 (2.1)	3 (1.0)
Injury, poisoning and procedural complications	0	2 (1.0)	0	2 (0.7)
Investigations	1 (1.0)	1 (0.5)	0	1 (0.3)
Nervous system disorders	0	5 (2.5)	0	5 (1.7)
Psychiatric disorders	0	3 (1.5)	0	3 (1.0)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	0	0	0

Primary & Secondary Efficacy Outcomes:

The LCM 400mg/day and 600mg/day treatment groups were statistically superior to the placebo group in the reduction of seizure frequency per 28 days for the Maintenance Phase (400mg/day p-value=0.0078; 600mg/day p-value=0.0061). The percent reduction in seizure frequency over placebo was 21.6% (95% CI: 6.3, 34.5) and 24.6% (95% CI: 7.8, 38.3) for LCM 400mg/day and 600mg/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, 400mg/day, and 600mg/day were 18.3%, 38.3% and 41.2%, respectively.

Conclusion
This adequate and well-controlled trial supports that LCM 400mg/day and LCM 600mg/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.

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Publication Reference(s) based on the study: None
Date of report: 13 Nov-2008