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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Lyrica®/Pregabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00468845

PROTOCOL NO.: A0081153

PROTOCOL TITLE: A Multiple Dose, Randomized, Double-Blind Multicenter Study of the Efficacy and Safety of Pregabalin Compared to Placebo in the Treatment of Patients With Post-Surgical Pain From Hysterectomy

Study Centers: 37 centers, 3 centers in Canada, 1 center in Czech Republic, 2 centers in Hong Kong, 6 centers in South Africa, 4 centers in Spain, 3 centers in Sweden, 3 centers in Thailand, 5 centers in the United Kingdom, and 10 centers in the United States.

Study Initiation Date and Completion Dates: 27 June 2007 and 05 October 2010

Phase of Development: Phase 3b

Study Objectives: The primary objective of this study was to assess the efficacy of pregabalin compared to placebo on pain following hysterectomy, measured using subject-reported assessments of pain.

The secondary objectives of this study were to evaluate the effect of pregabalin on pain with movement (pain with sitting and at peak expiratory flow, PEF) following surgery; the opioid-sparing effect of pregabalin compared to placebo when administered for the treatment of post-surgical pain following hysterectomy; the effect of pregabalin compared to placebo on the occurrence of opioid-related symptoms as assessed using the Opioid-Related Symptom Distress Scale (OR-SDS); the effect of pregabalin on pain at rest following surgery; the effect of pregabalin on the integrated analgesic assessment which combines pain and opioids use; the effect of pregabalin compared to placebo when administered for the treatment of post-surgical pain following hysterectomy on the use of non-opioid rescue medications; the effect of pregabalin compared to placebo on the time post-surgery (PS) to regain PEF capability; the effect of pregabalin on functional mobility following surgery using the Timed Up and Go (TUG) test; the time from end of the surgery, in hours, to meet hospital discharge criteria and time to actual hospital discharge; anxiety (Visual Analog Scale [VAS]-Anxiety) before the surgery and after the surgery; pain severity post-hospital discharge (Numeric Rating Scale [NRS]-Worst Pain and Average Pain); sleep interference post-hospital discharge (NRS-Sleep); pain severity and interference of pain on aspects of

daily activities using the Modified Brief Pain Inventory-Short Form (mBPI-sf); subject satisfaction with study medication with the Global Evaluation of Study Medication (GESM); subject satisfaction with pain treatment using Pain Treatment Satisfaction Scale (PTSS); the effect of pregabalin compared to placebo on quality of life using the EuroQol Health State Profile (EuroQol Health Questionnaire [EQ-5D]); the safety and tolerability of pregabalin in the peri-operative setting; and investigate the effect of pregabalin treatment on the incidence and severity of chronic post-operative pain (mBPI-sf, Neuropathic Pain Symptom Inventory [NPSI]).

METHODS

Study Design: This was a multi-center, multiple-dose, randomized, double-blind, placebo-controlled parallel group study involving approximately 490 subjects eligible for the efficacy analysis with pain following abdominal hysterectomy, with or without salpingo-oophorectomy.

Number of Subjects (Planned and Analyzed): A sample size of 100 per group would provide about 90% power to detect a treatment effect of 1.0 assuming a standard deviation of 2.2. Overall, 456 of the 494 treated subjects (92.3%) were included in the Modified intent to treat (MITT) population. A total of 487 and 363 subjects were included in the intent to treat (ITT) and per protocol (PP) populations, respectively. All 494 treated subjects comprised the safety population and were analyzed for adverse events (AEs), with 437 of these subjects analyzed for laboratory data.

Diagnosis and Main Criteria for Inclusion: Subjects were females aged between 25 and 70 years and who had elective abdominal hysterectomy using a transverse incision with or without bilateral salpingo-oophorectomy.

Study Treatment: Subjects were randomized to 1 of the following treatment arms:

- Group A - Matching placebo capsules orally twice daily (BID);
- Group B - Pregabalin capsules orally 75 mg BID (total dose of 150 mg/day);
- Group C - Pregabalin capsules orally 150 mg BID (total dose of 300 mg/day).

One group received placebo both before surgery and after surgery. A second group received pregabalin 75 mg the evening before surgery, pregabalin 75 mg 2 hours before surgery, and 150 mg/day (75 mg BID) after surgery and during the treatment period. The third group received pregabalin 75 mg the evening before surgery, pregabalin 150 mg 2 hours before surgery and 300 mg/day (150 mg BID) of pregabalin after surgery and during the treatment period.

At the Taper Visit (which could be Visit 10, 11, or 12), all subjects received blinded medication:

- Subjects who were taking pregabalin 300 mg/day had their dose reduced to 150 mg/day (75 mg BID);

- Subjects who were taking pregabalin 150 mg/day continued on 150 mg/day;
- Subjects who were taking placebo continued on placebo.

Efficacy Evaluations: The primary endpoint was pain reported by subjects, using the NRS-Worst Pain (Question 1 of the mBPI-sf) on the first day (approximately 24 hours) after surgery. The mBPI-sf questionnaire assessed current pain and average and worst pain for the previous 24 hours as well as pain interference with 7 aspects or activities of daily living. The full instrument was completed by subjects at baseline, at the time of hospital discharge and at each visit following discharge. It was also completed by subjects who reported surgery-related pain at the 3 and 6-month telephone interview assessment.

The key secondary efficacy endpoints were pain reported by the subjects with movement (NRS–Current Pain) at each assessment time during the hospital stay and the time-normalized area under the curve (AUC) of pain reported by the subjects with movement during the first 2 days of hospital stay, the amounts of opioids used following surgery and clinically meaningful event (CME) as defined using the OR-SDS.

The other secondary efficacy endpoints were pain reported by subjects, using the NRS-Worst Pain (Question 1 of the mBPI-sf) after the first day (approximately 24 hours) of the surgery, pain reported by the subjects at rest (NRS-Current Pain) at each assessment time during the hospital stay and the time-normalized AUC of pain reported by the subjects at rest during the first 2 days of hospital stay; integrated analgesic score; amounts of 2 most frequently used non-opioid rescue medications used by the subjects during the study, including anti-emetic medications; percentage change from baseline PEF measured at each post-operative assessment time; functional mobility after surgery as measured by the TUG test; VAS-Anxiety before and after the surgery; post-discharge average and worst pain severity measured in daily subject diaries (NRS-Average Pain); sleep interference PS measured in daily subject diaries (NRS-Sleep); interference of pain with aspects of daily activities measured using the mBPI-sf; subject satisfaction with study medication with the Global Evaluation of Study Medication; subject satisfaction with pain treatment using the PTSS; quality of life using EuroQol (EQ-5D) Health State Profile scores; OR-SDS dimension composite and overall composite scores; and NPSI total and subscales of burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia at discharge.

The following time-to-event parameters were defined in hours from the time when surgery ended: time from the end of surgery, in hours, to meet the hospital discharge criteria and time to actual hospital discharge.

The following parameters were summarized and compared between treatment groups at Month 3 and Month 6 post-surgery: incidence and rate of chronic post-operative pain as a result of abdominal hysterectomy and cumulative total daily dose of opioids and other rescue medications.

Safety Evaluations: AEs were monitored throughout the study. The laboratory assessments were performed at screening and Week 4. Other safety measures included medical history;

physical examination including general appearance, head, ears, eyes, nose, mouth, lungs, heart, abdomen, musculoskeletal, extremities and genitourinary; vital signs including supine and standing blood pressure and pulse rate, height, and weight; 12-lead electrocardiogram (ECG); and prospective assessment of AEs of wound healing complications.

Statistical Methods: The primary endpoint was pain reported by subjects, using the NRS-Worst Pain question (Question 1 of the mBPI-sf), on the first day (approximately 24 hours) after surgery.

An analysis of variance (ANOVA) model with model terms of treatment, study center, and salpingo-oophorectomy strata were used to compare pregabalin and placebo groups. If treatment-by-salpingo-oophorectomy strata interaction term was significant at a 0.05 significance level, pattern of interaction was investigated and appropriate subgroup analysis was performed.

Statistical testing was done using a step down procedure for multiple comparisons to control the maximum experiment wise type I error rate at the 0.05 level. The procedure was to test first the difference between high dose pregabalin group and placebo. Only if the difference between the high dose and placebo groups was statistically significant ($p<0.05$), the next step was conducted, in which the low dose pregabalin group was compared to placebo. This procedure was applied only to the analysis of the primary efficacy parameter.

MITT population based analyses were the primary analyses. ITT and PP population based analyses were regarded as secondary.

If the study completed at the pre-planned sample size, then the weighted z-score test was not to be used. In any case, the weighted z-score test was applied to the primary efficacy parameter (24 hours NRS-Worst Pain score) on the MITT population, but not to other populations (ITT and PP) or to secondary efficacy endpoints.

Prior to the second statistical analysis plan amendment, the unblinded interim analysis was conducted. The Data Monitoring Committee advised an increase of sample size based on the interim analysis results. Because sample size was increased after interim analysis, a weighted z-score test was applied to final analysis of the primary efficacy parameter on the MITT population.

The safety summaries and listings were created as per sponsor safety standards.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1. Seven subjects were randomized but not treated. Two subjects were treated but not randomized during the study. A total of 494 subjects received study treatment and 78 subjects discontinued from the study.

Table 1. Subject Disposition

	Pregabalin 150 mg	Pregabalin 300 mg	Placebo
Number (%) of subjects			
Screened 622			
Assigned to study treatment	162	170	169
Treated	161	166	167
Completed (%)	141 (87.0)	136 (80.0)	139 (82.2)
Discontinued (%)	20 (12.3)	30 (17.6)	28 (16.6)
Related to study treatment	5 (3.1)	7 (4.2)	6 (3.6)
Adverse event	5 (3.1)	7 (4.2)	6 (3.6)
Not related to study treatment	15 (9.3)	23 (13.9)	22 (13.2)
Adverse event	4 (2.5)	7 (4.2)	5 (3.0)
Lost to follow-up	2 (1.2)	1 (0.6)	2 (1.2)
Other	4 (2.5)	9 (5.4)	5 (3.0)
Subject no longer willing to participate in the study	5 (3.1)	6 (3.6)	10 (6.0)

Acute and Follow-up Phase: Of the 494 subjects who received study treatment, 400 subjects completed the acute and the follow-up phases. By the time of the follow-up phase, a total of 94 subjects had discontinued from the study, ie, an additional 16 subjects from the treatment phase. Of those, 21 subjects were lost to follow-up (8, 9, and 4 subjects in the pregabalin 150, pregabalin 300 mg and placebo groups, respectively).

The treatment groups were well balanced in terms of demographic characteristics (Table 2). The majority of subjects were white (67.8%).

Table 2. Demographic Characteristics

	Pregabalin 150 mg (N=161)	Pregabalin 300 mg (N=166)	Placebo (N=167)
Age, years			
Mean (SD)	44.9 (6.2)	44.6 (6.0)	44.4 (6.7)
Range	27-63	31-69	27-65
Race, number (%) of subjects			
White	112 (69.6)	114 (68.7)	109 (65.3)
Black	17 (10.6)	21 (12.7)	22 (13.2)
Asian	25 (15.5)	27 (16.3)	29 (17.4)
Other	7 (4.3)	4 (2.4)	7 (4.2)
Weight (kg)			
Mean (SD)	72.3 (15.6)	72.1 (14.5)	72.4 (17.0)
Range	43.0-115.0	44.7-124.9	44.0-131.0
Height (cm)			
Mean (SD)	161.9 (6.6)	162.5 (7.2)	162.4 (7.0)
Range	147.0-178.0	142.0-186.0	148.0-186.0
Body Mass Index (kg/m^2)			
Mean (SD)	27.6 (5.7)	27.3 (5.3)	27.4 (6.2)
Range	16.3-43.1	18.1-44.8	17.1-49.6

N=total number of subjects; SD = standard deviation

Efficacy Results: The primary efficacy endpoint was NRS-Worst Pain score (Question 1 of mBPI-sf) in the MITT population at 24 hours PS from weighted z-score test. There was no statistically significant difference between either of the pregabalin doses (300 mg and 150 mg) and placebo in the worst pain score at 24 hours PS (Table 3).

Table 3. Weighted Z-Score Test for NRS-Worst Pain at 24 Hours Post-Surgery – MITT Population

Analysis	Treatment	N	LS Mean (SE)	Z-Score Statistics	Difference (SE)	95% CI	p-value
Weighted Z-Score Test	Pregabalin 150 mg	151	7.1 (0.18)	-1.4842	-0.4 (0.25)	(-0.85, 0.12)	0.1378
	Pregabalin 300 mg	149	7.2 (0.18)	-0.7208	-0.2 (0.25)	(-0.66, 0.31)	0.4710
	Placebo	156	7.4 (0.18)	-	-	-	-
Interim	Pregabalin 150 mg	43	6.7 (0.38)	-1.6100	-0.8 (0.48)	(-1.74, 0.18)	-
	Pregabalin 300 mg	48	6.8 (0.36)	-1.3919	-0.7 (0.48)	(-1.61, 0.28)	-
	Placebo	46	7.4 (0.36)				
Post-Interim	Pregabalin 150 mg	108	7.3 (0.21)	-0.5374	-0.1 (0.28)	(-0.69, 0.39)	-
	Pregabalin 300 mg	101	7.6 (0.22)	0.2982	0.1 (0.28)	(-0.47, 0.64)	-
	Placebo	110	7.5 (0.21)	-			

NRS = numeric rating scale, MITT = Modified intent to treat, N = total number of subjects, LS = least square, SE = standard error, CI = confidence interval, ANOVA = analysis of variance
Based on ANOVA model with model terms of treatment, study center, and salpingo-oophorectomy strata.

There were no significant differences in the 3 key secondary efficacy parameters (movement pain caused by sitting/PEF test and total amount of opioids) at 24 hours PS. There was a statistically significant difference in favor of pregabalin 300 mg when compared with placebo in the MITT population for the CMEs of nausea and itching at Day 1 PS (as measured on the OR-SDS).

There were statistically significant differences in favor of pregabalin 300 mg when compared with placebo in the MITT population in the current pain (NRS) at rest at 72 hours PS, current pain (NRS) at rest (integrated analgesic score – Silverman Algorithm) at 24-48 hours PS and 48-72 hours PS, OR-SDS symptoms (by frequency) of nausea at Day 1 PS, Day 2 PS and discharge, and itching at Day 1 PS, OR-SDS symptoms (by severity) of nausea at Day 1 PS, Day 2 PS and discharge, itching at Day 1 PS, and retching/vomiting at Day 1 PS, Day 3 PS and discharge, OR-SDS symptoms (by degree of bother) of nausea at Day 1 PS, Day 2 PS and discharge, inability to concentrate at Day 2 PS, itching at Day 1 PS, and retching/vomiting at Day 1 PS, Day 3 PS and discharge, OR-SDS degree of bother composite score at Day 1 PS, and overall composite score at Day 1 PS, and cumulative total amount of paracetamol at first week PS, percent change from baseline in PEF at 48 hours PS.

There were statistically significant differences in favor of pregabalin 150 mg when compared with placebo in the MITT population in the current pain (NRS) at rest (Sum of Pain Intensity [SPI]) at 0-24 hours PS, OR-SDS symptoms (by frequency) of nausea at Day 2 PS, and itching at Day 1 PS, OR-SDS symptoms (by severity) of nausea at Day 2 PS, and itching at Day 1 PS, and OR-SDS symptoms (by degree of bother) of nausea at Day 2 PS and itching at Day 1 PS.

There was a big difference in favor of placebo in 3 countries (South Africa, Thailand and Czech Republic), and when these 3 countries were excluded from the primary endpoint analysis (worst pain at 24 hours PS), the results showed significant differences in favor of both pregabalin treatment arms.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Results: There were no pharmacokinetic or pharmacodynamic evaluations done in this study. Pharmacogenomic results were listed.

Safety Results: There were no deaths reported in the study. Thirty-five subjects experienced serious AEs (SAEs) and 419 subjects experienced a total of 1964 AEs, of which 779 were treatment-related.

Pregabalin was well-tolerated with nausea, constipation, dizziness, fatigue and somnolence, being the most common AEs. Nausea and vomiting were less frequent in the pregabalin 300 mg group compared with the pregabalin 150 mg and placebo groups. Treatment-emergent AEs are summarized in Table 4.

Table 4. Summary of Treatment-Emergent (All Causality) Adverse Events

	Pregabalin 150 mg (N=161)	Pregabalin 300 mg (N=166)	Placebo (N=167)
Number (%) of subjects:			
Subjects evaluable for adverse events	161	166	167
Number of adverse events	658	690	616
Subjects with adverse events	137 (85.1)	145 (87.3)	137 (82.0)
Subjects with serious adverse events	9 (5.6)	11 (6.6)	15 (9.0)
Subjects with severe adverse events	27 (16.8)	40 (24.1)	31 (18.6)
Subjects who discontinued due to adverse events	9 (5.6)	14 (8.4)	12 (7.2)
Subjects with dose reductions or who temporarily discontinued due to an adverse event	2 (1.2)	5 (3.0)	6 (3.6)

N=total number of subjects

Acute and Follow-up Phase: The AE results during the acute and follow-up combined phase were similar to those mentioned in Table 4 except for an increase in the number of treatment-emergent AEs from 616 to 617 following placebo. Treatment-related AEs reported during the acute and follow-up combined phase were similar to those reported during the treatment phase.

The incidence of treatment-emergent AEs (in ≥2% subjects in any treatment group) is summarized by Medical Dictionary for Regulatory Activities (v13.0) preferred term and by body system in Table 5.

Table 5. Incidence of Treatment-Emergent Adverse Events in ≥2% Subjects in Any Treatment Group

Page 1 of 2

Body System Class and MedDRA Preferred Term (v13.0) n (%)	Pregabalin 150 mg (N=161)	Pregabalin 300 mg (N=166)	Placebo (N=167)
Gastrointestinal Disorders			
Nausea	67 (41.6)	60 (36.1)	76 (45.5)
Constipation	46 (28.6)	49 (29.5)	46 (27.5)
Somnolence	39 (24.2)	39 (23.5)	36 (21.6)
Vomiting	33 (20.5)	20 (12.0)	30 (18.0)
Flatulence	16 (9.9)	10 (6.0)	13 (7.8)
Abdominal pain	7 (4.3)	4 (2.4)	10 (6.0)
Dyspepsia	5 (3.1)	6 (3.6)	6 (3.6)
Abdominal distension	6 (3.7)	5 (3.0)	4 (2.4)
Diarrhea	4 (2.5)	2 (1.2)	7 (4.2)
Retching	0	6 (3.6)	4 (2.4)
Nervous System Disorders			
Dizziness	51 (31.7)	52 (31.3)	37 (22.2)
Disturbance in attention	24 (14.9)	30 (18.1)	23 (13.8)
Headache	27 (16.8)	23 (13.9)	19 (11.4)
Hypoesthesia	0	4 (2.4)	4 (2.4)
Migraine	2 (1.2)	4 (2.4)	2 (1.2)
Paresthesia	4 (2.5)	0	2 (1.2)
General Disorders and Administration Site Conditions			
Fatigue	38 (23.6)	46 (27.7)	34 (20.4)
Pyrexia	32 (19.9)	29 (17.5)	25 (15.0)
Pain	4 (2.5)	3 (1.8)	3 (1.8)
Chills	1 (0.6)	2 (1.2)	4 (2.4)
Edema peripheral	4 (2.5)	1 (0.6)	1 (0.6)
Skin and Subcutaneous Tissue Disorders			
Pruritus	27 (16.8)	22 (13.3)	26 (15.6)
Rash	0	4 (2.4)	0
Renal and Urinary Disorders			
Dysuria	14 (8.7)	22 (13.3)	17 (10.2)
Infections and Infestations			
Urinary tract infection	13 (8.1)	13 (7.8)	9 (5.4)
Wound infection	5 (3.1)	6 (3.6)	4 (2.4)
Psychiatric Disorders			
Confusional state	12 (7.5)	12 (7.2)	9 (5.4)
Insomnia	9 (5.6)	9 (5.4)	10 (6.0)
Blood and Lymphatic System Disorders			
Anemia	9 (5.6)	6 (3.6)	5 (3.0)
Vascular Disorders			
Hematoma	6 (3.7)	7 (4.2)	2 (1.2)
Hypertension	3 (1.9)	5 (3.0)	2 (1.2)
Musculoskeletal and Connective Tissue Disorders			
Back pain	6 (3.7)	4 (2.4)	4 (2.4)
Cardiac Disorders			
Tachycardia	4 (2.5)	7 (4.2)	3 (1.8)
Respiratory, Thoracic and Mediastinal			
Cough	4 (2.5)	3 (1.8)	2 (1.2)

MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with MedDRA coded adverse event; N = number subjects analyzed for adverse events

Table 5. Incidence of Treatment-Emergent Adverse Events in ≥2% Subjects in Any Treatment Group

Page 2 of 2			
Body System Class and MedDRA Preferred Term (v13.0) n (%)	**Pregabalin 150 mg (N=161)**	**Pregabalin 300 mg (N=166)**	**Placebo (N=167)**
Injury, Poisoning and Procedural Complications			
Procedural pain	2 (1.2)	4 (2.4)	2 (1.2)
Eye Disorders			
Vision blurred	2 (1.2)	4 (2.4)	0

MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with MedDRA coded adverse event; N = number subjects analyzed for adverse events

Acute and Follow-up Phase: Apart from the AEs captured in the acute phase tables, 1 additional AE was reported during the follow-up phase. A 51-year-old female in the placebo group had moderate fungal skin infection that started on Day 106 and was ongoing at the end of the study. The causality of this event was attributed to injection/procedure-related.

Table 6 summarizes discontinuations due to AEs.

Table 6. Discontinuations due to Treatment-Emergent Adverse Events

Sex/age (years)	Preferred term[a]	Start day[b]	Stop day[b]	Severity	Outcome	Causality	SAE
Page 1 of 2							
Pregabalin 150 mg							
F/59	Headache	4	7	Severe	Resolved	Study drug	No
F/51	Headache	3	[>66]	Severe	Still present	Other - unknown	No
F/58	Liver function test abnormal	9	29	Severe	Resolved	Study drug	Yes
F/37	Pain	2	[>5]	Moderate	Still present	Study drug	No
F/42	Migraine	2	3	Severe	Resolved	Study drug	No
F/55	Pelvic hematoma	7	[>7]	Severe	Still present	Other – surgical procedure	No
F/37	Constipation	3	9	Mild	Resolved	Concomitant treatment	No
F/45	Umbilical hernia	4	23	Mild	Resolved	Other illness - hernia	Yes
F/38	Postoperative ileus	6	11	Moderate	Resolved	Study drug	Yes
Pregabalin 300 mg							
F/45	Dizziness	3	3	Moderate	Resolved	Study drug	No
F/45	Anxiety	7	7	Moderate	Resolved	Study drug	No
F/55	Rash	9	94	Mild	Resolved	Study drug	No
F/51	Dizziness	3	[>4]	Mild	Still present	Other - unknown	No
F/41	Cervix carcinoma	1	[>2]	Severe	Still present	Other illness – cancer of cervix	Yes
F/49	Hyperthyroidism	2	[>2]	Moderate	Still present	Other illness – newly diagnosed illness	No
F/54	Liver function test abnormal	6	[>8]	Moderate	Still present	Study drug	No
F/44	Headache	2	2	Moderate	Resolved	Study drug	No
F/47	Somnolence	3	36	Moderate	Resolved	Study drug	No
F/44	Nausea	4	9	Severe	Resolved	Concomitant treatment - morphine	No
F/48	Dizziness	3	15	Severe	Resolved	Concomitant treatment - opioids	No
F/52	Endometrial cancer	2	2	Moderate	Resolved	Other illness – concurrent medical history	Yes
F/56	Somnolence	1	20	Severe	Resolved	Study drug	No
F/49	Sepsis	5	16	Severe	Resolved	Other illness – uretal injury	Yes

MedDRA = Medical Dictionary for Regulatory Activities; F = female; SAE = serious adverse event
[a]MedDRA v13.0
[b]Day relative to start of study treatment
[ ] Values in brackets were imputed from incomplete dates and times.

Table 6. Discontinuations due to Treatment-Emergent Adverse Events

Sex/age (years)	Preferred term[a]	Start day[b]	Stop day[b]	Severity	Outcome	Causality	SAE
Page 2 of 2							
Placebo							
F/44	Sleep disorder	10	25	Mild	Resolved	Study Drug	No
F/45	Pruritus	3	[>4]	Mild	Still present	Other - unknown	No
F/45	Dizziness	2	[>4]	Mild	Still present	Other - unknown	No
F/53	Rash generalized	4	13	Severe	Resolved	Study drug	No
F/40	Hallucination	5	5	Mild	Resolved	Study drug	No
F/57	Tinnitus	8	9	Severe	Resolved	Study drug	No
F/59	Hypoxia	2	5	Severe	Resolved	Other illness - COPD	Yes
F/40	Nausea	6	10	Moderate	Resolved	Study drug	No
F/50	Atrioventricular block complete	2	2	Mild	Resolved	Study drug	Yes
F/46	Pyelonephritis	21	33	Severe	Resolved	Injection/procedure related	Yes
F/40	Incision site infection	13	[>18]	Moderate	Still present	Other –post operation complication	Yes

MedDRA = Medical Dictionary for Regulatory Activities; F = female; SAE = serious adverse event; COPD = chronic obstructive pulmonary disease
[a]MedDRA v13.0
[b]Day relative to start of study treatment
[ ] Values in brackets were imputed from incomplete dates and times.

Table 7 summarizes the SAEs. Of the 35 subjects with treatment-emergent SAEs, 4 subjects reported treatment-related SAEs.

Table 7. Serious Adverse Events

Sex/age (years)	Preferred term[a]	Action Taken (Drug Level)	Therapy Stop Day	Event Onset Day	Outcome	Sponsor/ Investigator Causality
Page 1 of 2						
Pregabalin 150 mg						
F/58	Liver function test abnormal	Permanently withdrawn	15	9	Resolved	Related/ Related
F/64	Gastritis	Post-therapy	33	39	Resolved	Unrelated/ Unrelated
F/51	Hematoma	Dose not changed	NA	16	Resolved	Unrelated/ Unrelated
F/44	Abdominal pain Pyrexia	Dose not changed	NA	17	Resolved	Unrelated/ Unrelated
F/45	Umbilical hernia	Permanently withdrawn	4	4	Resolved	Unrelated/ Unrelated
F/46	Oxygen saturation decreased	Dose not changed	NA	1	Not Resolved	Unrelated/ Unrelated
F/38	Postoperative ileus	Permanently withdrawn	5	6	Resolved	Related/Related
F/46	Postoperative wound infection	Dose not changed	NA	5	Resolved	Unrelated/ Unrelated
F/45	Ileus Wound infection	Dose not changed	NA	5	Resolved	Unrelated/ Unrelated
Pregabalin 300 mg						
F/50	Anemia	Dose not changed	NA	4	Resolved	Unrelated/ Unrelated
F/51	Impaired healing	Post-therapy	17	25	Resolved	Unrelated/ Unrelated
F/45	Wound infection Hematoma Urinary tract infection	Dose not changed	NA	7	Resolved	Unrelated/ Unrelated
F/41	Cervix cancer	Permanently withdrawn	1	1	Not resolved	Unrelated/ Unrelated
F/39	Abdominal pain lower	Dose not changed	NA	25	Resolved	Unrelated/ Unrelated
F/48	Ureteric stenosis	Dose not changed	22	2	Resolved	Unrelated/ Unrelated
F/48	Pyrexia	Dose not changed	22	3	Resolved	Unrelated/ Unrelated
	Tachycardia		22	2	Resolved	Related/ Related
F/58	Dyspnea	Dose not changed	NA	5	Resolved	Unrelated/ Unrelated
	Hypertension	Dose not changed	NA	2	Resolved	Unrelated/ Unrelated
F/46	Hematoma	Dose not changed	16	14	Resolved	Unrelated/ Unrelated
	Hematoma	Post-therapy	16	34	Resolved	Unrelated/ Unrelated

M = male, F = Female, [a]MedDRA = Medical Dictionary for Regulatory Activities v13.0; NA = not available or not applicable.

Table 7. Serious Adverse Events

Sex/age (years)	Preferred term[a]	Action Taken (Drug Level)	Therapy Stop Day	Event Onset Day	Outcome	Sponsor/ Investigator Causality
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Pregabalin 300 mg						
F/52	Endometrial cancer	Permanently withdrawn	22	2	Resolved	Unrelated/ Unrelated
F/49	Sepsis	Permanently withdrawn	5	5	Resolved	Unrelated/ Unrelated
F/40	Wound infection	Dose not changed	NA	7	Resolved	Unrelated/ Unrelated
Placebo						
F/36	Urinary tract infection	Dose not changed	NA	16	Resolved	Unrelated/ Unrelated
F/45	Rectal perforation	Dose not changed	NA	2	Resolved	Unrelated/ Unrelated
F/43	Pyrexia	Dose not changed	NA	3	Resolved	Unrelated/ Unrelated
	Dysuria Wound complication	Dose not changed	NA	6	Resolved	Unrelated/ Unrelated
F/45	Abdominal pain Abdominal distension	Post-therapy	4	16	Resolved	Unrelated/ Unrelated
F/46	Wound infection	Dose not changed	NA	9	Resolved	Unrelated/ Unrelated
F/35	Pelvic hematoma	Dose not changed	NA	4	Resolved	Unrelated/ Unrelated
	Chest pain	Dose not changed	NA	7	Resolved	Unrelated/ Unrelated
F/42	Intestinal obstruction	Dose not changed	NA	11	Resolved	Unrelated/ Unrelated
	Abdominal wound dehiscence	Dose not changed	NA	9	Resolved	Unrelated/ Unrelated
F/51	Ureteric injury	Temporarily withdrawn	NA	4	Resolved	Unrelated/ Unrelated
F/48	Constipation	Dose not changed	NA	11	Resolved	Unrelated/ Unrelated
F/59	Hypoxia	Permanently withdrawn	2	2	Resolved	Unrelated/ Unrelated
F/34	Pneumonia	Dose not changed	18	3	Resolved	Unrelated/ Unrelated
F/50	Atrioventricular block complete	Permanently withdrawn	2	2	Resolved	Related/ Unrelated
F/46	Pyelonephritis	Permanently withdrawn	21	21	Resolved	Unrelated/ Unrelated
F/40	Incision site infection	Permanently withdrawn	18	13	Not Resolved	Unrelated/ Unrelated
F/38	Post-operative wound infection	Dose not changed	NA	7	Resolved	Unrelated/ Unrelated

M = male, F = Female, [a]MedDRA = Medical Dictionary for Regulatory Activities v13.0; NA = not available or not applicable.

The median changes from baseline to last observation in laboratory parameters were small and not considered to be clinically significant. The median changes from baseline in vital sign parameters were small and not considered to be clinically significant.
One (0.6%) subject in the placebo group had an abnormal ECG on Day -6 that was considered clinically significant. Abnormalities were most frequently noted at screening for abdomen and genitourinary sites, related to medical cause leading to hysterectomy.

The majority of subjects had no surgical wound healing complications at the scheduled visits. The percentage of subjects with no surgical wound healing complications was similar across treatment groups at discharge, Days 7, 14 and 28.

Summary of Results

There was no statistically significant difference between either of the pregabalin doses (300 mg and 150 mg) and placebo in the worst pain score at 24 hours PS. There were no significant differences in the 3 key secondary efficacy parameters (movement pain caused by sitting, PEF test and total amount of opioids) at 24 hours PS. There was a statistically significant difference in favor of pregabalin 300 mg when compared with placebo in the MITT population for the CMEs of nausea and itching at Day 1 PS (as measured on the OR-SDS).

There were statistically significant differences in favor of pregabalin 300 mg when compared with placebo in the MITT population in the current pain (NRS) at rest at 72 hours PS, current pain (NRS) at rest (integrated analgesic score – Silverman Algorithm) at 24-48 hours PS and 48-72 hours PS, OR-SDS symptoms (by frequency) of nausea at Day 1 PS, Day 2 PS and discharge, and itching at Day 1 PS, OR-SDS symptoms (by severity) of nausea at Day 1 PS, Day 2 PS and discharge, itching at Day 1 PS, and retching/vomiting at Day 1 PS, Day 3 PS and discharge, OR-SDS symptoms (by degree of bother) of nausea at Day 1 PS, Day 2 PS and discharge, inability to concentrate at Day 2 PS, itching at Day 1 PS, and retching/vomiting at Day 1 PS, Day 3 PS and discharge, OR-SDS degree of bother composite score at Day 1 PS, and overall composite score at Day 1 PS, and cumulative total amount of paracetamol at first week PS, percent change from baseline in PEF at 48 hours PS.

There were statistically significant differences in favor of pregabalin 150 mg when compared with placebo in the MITT population in the current pain (NRS) at rest (SPI) at 0-24 hours PS, OR-SDS symptoms (by frequency) of nausea at Day 2 PS, and itching at Day 1 PS, OR-SDS symptoms (by severity) of nausea at Day 2 PS, and itching at Day 1 PS, and OR-SDS symptoms (by degree of bother) of nausea at Day 2 PS and itching at Day 1 PS.

There were no deaths reported in the study. Thirty-five subjects experienced SAEs and 419 subjects experienced a total of 1964 AEs, of which 779 were treatment-related. Pregabalin was well-tolerated with nausea, constipation, dizziness, fatigue and somnolence, being the most common AEs. Nausea and vomiting were less frequent in the pregabalin 300 mg group compared with the pregabalin 150 mg and placebo groups.

CONCLUSIONS

- Pregabalin did not show any separation from placebo for the primary endpoint for this study (worst pain at 24 hours). However, there was a statistically significant difference from placebo in the other important endpoints related to pain intensity (eg, SPI at 0-24 hours and Silverman Index at 24-48 hours PS). Analysis of the primary endpoint, worst pain, showed that there were site issues in some of the countries favoring placebo (South Africa, Czech Republic, Thailand), and when these countries were removed from the analysis, a statistically significant difference favoring pregabalin was observed in all the other sites.

- There was no separation from placebo in opioid dose. There were significant differences in opioid-related symptoms like nausea, vomiting and itching as demonstrated by the OR-SDS scale.

- Pregabalin 300 and 150 mg were safe and well-tolerated. AEs were consistent with the known profile of pregabalin, and no new or unexpected safety/tolerability findings were observed in the study.